Clinical Study Protocol

Study Title: An open-label, multi-centre, randomised, single-period, parallel study to assess the efficacy, safety and utility of 6 month day-and-night automated closed-loop insulin delivery under free living conditions compared to insulin pump therapy in children and adolescents with type 1 diabetes

Short Title: Day and night closed-loop in young people with type 1 diabetes (DAN05)

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This protocol has been written in accordance with current ISO 14155:2011 standard

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PROTOCOL SIGNATURE PAGE

The signature below documents the approval of the protocol entitled “An open-label, multi-centre, randomised, single-period, parallel study to assess the efficacy, safety and utility of 6 month day and night automated closed-loop insulin delivery under free living conditions compared to insulin pump therapy in children and adolescents with type 1 diabetes" version 7.0 dated 11 June 2019 and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, the principles of GCP and the appropriate reporting requirements.

Signature …… Date…….

Dr Roman Hovorka, Chief Investigator

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1 List of Abbreviations and Relevant Definitions

ADA	American Diabetes Association
ADE	Adverse Device Effect
AE	Adverse Event
AP	Artificial Pancreas
ANCOVA	Analysis of Covariance
AR	Adverse Reaction
ASADE	Anticipated Serious Adverse Device Effect
AUC	Area under the Curve
CE	Conformité Européenne (CE-mark)
CGM	Continuous Glucose Monitoring
CI	Chief Investigator or Confidence Interval
CL	Closed-loop
CRF	Case Report Form
CSII	Continuous subcutaneous insulin infusion
DCE	Discrete Choice Experiment
DKA	Diabetic Ketoacidosis
DSMB	Data Safety and Monitoring Board
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Glycated Haemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	Health Related Quality of Life
IDE	US Investigational Device Exemption
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IRB	Institutional Review Board
ISPAD	International Society for Pediatric and Adolescent Diabetes
i.v.	Intravenous
JCHR	Jaeb Center for Health Research
JDRF	Juvenile Diabetes Research Foundation
MDI	Multiple Daily Injections

MHRA	Medicine and Healthcare Products Regulatory Agency
MPC	Model Predictive Control
NGP	Next Generation Insulin Pump (Medtronic)
NGSP	National Glycohemoglobin Standardization Program
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
PBM	Preference Based Measures
PIC	Participant Identification Centre
R & D	Research and Development
QA	Quality Assurance
QALY	Quality Adjusted Life Years
QC	Quality Control
RBM	Risk-based Monitoring
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RF	Radio Frequency
s.c.	Subcutaneous
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Sensor Augmented Pump Therapy
SD	Standard Deviation
SMBG	Self-Monitoring of Blood Glucose
T1D	Type 1 Diabetes Mellitus
USADE	Unanticipated Serious Adverse Device Effect
WHO	World Health Organization

2 Study Synopsis

Title of clinical trial	An open-label, multi-centre, randomised, single-period, parallel study to assess the efficacy, safety and utility of 6 month day and night automated closed-loop insulin delivery under free living conditions compared to insulin pump therapy in children and adolescents with type 1 diabetes
Short title	Day and night closed-loop in young people with type 1 diabetes
Sponsor name	**UK** - University of Cambridge and Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK. **USA** - Jaeb Centre for Health Research, USA
Medical condition or disease under investigation	Type 1 diabetes
Purpose of clinical trial	To determine whether 24/7 automated closed-loop glucose control will improve glucose control as measured by glycated haemoglobin and reduce the burden of hypoglycaemia compared to usual care (conventional or sensor-augmented insulin pump therapy)
Study objectives	**1. EFFICACY:** The objective is to assess efficacy of day and night automated closed-loop glucose control in improving glucose control as measured by glycated haemoglobin, as compared to insulin pump therapy alone. **2. SAFETY:** The objective is to evaluate the safety of day and night automated closed-loop glucose control, in terms of episodes of severe hypoglycaemia and other adverse events. **3. SYSTEM USE:** The objective is to determine the duration of the use of the automated closed-loop system. **4. HUMAN FACTORS:** The objective is to assess cognitive, emotional, and behavioural characteristics of participating subjects and family members and their response to the closed-loop system and clinical trial using validated surveys and focus groups. **5. HEALTH ECONOMICS**: The objective is to perform a cost utility analysis to inform reimbursement decision-making.
Study design	An open-label, multi-centre, randomised, single-period parallel study, contrasting day-and-night automated closed-loop glucose control with insulin pump therapy

Primary endpoint	The primary outcome is the centralised measurement of glycated haemoglobin (HbA1c) at 6 months.
Other key endpoints	• Time spent in the target glucose range (3.9 to 10mmol/l) (70 to 180mg/dl) • Mean sensor glucose • Time spent above target glucose (10.0 mmol/l) (180 mg/dl) • Time spent below target glucose (3.9mmol/l)(70mg/dl)
Secondary endpoint(s)	• Standard deviation, and coefficient of variation of glucose levels • The time with glucose levels < 3.5 mmol/l (63 mg/dl) and <3.0 mmol/l (54mg/dl) • AUC of glucose below 3.5mmol/l (63mg/dl) • Time with glucose levels in significant hyperglycaemia (glucose levels > 16.7 mmol/l) (300mg/dl) • AUC of glucose above 10.0 mmol/l (180 mg/dl) • Binary metrics for HbA1c (HbA1c<7.0%, HbA1c <7.5%, relative reduction ≥10% from baseline, absolute reduction ≥0.5% from baseline, absolute reduction ≥1% from baseline, absolute reduction ≥1% from baseline or HbA1c <7.0%) • Total, basal and bolus insulin dose • Body weight (BMI z-score) • Blood pressure Secondary endpoints regarding glucose levels will be based on sensor glucose data.
Exploratory endpoint(s)	Day (08:00 to 24:00) vs. night (00:00 to 08:00) glucose control, 3-monthly trends in glucose control and insulin delivery, relationships between compliance and glucose outcomes
Safety evaluation	Frequency of severe hypoglycaemic episodes as defined by American Diabetes Association (adolescents), and International Society for Pediatric and Adolescent Diabetes (children), frequency of diabetic ketoacidosis (DKA) and nature and severity of other adverse events
System use evaluation	Assessment of the duration of use of the closed-loop system
Human factors assessment	Cognitive, emotional, and behavioural characteristics of participating subjects and family members and their response to the closed-loop system and clinical trial will be assessed gathering both quantitative (validated surveys) and qualitative data (focus groups)
Health economic evaluation	Cost utility analysis on the benefits of closed loop insulin delivery to inform reimbursement decision-making

Sample size	130 participants randomised (equal proportion of those aged 6 to 12 years and 13 to 18 years, a minimum quota of 25% participants with baseline HbA1c >8.5%
Summary of eligibility criteria	Key inclusion criteria: 1. Age ≥ 6 and <19 years 2. Type 1 diabetes as defined by WHO for at least 1 year 3. Use of an insulin pump for at least 3 months, with good knowledge by subject or caregiver of insulin self-adjustment as judged by the investigator 4. Using U-100 rapid acting insulin analogues Aspart or Lispro only) 5. Willing to perform regular finger-prick blood glucose monitoring, with at least 4 blood glucose measurements per day 6. HbA1c ≥ 7.0% (53 mmol/mol) and ≤ 10% (86mmol/mol) based on analysis from local laboratory 7. Literate in English 8. Willing to wear study devices 9. Access to WiFi 10. The subject lives with someone who is trained to administer intramuscular glucagon and is able to seek emergency assistance Key exclusion criteria: 1. Living alone 2. Current use of any closed-loop system 3. Any other physical or psychological disease likely to interfere with the normal conduct of the study and interpretation of the study results as judged by the investigator 4. Untreated coeliac disease, adrenal insufficiency or thyroid disease 5. Current treatment with drugs known to interfere with glucose metabolism, e.g. systemic corticosteroids, non-selective beta-blockers and MAO inhibitors etc. 6. Known or suspected allergy against insulin 7. Clinical significant nephropathy, neuropathy or retinopathy as judged by the investigator 8. Recurrent incidents of severe hypoglycaemia during previous 6 months 9. Recurrent incidents of diabetic ketoacidosis during previous 6 months. 10. Unwilling to avoid regular use of acetaminophen 11. Lack of reliable telephone facility for contact 12. Total daily insulin dose ≥ 2 IU/kg/day 13. Total daily insulin dose < 15 IU/day 14. Pregnancy, planned pregnancy, or breast feeding 15. Severe visual impairment 16. Severe hearing impairment

	17. Seizure disorder 18. Medically documented allergy towards the adhesive 19. Serious skin diseases 20. Illicit drugs abuse 21. Prescription drugs abuse 22. Alcohol abuse 23. Use of pramlintide (Symlin), sulphonylureas, biguanides, DPP4-Inhibitors, , GLP-1 analogues, SGLT-1/ 2 inhibitors at time of screening 24. Shift work with working hours between 10pm and 8am 25. Sickle cell disease or haemoglobinopathy 26. Eating disorder such as anorexia or bulimia 27. Employed by Medtronic Diabetes or with immediate family members employed by Medtronic Diabetes
Maximum duration of study for a subject	8 months
Recruitment	The subjects will be recruited through the paediatric diabetes outpatient clinics at each centre
Consent	Written consent/assent will be obtained from participants and/or guardians according to REC/IRB requirements
Screening and baseline assessment	Eligible participants will undergo a screening evaluation where blood samples for full blood count, liver, thyroid function and anti-transglutaminase antibodies (with IgA levels if not done within previous 12 months) will be taken. Non-hypoglycaemia C-peptide, glucose and HbA1c will also be measured, and a urine pregnancy test in females of child-bearing potential will be performed. Surveys investigating participants' quality of life, psychosocial and cognitive functioning, and response to their current treatment will be distributed. Participants will be fitted with a blinded continuous glucose monitoring (CGM) device to assess baseline glycaemic control. Instructions on how to safely use, remove and send back the device will be provided.
Run-in Period	During a 2-3 week run-in period, subjects will continue using their own insulin pump. Data obtained from blinded CGM and pump downloads may be utilised for therapy adjustment.
Randomisation	Eligible subjects will be randomised using randomisation software to the use of real-time CGM and low glucose feature combined with day and night closed-loop or to conventional insulin pump therapy alone.

	A blood sample for centralised analysis of HbA1c will be taken if screening and randomisation are >28 days apart. A urine pregnancy test in females of child-bearing potential will be performed.
1. Automated day and night closed-loop insulin delivery (intervention arm) combined with low glucose feature (interventional arm)	Participants in the closed-loop group will receive additional training sessions following randomisation covering the use of the study insulin pump and real-time CGM, prior to starting closed-loop insulin delivery. Once confident with the use of the study pump and CGM system, participants will receive training required for safe and effective use of the closed-loop system approximately 2-4 weeks after randomisation. During this 2-4 hour session participants will operate the system under the supervision of the clinical team. Competency on the use of closed-loop system will be evaluated. Thereafter, participants are expected to use closed-loop for 6 months without direct real-time remote monitoring.
2. Usual care (conventional or sensor-augmented pump therapy) **(control arm)**	Refresher training on key aspects of insulin pump therapy will be provided. Subjects will continue using their own insulin pump and CGM if a regular CGM user for 6 months.
3-month and 6-month assessments	A blood sample will be taken for measurement of HbA1c. A urine pregnancy test in females of child-bearing potential will be performed during the 3-month visit. Validated surveys evaluating the impact of the devices employed on quality of life, psychosocial and cognitive functioning, diabetes management and treatment satisfaction will be completed. Participants of both study arms will be fitted with blinded CGM systems at the end of each follow up visit. The sensors will be worn at home for up to 14 days and will be sent back to the research team. 6 months only: Subjects/guardians will be invited to join follow-up focus groups to gather feedback and reactions to their current treatment (closed-loop or insulin pump), the clinical trial, and quality of life changes.

Study contacts	In between study visits, participants will be contacted by the study team (email or phone) once monthly in order to record any adverse events, device deficiencies, and changes in insulin settings, other medical conditions and/or medication. In case of any technical device or problems related to diabetes management such as hypo- or hyperglycaemia, subjects will be able to contact a 24-hour telephone helpline to the local research team at any time. The local research team will have access to central 24 hour advice on technical issues.
Procedures for safety monitoring during trial	Standard operating procedures for monitoring and reporting of all adverse events will be in place, including serious adverse events (SAE), serious adverse device effects (SADE) and specific adverse events (AE) such as severe hypoglycaemia. Subjects will be asked to test and record blood ketones if their finger prick glucose is $\geq$ 16.7mmol/l (300mg/dl) upon awakening, $\geq$300 for more than 1 hour, or >22.2mmo/l (400mg/dL) at any time as part of the safety assessment for DKA. A data safety and monitoring board (DSMB) will be informed of all serious adverse events and any unanticipated serious adverse device effects that occur during the study and will review compiled adverse event data at periodic intervals.
Criteria for withdrawal of patients on safety grounds	A subject, parent, or guardian may terminate participation in the study at any time without necessarily giving a reason and without any personal disadvantage. An investigator can stop the closed-loop intervention after consideration of the benefit/risk ratio. Possible reasons are: 1. Serious adverse events 2. Significant protocol violation or non-compliance 3. Failure to satisfy competency assessment 4. Decision by the investigator, or the sponsor, that termination is in the subject's best medical interest 5. Pregnancy, planned pregnancy, or breast feeding 6. Allergic reaction to insulin Efforts will be made to retain subjects in follow up for the final primary outcome assessment even if the intervention is discontinued, unless the investigator believes that it will be harmful for the subject to continue in the trial.

3 Summary

The main study objective is to determine whether 24/7 automated closed-loop glucose control combined with low glucose feature will improve glucose control as measured by HbA1c.

This is an open-label, multi-centre, multi-national, single-period, randomised, parallel group design study, involving a 6 month period of home study during which day and night glucose levels will be controlled either by a closed-loop system combined with low glucose feature (intervention group) or by insulin pump therapy (usual care; control group).

It is expected that a total of up to 150 subjects (aiming for 130 randomised subjects) with type 1 diabetes will be recruited through paediatric outpatient diabetes clinics of the investigation centres. Participants will all be on subcutaneous insulin pump therapy.

Subjects in the intervention group will have proven competencies both in the use of the study insulin pump and the study continuous glucose monitoring (CGM) device, and will receive appropriate training in the safe use of closed-loop insulin delivery system and low glucose feature. All subjects will have regular contact with the study team during the home study phase including 24/7 telephone support. The primary outcome is between group differences in HbA1c levels at 6 months post study arm initiation. Secondary outcomes are the time spent in the glucose target (3.9 to 10.0mmol/l; 70 to 180mg/dl), time spent with glucose levels above and below target, as recorded by CGM, and other CGM-based metrics. Safety evaluation comprises assessment of the frequency of severe hypoglycaemic episodes and diabetic ketoacidosis (DKA).

4 Background

Type 1 diabetes mellitus (T1D) is characterised by an absolute deficiency of insulin caused by immunologically-mediated damage to the beta cells in the pancreas and raised blood glucose levels. It is one of the commonest endocrine and metabolic conditions in both children and adults. It is estimated that approximately 285 million adults (5-15% type 1 diabetes) and 480,000 children (95% type 1 diabetes) worldwide suffer from diabetes (1). Recent reports suggest that incidence and prevalence of T1D is increasing in many countries, at least in the under 15 year age group with the predicted number of new cases of childhood diabetes in Europe increasing to 24 400 in 2020 from 15 000 in 2005 (2; 3). This younger age at onset means that complications appear at a younger age, and dependence on lifelong insulin imposes a heavy burden on patients as well as health services. A survey conducted by Royal College of Paediatrics & Child Health in UK established that there were 22,783 children and young people 0-17 years with diabetes in England on 1st January 2009 out of which 97% had type 1 diabetes (4).

Until the introduction of insulin replacement therapy in early 1920s T1D was a uniformly fatal condition. While significant advancements have been made in insulin therapy since, major limitations still exist, frequent hypoglycaemia (low blood glucose) being the most significant. Despite the availability of therapeutic options such as self-monitoring of blood glucose, structured patient education, rapid-acting insulin analogues and insulin pump therapy, glycaemic control in the majority of patients with type 1 diabetes remains suboptimal and they are prone to get complications associated with poor control such as kidney failure and blindness. Risk of these complications can be reduced by intensive insulin therapy (5) but for most patients this is associated with hypoglycaemia (too low blood sugar) limiting the intensification of treatment (6; 7). The average patient with T1D suffers two symptomatic episodes of hypoglycaemia per week, and one episode of severe hypoglycaemia, defined as an event requiring assistance of another person to administer rescue treatment in the form of carbohydrate and/or glucagon, per year (8). Even in patients with good control, as judged by average HbA1c, significant glucose excursions occur with periods of silent hyper- and hypoglycaemia (9; 10). Further some patients with T1D have impaired defence mechanisms (counter-regulatory responses) to low glucose, thus impairing recovery and increasing the threat of future episodes (11). Recurrent episodes may lead to hypoglycaemic unawareness, a condition which increases the risk of severe hypoglycaemia (12). In addition to the physical morbidity, hypoglycaemia also has significant psychological consequences including fear of future episodes with resulting maladaptive coping behaviours such as excessive eating or under-insulinising that may negatively impact glycaemic control (13).

4.1 Insulin Pump Therapy

Over the last 15 years, insulin pump use in children and adolescents has increased considerably. Data from large paediatric registries in developed Western countries indicate that 41 to 47% (14) of young people with type 1 diabetes are pump users. Increased use has been driven by advances in pump technology and recognition of the importance of tight glycaemic control to delay or prevent long-term diabetes complications (5). Insulin pumps better address the flexibility in insulin delivery essential to paediatric needs (15). The increased adoption reflects emerging evidence that pump therapy in the paediatric population compared to standard multiple daily injection therapy (MDI) is beneficial regarding HbA1c levels, hypoglycaemia burden, glucose variability and quality of life (16-19).

4.2 Continuous Glucose Monitoring and Sensor-Augmented Pump Therapy

Despite the rapid advancements in insulin pump technology and the ongoing development of more physiological insulin preparations, the currently available therapeutic regimens are still unable to achieve optimal glycaemic control. The emergence of continuous glucose monitoring (CGM) over the last decade, which enables users to view real-time interstitial glucose readings and receive alarms for impending hypo- or hyperglycaemia, thus facilitating appropriate changes in insulin therapy, is a major step towards improved diabetes monitoring. Several recent studies have shown a clinical benefit of CGM on reduction in HbA1c, in those patients who are compliant with using the device (20-23).

Sensor-augmented pumps (SAP) combine real-time CGM with insulin pump therapy. In the first major study (485 patients, 329 adults and 156 children) comparing SAP with MDI, SAP treatment showed superior HbA1c reduction (at 1 year, from 8.3% to 7.5% in SAP vs. from 8.3% to 8.1% in MDI group, between-group difference in the SAP group of -0.6% (95% CI, -0.7 to -0.4; $P < 0.001$), but showed no difference in hypoglycaemia or severe hypoglycaemia rates between groups (24). Patients with more than one severe hypoglycaemic event in the preceding year were excluded from this study. A smaller multi-centre study in Europe (86 patients) has also shown improvements in HbA1c with SAPs (mean difference in change in HbA1c after 26 weeks was -1.21% (95% CI -1.52 to -0.90, $P < 0.001$), but there was no difference in biochemical or severe hypoglycaemia between groups (25).

4.3 Closed-Loop Insulin Delivery

The development of a closed-loop system that combines glucose monitoring with computer-based algorithm informed insulin delivery, may provide further improvements in glycaemic control while reducing hypoglycaemia and ultimately represent a realistic treatment option for people with type 1 diabetes. The vital component of such a system, also known as an artificial pancreas (AP), is a computer-based algorithm. The role of the control algorithm is to translate, in real-time, the information it receives from the CGM and to compute the amount of insulin to be delivered by the pump. The other

components include a real-time continuous glucose monitor and an infusion pump to titrate and deliver insulin (26).

Automatic suspension of insulin delivery by the pump when a predefined glucose level is reached represents the simplest form of closed-loop insulin delivery. Such a system (Veo (non-US) or Medtronic 530G (US) insulin pump coupled with Minilink sensor, Medtronic Minimed, Northridge, CA, USA) which stops insulin delivery for up to 2 hours is currently commercially available. This approach aims to reduce the severity of hypoglycaemia. Since insulin is not delivered in an automated fashion there is no risk of system-induced hypoglycaemia. In an in-clinic study, following a period of exercise, the threshold based pump interruption feature has been shown to reduce the duration of hypoglycaemia (27). Two relatively small out-patient studies of short duration (21 children for 6 weeks (28) and 31 adults (29) for 3 weeks have also shown that threshold based pump interruption may reduce the time spent in hypoglycaemia without leading to rebound hyperglycaemia or ketosis. A recent large RCT (247 patients with type 1 diabetes; age range 16 to 70 years; threshold based pump interruption group, 121 patients), has confirmed these findings with a 37% lower mean area under the curve (AUC) for nocturnal hypoglycaemic events in the threshold based pump interruption group than in the control group (54.4 ± 66.6 vs. 87.0 ± 110.7 mmol/l × minutes, $P < 0.001$) without any rise in HbA1c after 3 months (30).

Closed loop approaches beyond insulin suspension have been successfully evaluated in children and adolescents in controlled laboratory studies (31-33) and in home settings (34-37). Investigations in adults have also been conducted (35; 38; 39). The results demonstrated improved glucose control and reduced risk of hypoglycaemia events. Psychosocial assessments supported acceptability and positive impact of this novel therapeutic approach among children/adolescents and carers (40). However, evaluations under at-home, free living conditions have been limited to 3 months (35).

4.4 Artificial Pancreas Research at Cambridge

4.4.1 Preclinical Testing of Cambridge Closed-loop Algorithm

The research we are conducting at the University of Cambridge has been focused on developing a closed-loop system for overnight and 24/7 glucose control in patients with T1D. The studies that have been performed so far employ model predictive control (MPC) – this algorithm estimates patient-specific parameters from CGM measurements taken every 1 to 15 minutes and makes predictions of glucose excursions, which are then used to calculate basal insulin infusion rates (41).

The closed-loop MPC algorithm has been studied extensively using *in silico* testing utilising a simulator developed by members of the study team (42). The simulations suggested a reduced risk of nocturnal hypoglycaemia and hyperglycaemia with the use of the MPC algorithm (43).

4.4.2 Studies of Closed-Loop in Children and Adolescents with Type 1 Diabetes in the Clinical Research Facility

To date around sixty children and adolescents with type 1 diabetes have been studied at the clinical research facility using the Cambridge control algorithm. Closed-loop insulin delivery was maintained on more than 100 nights. No episodes of significant hypoglycaemia (plasma glucose concentration less than 2.8 mmol/l) have been observed thus far during closed-loop blood glucose control. Results from these studies were published in The Lancet (31) and showed that overnight closed-loop therapy increased the time spent euglycaemic by 37% and reduced the risk of overnight hypoglycaemia eight-fold, as compared to conventional pump treatment. Different real-life scenarios predisposing to nocturnal hypoglycaemia, such as afternoon exercise, were explored and closed-loop therapy reduced the risk of overnight hypoglycaemia as compared to conventional insulin pump therapy in a randomised, cross-over design.

4.4.3 Studies of Closed-Loop in Adults with Type 1 Diabetes in the Clinical Research Facility

We have completed two randomised overnight closed-loop studies in 24 adults with T1D, testing a similar closed-loop system comprising “off the shelf” CGM and pump devices and the Cambridge control algorithm. The first study (n=12) assessed the feasibility and efficacy of overnight closed-loop insulin delivery following a moderate-sized (60g carbohydrate) evening meal compared with conventional pump therapy. We demonstrated that overnight closed-loop insulin delivery, compared with usual continuous subcutaneous insulin infusion (CSII), significantly increased time in target plasma glucose range (3.9-8 mmol/l) by 24% and reduced glycaemic variability as measured by standard deviation of plasma glucose. The improvements in glucose control seen on closed-loop were even greater after midnight, when time in target increased by 41%. In the second study we tested the efficacy of overnight closed-loop following a common situation such as consuming a large (100g carbohydrate) evening meal and drinking alcohol (0.75g ethanol/kg body weight of 13%abv white wine). We showed that overnight closed-loop insulin delivery, compared with conventional CSII, similarly increased time in target plasma glucose between 3.9 and 8.0 mmol/l by 24% and reduced time spent above target by 11%, even following such challenges. Importantly these improvements during closed-loop were achieved with no increased requirement in the average rate of insulin infusion overnight. These results have been published in the British Medical Journal (44).

4.4.4 Overnight Closed-Loop study in Children and Adolescents with Type 1 Diabetes in Home Setting

Following successful demonstration of safety and efficacy of closed-loop insulin delivery in the research facility, overnight closed-loop studies using the Cambridge control algorithm under free living conditions were commenced in July 2012. The first study compared the efficacy and safety of closed-loop with sensor augmented pump therapy in 16 adolescents (34). Closed-loop was activated over at least 4 hours on 269 nights (80%); sensor data were collected over at least 4hours on 282 control nights (84%). Closed-loop increased the time when glucose was in target range by a median 15% (interquartile range −9 to +43), P<0.001. Mean overnight glucose was reduced by a mean 0.8±3.2mmol/l, P<0.001. Time when glucose was below 3.9mmol/l was low in both groups but nights with glucose below 3.5mmol/l for at least 20min were less frequent during closed-loop (10% vs. 17%, P=0.01). Despite lower total daily insulin doses by a median 2.3 (interquartile range -4.7 to +9.3)units, P=0.009, overall 24h glucose was reduced by a mean 0.5 (standard deviation 2.3)mmol/l (P=0.006) during closed-loop.

In a second multicentre, crossover, randomised, controlled study, we compared 12 week use of an overnight closed-loop insulin delivery system with sensor augmented pump therapy in children and adolescents aged 6 to 18 years (35). The proportion of time with the night-time glucose level in the target range (3.9 to 8.0 mmol/l) was higher during the closed-loop phase than during the control phase (by 24.7 percentage points; 95% CI, 20.6 to 28.7; P<0.001), and the mean night-time glucose level was lower (difference, −1.6 mmol/l; 95% CI,−2.2 to −1.1; P<0.001). The area under the curve for the period in which the day-and-night glucose levels were less than 3.5 mmol/l was lower by 42% (95% CI, 4 to 65; P = 0.03). Two severe hypoglycaemic episodes occurred during the closed-loop phase when the closed-loop system was not in use.

4.4.5 Overnight Closed-Loop Study in Adults with Type 1 Diabetes in Home Setting

We completed a four week overnight closed-loop study under free living conditions in 24 adults with type 1 diabetes on insulin pump therapy in a multicentre crossover study design (39). Closed-loop was utilised over median 8.3 (interquartile range 6.0, 9.6) hours on 555 nights (86%). The proportion of time when overnight glucose was in target range between 3.9 and 8.0mmol/l from midnight to 07:00 was significantly higher during closed-loop compared to sensor augmented pump therapy (52.6%±10.6 vs. 39.1%±12.8, mean±SD; p<0.001). Mean overnight glucose (8.2±0.9 vs. 9.0±1.3mmol/l, p=0.005) and time spent above target (44.3%±11.9 vs. 57.1%±15.6, p=0.001) were significantly lower during closed-loop. Time spent below target was low and comparable between interventions [1.8%(0.6, 3.6) vs. 2.1%(0.7, 3.9), p=0.28].

4.4.6 Day and Night Closed-Loop Studies in Adolescents with Type 1 Diabetes in Home Setting

We have recently completed a randomised, crossover design study in adolescents aged 10 to 18 years who underwent two 7-day home periods of sensor-augmented insulin pump therapy or closed-loop insulin delivery without supervision or remote monitoring (37). The proportion of time when the sensor glucose level was in the target range (3.9–10 mmol/L) was increased during closed-loop insulin delivery compared with sensor-augmented pump therapy (72% vs. 53%, P < 0.001; primary end point), the mean glucose concentration was lowered (8.7 vs. 10.1 mmol/L, P = 0.028), and the time spent above the target level was reduced (P = 0.005) without changing the total daily insulin amount (P = 0.55). The time spent in the hypoglycaemic range was low and comparable between interventions. A three week single centre study in children and adolescents has been completed with comparable results as the one week study (N = 12) (45).

4.4.7 Day and Night Closed-Loop Studies in Adults with Type 1 Diabetes in Home Setting

In 2014, we completed a first seven day, day-and-night home study in 17 adults in a multicentre, multi-national crossover study design (46). During the home phase, the percentage time when glucose was in target range was significantly higher during closed-loop compared to sensor augmented pump therapy (75 [61, 79] vs. 62 [53, 70]%, median [IQR], p=0.005). Mean glucose (8.1 vs. 8.8 mmol/l, p=0.027) and time spent above target (p=0.013) were lower during closed-loop while time spent below target was comparable (p=0.339). Increased time in target was observed during both day-time (p=0.017) and night-time (p=0.013).

We have recently completed another multicentre, multinational, crossover, randomised, controlled study under free living home conditions comparing 24/7 closed-loop insulin delivery with sensor augmented pump therapy (control intervention) in 33 adults with type 1 diabetes (35). The proportion of time that the glucose level was in the target range (3.9 to 10.0 mmol/l) was 11.0 percentage points (95% confidence interval [CI], 8.1 to 13.8) greater with the use of the closed-loop system day and night than with control therapy (P<0.001). The mean glucose level was lower during the closed-loop phase than during the control phase (difference, −0.6 mmol/l; 95% CI, −0.9 to −0.3; P<0.001), as were the area under the curve for the period when the glucose level was less than 3.5 mmol/l (39% lower; 95% CI, 24 to 51; P<0.001) and the mean glycated haemoglobin level (difference, −0.3%; 95% CI, −0.5 to −0.1; P = 0.002).

4.5 Automated Closed-Loop System (FlorenceM) to be used in the Present Study

The automated closed-loop system (FlorenceM) consists of:

- Next generation sensor augmented Medtronic insulin pump 640G (Medtronic Minimed, CA, USA) incorporating the Medtronic Enlite 3 family real time CGM and low glucose feature (predictive low glucose management and low glucose suspend)

- An Android smartphone containing the Cambridge model predictive algorithm and communicating wirelessly with the insulin pump using a proprietary translator device. The smartphone will be locked-down to exclusively run the control algorithm. All other applications and functionality (e.g. making and receiving calls, text messaging, internet browsing and playing games) will not be available.

An overview of this proposed automated closed-loop system is given in Figure 1.

Figure 1. FlorenceM comprises Samsung Galaxy S4 phone running Cambridge control algorithm and Medtronic components codenamed ENCORE comprising phone enclosure including an embedded Carelink USB to allow the phone to communicate with 640G pump. The pump is connected to Enlite 3 sensor.



4.6 Rationale for the Current Study

Despite advances in insulin pump and sensor technology, the majority of children and adolescents with type 1 diabetes are still unable to achieve optimal glycaemic control (47; 48). Application of closed-loop insulin delivery systems in a range of populations and settings, including children and adolescents in home settings, has been shown to improve glycaemic control, and to reduce the burden of hypoglycaemia (33; 35-37; 49). However, studies involving patients under free-living

conditions have been limited to 3 months only (35). Performance and benefits of closed loop systems in children and adolescents over a prolonged period is yet to be determined.

No study thus far has combined predictive low glucose management or low glucose suspend with closed-loop insulin delivery. During our previous closed-loop studies, if there is a communication failure between the algorithm device and the insulin pump, the pump is set to deliver pre-programmed basal insulin rates after about 30 to 60 minutes. Adding the low glucose feature to closed-loop will further increase patient safety by stopping the pump at low glucose levels even if there is a communication failure between control algorithm device and the insulin pump.

In addition, the current study will provide further evidence on the effect of consecutive closed-loop day and nights over 6 months in a relatively large group of children with type 1 diabetes in a multi-centre and multi-national setting to demonstrate the generalisability of results.

The choice of the control group follows the intention to perform a pragmatic trial. Sensor-augmented pump therapy, currently best available treatment option, is becoming more widely adopted though still somewhat limited for reasons including limited reimbursement, technological imperfections and device burden. Earlier data from the T1D Exchange clinic registry suggested that only 6% of young people with T1D use CGM (50) compared to 47% insulin pump users (14; 51) but this is changing rapidly with up to 36% pump users aged 6 to 13 years using CGM (recent unpublished data from T1D Exchange). The present design will broaden the applicability of the results to a wider population of people with type 1 diabetes.

5 Objectives

5.1 Efficacy

The objective is to assess efficacy of day and night automated closed-loop glucose control combined with low glucose feature in improving HbA1c, as compared with usual care (conventional or sensor–augmented insulin pump therapy).

5.2 Safety

The objective is to evaluate the safety of day and night automated closed-loop glucose control combined with low glucose feature in terms of episodes of severe hypoglycaemia, frequency of diabetic ketoacidosis and other adverse events.

5.3 Utility

The objective is to determine the frequency and duration of use of the automated closed-loop system with low glucose feature.

5.4 Human factors

The objective is to assess cognitive, emotional, and behavioural characteristics of participating subjects and family members and their response to the closed-loop system and clinical trial by gathering both quantitative (validated surveys) and qualitative data (focus groups).

5.5 Health economics

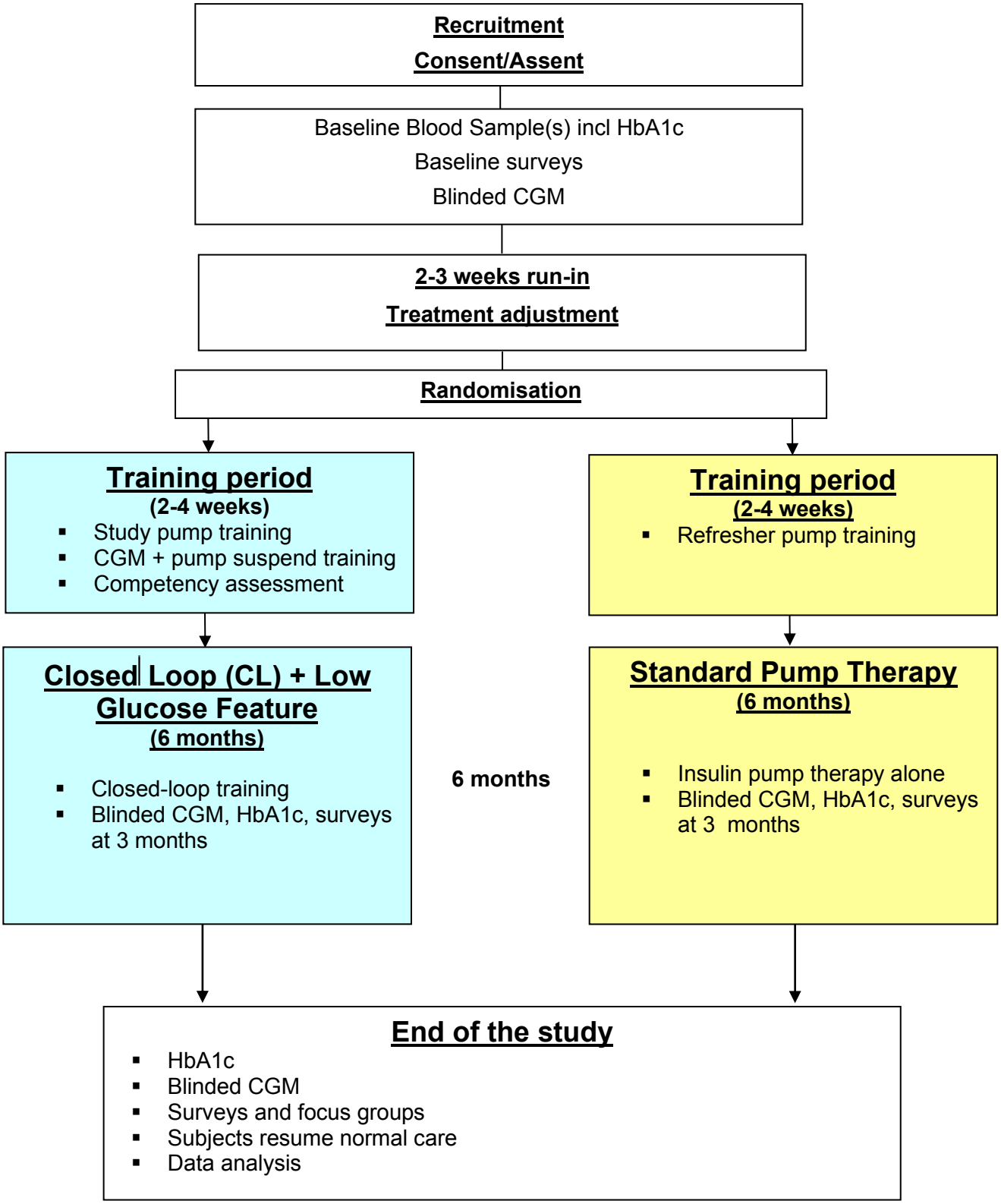
The objective is to perform a cost utility analysis on the benefits of closed loop insulin delivery to inform reimbursement decision-making

6 Study Design

An open-label, multi-centre, multi-national, randomised, single-period parallel study, in youth (≥6 to <19 years) with type 1 diabetes on insulin pump treatment contrasting day and night automated closed-loop glucose control combined with low glucose feature with usual care (conventional or sensor–augmented insulin pump therapy).

It is expected that up to 150 youths with type 1 diabetes with T1D will be recruited, aiming for 130 randomised subjects. The study flow chart is outlined in Figure 2.

Figure 2. Study flow chart.



7 Study Subjects

7.1 Study Population

This is a multicentre and multinational study and recruitment will take place at the following centres (additional sites may be added if needed):

1. Addenbrooke's Hospital, Cambridge, UK
2. Barbara Davis Center for Childhood Diabetes, Aurora, CO USA
3. Indiana University, Indianapolis, IN USA
4. Leeds Teaching Hospital, Leeds, UK
5. Nemours Children's Health System, Jacksonville, FL USA
6. Nottingham Children's Hospital, Nottingham, UK
7. Royal Hospital for Children and Young People, Edinburgh, UK
8. Southampton Children's Hospital, Southampton, UK
9. Stanford University, Stanford, California, USA10. Yale University School of Medicine, New Haven, Connecticut, USA

Up to a total of 150 youths aged ≥6 to <19 years with type 1 diabetes on insulin pump therapy will be recruited [approximately equal proportion of those aged ≥6 to 12 years and 13 to <19 years, a minimum quota of 25% participants with baseline HbA1c >8.5%].

Paediatric Diabetes Centres in the East Anglia region and London may be included as a Patient Identification Centre (PIC) to recruit participants for the Addenbrooke's site, and centres in York, Doncaster, and Bradford will be PICs for the Leeds site.

Potential participants will be identified by their treating clinicians and invited to contact the research team. They will be sent the study information leaflets and an invitation to join the study by the research team at least one day before the recruitment visit.

7.2 Inclusion Criteria

1. Age ≥6 and <19 years
2. Type 1 diabetes as defined by WHO (52) for at least 1 year
   [WHO definition: 'The aetiological type named type 1 encompasses the majority of cases with are primarily due to beta-cell destruction, and are prone to ketoacidosis. Type 1 includes those cases attributable to an autoimmune process, as well as those with beta-cell destruction for which neither an aetiology nor a pathogenesis is known (idiopathic). It does not include those forms of beta-cell destruction or failure to which specific causes can be assigned (e.g. cystic fibrosis, mitochondrial defects, etc.).']

3. Use of an insulin pump for at least 3 months, with good knowledge of insulin self-adjustment by subject or caregiver as judged by the investigator
4. Using U-100 rapid acting insulin analogues Aspart or Lispro only
5. Willing to perform regular finger-prick blood glucose monitoring, with at least 4 blood glucose measurements per day day
6. Screening HbA1c ≥ 7.0% (53 mmol/mol) and ≤10 % (86mmol/mol) based on analysis from local laboratory
7. Literate in English
8. Willing to wear glucose sensor
9. Willing to wear closed-loop system at home
10. Willing to follow study specific instructions
11. Willing to upload pump and CGM data at regular intervals
12. Access to WiFi.
13. The subject lives with someone who is trained to administer intramuscular glucagon and is able to seek emergency assistance

7.3 Exclusion Criteria

1. Living alone
2. Current use of any closed-loop system
3. Any other physical or psychological disease likely to interfere with the normal conduct of the study and interpretation of the study results as judged by the investigator
4. Untreated coeliac disease, adrenal insufficiency, or untreated thyroid disease
5. Current treatment with drugs known to interfere with glucose metabolism, e.g. systemic corticosteroids, non-selective beta-blockers and MAO inhibitors etc.
6. Known or suspected allergy to insulin
7. Clinically significant nephropathy (eGFR < 45ml/min) or on dialysis, neuropathy or active retinopathy (defined as presence of maculopathy or proliferative changes) as judged by the investigator
8. Recurrent incidents of severe hypoglycaemia (>1 episode) during the previous 6 months (adolescents: severe hypoglycaemia is defined as an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions including episodes of hypoglycaemia severe enough to cause unconsciousness, seizures or attendance at hospital; children: severe hypoglycaemia is defined as an event associated with a seizure or loss of consciousness)
9. Recurrent incidents of diabetic ketoacidosis (>1 episode) during previous 6 months
10. Unwilling to avoid regular use of acetaminophen
11. Lack of reliable telephone facility for contact
12. Total daily insulin dose ≥ 2 IU/kg/day

13. Total daily insulin dose < 15 IU/day
14. Pregnancy, planned pregnancy, or breast feeding
15. Severe visual impairment
16. Severe hearing impairment
17. Seizure disorder
18. Medically documented allergy towards the adhesive (glue) of plasters or unable to tolerate tape adhesive in the area of sensor placement
19. 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)
20. Illicit drugs abuse
21. Subject is currently abusing prescription drugs
22. Alcohol abuse
23. Use of pramlintide (Symlin), or other non-insulin glucose lowering agents including sulphonylureas, biguanides, DPP4-Inhibitors, , GLP-1 analogues, SGLT-1/ 2 inhibitors at time of screening
24. Shift work with working hours between 10pm and 8am
25. Sickle cell disease, haemoglobinopathy, or has received red blood cell transfusion or erythropoietin within 3 months prior to time of screening
26. Eating disorder such as anorexia or bulimia
27. Employed by Medtronic Diabetes or with immediate family members employed by Medtronic Diabetes

7.4 Randomisation

Eligible subjects will be randomised using central randomisation software to the use of day and night closed-loop combined with low glucose feature or to insulin pump therapy alone. The randomisation will be stratified at each centre by local baseline HbA1c measurement.

8 Methods under Investigation

8.1 Name and Description of the Method of Investigation

The investigational treatment is the FlorenceM, see section 4.5, or follow up prototypes of the automated day and night closed-loop system manufactured by the Cambridge University Hospitals NHS Foundation Trust and supported by Medtronic Minimed Inc. Northridge, CA, USA. Component versions will be identified during regulatory submission to the MHRA / FDA.

8.2 Intended Purpose

The intended purpose of the investigational treatment is automated day and night closed-loop insulin delivery combined with low glucose feature.

8.3 Method of Administration

The closed-loop system consists of components directly attached to the patient, which are the CGM sensor/transmitter and the insulin pump. The component not directly attached to the patient is the handheld smartphone containing closed-loop algorithm and communicating wirelessly with the insulin pump.

8.4 Required Training

Prior to commencement of the study, the research team nurses/clinicians at each of the investigation centres will be trained to use the closed-loop system and its components. Prior to the use of study devices, participants will be trained to use the blinded CGM device, and where appropriate the study pump and real-time CGM device, and the closed-loop system. Competency assessments of the participants' capability to use study devices including the closed-loop system will be made.

8.5 Precautions

During treatment with insulin there is a risk of hypoglycaemia and hyperglycaemia. In-hospital testing and Hazard Analysis both documented reduced risk of hypoglycaemia and hyperglycaemia during day and night closed-loop compared to conventional treatment. Addition of low glucose feature will further increase safety.

8.6 Accountability of the Method under Investigation

The local Investigator will provide training for the study participants and will make every effort, through regular contact, to ascertain that the closed-loop system is used for the study purposes only. Devices will be identified using batch/lot/serial numbers and the location of investigational devices and their dates of use by subjects will be documented throughout the study.

9 Study Schedule

9.1 Overview

The study will be co-ordinated from the Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, UK (for UK sites), and the Jaeb Centre for Health Research, Tampa, Florida, US (for US sites). The study will be performed at the following sites (additional sites may be added if needed):

1. Addenbrooke's Hospital, Cambridge, UK
2. Barbara Davis Center for Childhood Diabetes, Aurora, CO USA
3. Indiana University, Indianapolis, IN USA
4. Leeds Teaching Hospital, Leeds, UK
5. Nemours Children's Health System, Jacksonville, FL USA
6. Nottingham Children's Hospital, Nottingham, UK
7. Royal Hospital for Children and Young People, Edinburgh, UK
8. Southampton Children's Hospital, Southampton, UK

9. Stanford University, Stanford, California, USA
10. Yale University School of Medicine, New Haven, Connecticut, USA

After recruitment, consent, and run-in period, subjects will be randomised for 6 months home use of real-time CGM combined with automated day and night closed-loop insulin delivery or 6 months during which they will use pump therapy alone or sensor augmented pump if a current CGM user.

The study includes up to 8 visits and 6 telephone/email contacts for subjects completing the study. The visit to set up automated closed-loop for the first time may take place in the home setting or alternatively in a clinical facility. All other visits can take place at the hospital clinic, home or other suitable meeting place, according to participants' convenience. Maximum time in study is 8 months.

Table 1 outlines study activities when participant is randomised to day and night closed-loop (intervention group).
Table 2 outlines study activities when participant is randomised to usual care (conventional or sensor-augmented insulin pump therapy) (control group).

Table 1. Schedule of study visits / phone contacts when the participant is randomised to day and night closed-loop combined with low glucose feature (intervention group).

	Visit/ contact	Description	Start relative to previous / next Visit / Activity	Duration
Run-in	**Visit 1**	Recruitment visit: Consent, HbA1c, screening bloods, urine pregnancy test, baseline surveys, blinded CGM training and insertion		1-4 hours
	Visit 2	Review of baseline bloods, pump settings and CGM data; adjustment of treatment	2 weeks after Visit 1 (+1 week); Run-in could be repeated	1-2 hours
Training Period	**Visit 3**	Randomisation, repeat HbA1c if Visit 3 and Visit 1 are >28 days apart, urine pregnancy test, study pump training and initiation, competency assessment	May coincide with Visit 2, within 8 weeks of Visit 1	3-4 hours
	Visit 3a	Real-time CGM training and initiation, competency assessment	Within 0 to 7 days of Visit 3 (Visit 3a may coincide with Visit 3; training visits can be repeated)	2-4 hours
CL + LGS Intervention (6 months)	**Visit 4**[1]	CL initiation at clinic/home; data download, CL and low glucose feature training, competency assessment, blinded CGM	4 weeks after Randomisation (±1 week)	2-6 hours
	Contact 1	Review use of study devices; study update	within 24 to 48 hours after Visit 4	<1 hour
	Visit 5 [2]	Review use of study devices; study update	1 week after Visit 4 (± 3 days)	<1 hour
	Contact 2	Review use of study devices; study update	2 weeks after Visit 4 (±3 days)	<1 hour
	Contact 3	Review use of study devices; study update	1 month after Visit 4 (±2 weeks)	<1 hour
	Contact 4	Review use of study devices; study update	2 months after Visit 4 (±2 weeks)	<1 hour
	Visit 6	3-month visit, HbA1c, urine pregnancy test data download, blinded CGM, surveys	4 months after Randomisation (±2 week)	1-3 hours
	Contact 5	Review use of study devices; study update	5 months after Randomisation (±2 weeks)	<1 hour
	Contact 6	Review use of study devices; study update	6 months after Randomisation (±2 weeks)	<1 hour
	Visit 7	Blinded CGM	2-4 weeks before planned Visit 8	<0.5 hour
	Visit 8[3]	End of closed-loop treatment arm (6 months of CL); HbA1c, data download, surveys and focus groups; resume usual pump therapy	7 months after Randomisation (±2 weeks)	1-3 hours

[1] In-person clinic visit mandatory in US only.
[2] Could be done via phone / e-mail in UK. In-person visit mandatory in US only.
[3] Could be done via visit in clinic or home/alternate location or via phone/remotely

Table 2. Schedule of study visits / phone contacts when the participant is randomised to usual care.

	Visit/ contact	Description	Start relative to previous / next Visit / Activity	Duration
Run-in	**Visit 1**	Recruitment visit: Consent, HbA1c, screening bloods, urine pregnancy test, baseline surveys, blinded CGM training and insertion		1-4 hours
	Visit 2	Review of baseline bloods, pump settings and CGM data; adjustment of treatment	2 weeks after Visit 1 (+1 week); Run-in could be repeated	1-2 hours
Training period	**Visit 3**	Randomisation, repeat HbA1c if Visit 3 and Visit 1 are >28 days apart; urine pregnancy test, Insulin pump refresher training, competency assessment	May coincide with Visit 2, within 8 weeks of Visit 1	3-4 hours
Usual insulin pump therapy Intervention (6 months)	**Visit 4**[1]	Initiation of standard therapy arm at clinic/home, glucometer download, recording of current insulin requirements, blinded CGM	4 weeks after Randomisation (±1 week)	2-6 hours
	Contact 1	Study update	within 24 to 48 hours after Visit 4	<1 hour
	Visit 5[2]	Study update	1 week after Visit 4 (±3 days)	<1 hour
	Contact 2	Study update	2 weeks after Visit 4 (±3 days)	<1 hour
	Contact 3	Study update	1 month after Visit 4 (±2 weeks)	<1 hour
	Contact 4	Study update	2 months after Visit 4 (±2 weeks)	<1 hour
	Visit 6	3 month visit; HbA1c, urine pregnancy test, glucometer download, recording of current insulin requirements, surveys, blinded CGM	4 months after Randomisation (±2 weeks)	1-3 hours
	Contact 5	Study update	5 months after Randomisation (±2 weeks)	<1 hour
	Contact 6	Study update	6 months after Randomisation (±2 weeks)	<1 hour
	Visit 7	Blinded CGM	2-4 weeks before planned Visit 8	<0.5 hour
	Visit 8[3]	End of standard pump therapy treatment arm (6 months); HbA1c, glucometer download, recording of current insulin requirements, surveys and focus groups, resume usual care	7 months after Randomisation (±2 weeks)	1-3 hours

1 In-person clinic visit mandatory in US only.
2 Could be done via phone / e-mail.
3 Could be done via visit in clinic or home/alternate location or via phone/remotely

9.2 Visit 1 (Recruitment Visit, Screening Assessment)

Once the subjects have agreed to participate in the study, they will be invited for the recruitment visit, when the following activities will be performed by the research team:

- written informed consent/assent
- checking inclusion and exclusion criteria
- medical (diabetes) history
- body weight and height measurement; calculation of BMI
- blood pressure measurement
- record of current insulin therapy
- urine pregnancy test (females of child-bearing potential)
- record of occupation and educational attainment
- record current pump model
- capillary blood glucose measurement

9.2.1 Screening Blood Sampling

HbA1c, liver function (AST, ALT, GGT, albumin, total bilirubin), thyroid function (TSH, fT4), full blood count, anti-transglutaminase antibodies (and IgA if not previously done within previous 12 months) will be measured locally. Additional blood samples will be taken for the measurement of non-hypoglycaemia C-peptide, glucose, and HbA1c at a central laboratory. HbA1c eligibility criterion will be based on local measurement. Less than 35 ml of whole blood will be taken from each participant.

Blood sample for the measurement of C-peptide must only be collected when simultaneous exclusion of biochemical hypoglycaemia (plasma glucose <4.0 mmol/l (72mg/dl) is confirmed. A fingerprick will be taken prior to central lab sample collection to confirm normoglycaemia. If subject is hypoglycaemic, the glucose will be treated and fingerprick glucose checked again. Repeat until normoglycaemic.

9.2.2 Surveys at Screening

A battery of validated surveys (see section 12.2) will be distributed to assess the participants' and families' quality of life, psychosocial and cognitive functioning, diabetes management and response to their current treatment before entering the study. For parents/guardians a discrete choice experiment will be included to assess how strongly potential benefits of the closed loop system are valued (see section 12.2.2). It is estimated that youth will take 45-50 minutes to complete their surveys; parents will take 30-35 minutes. If not done face-to-face during the visit, web-based versions of the surveys will be available for completion at home.

9.2.3 Blinded CGM

At the end of this session, participants will be fitted with a blinded CGM device to assess baseline glycaemic control. Instructions on how to safely use and remove the device will be provided. The sensors will be worn during the run-in period at home for up to 14 days. If the sensor fails (i.e. does not provide any data) or sensor life gets interrupted prematurely (detached sensor), another sensor may be inserted . Re-insertion will be done by study staff at the clinical facility or at home. The sensor will be sent back to the research team by mail or collected by the research team once the sensor life has expired and/or the sensor has detached, or will be returned at visit 2 (if conducted at the research centre). The sensor data may be used to optimise insulin delivery.

9.3 Visit 2

The subject will be invited to attend the research centre approximately 2 weeks after Visit 1. The purpose of this visit will be to review baseline blood results and eligibility criteria. Sensor glucose data gathered during Run-in (blinded CGM) may be used for adjustment of insulin pump therapy. The run-in period could be extended/repeated if no or limited sensor data was available, and/or if further optimisation is indicated. At least 10 full days of sensor data need to be collected.

9.4 Visit 3 including Randomisation (all Participants) and Visit 3a (Closed-loop Intervention)

The subject will be invited to attend the research centre. Visit 3 has to be completed within 8 weeks of Visit 1, but could coincide with Visit 2.

- Eligible subjects will be randomised using a randomisation based on a computer-generated random code at the beginning of Visit 3. Subjects will be allocated to one of the two intervention arms in a 1:1 ratio: 6 months use of day and night closed-loop combined with low glucose feature or 6 months use of insulin pump therapy alone or sensor augmented pump if participant is a current CGM user.

- If Visit 3 and Visit 1 are more than 28 days apart, an HbA1c sample will be repeated for analysis at a central lab.

- A urine pregnancy test will be performed on all females of child-bearing potential

- For self-monitoring of blood glucose (SMBG) for the closed-loop arm, Bayer CONTOUR™ Next Link blood glucose meters will be used exclusively. Appropriate devices and test strips will be provided at Visit 3 as required. Closed-loop subjects are expected to use Bayer CONTOUR™ Next Link glucometers at all times during the 6 months intervention period.

    - **UK Sites:** Subjects in the control arm will continue using their own glucose meter during the 6 months intervention period.

- **US Sites:** Subjects in the control arm will continue using their own glucose meter during the 6 months intervention period as long as the following conditions are met:
    - Only FDA-cleared glucose meters may be used.
    - The meter should have the capability to allow study staff to download glucose data ate each visit.
    - Whenever possible, the participant should use the same blood glucose meter throughout the study.
    - If the participant needs to change blood glucose meters during the study, he/she should notify the research staff who will confirm the blood glucose meter is FDA-cleared and downloadable.
    - If the subject's current meter is not FDA-cleared and/or downloadable, a study meter will be provided for use.

- Participants will receive additional study arm specific training as outlined below.

9.4.1 Closed-loop with Low Glucose Feature

For participants randomised to closed-loop, two introductory training sessions (study pump, study CGM) will be provided prior to initiation of closed-loop intervention.

The following description requires the study pump training to be covered during Visit 3, and the study CGM training to be conducted during Visit 3a. However, Visit 3a may coincide with Visit 3, and contents covered during these sessions are interchangeable between Visit 3 and Visit 3a in order to meet the requirements, as well as the prior knowledge, of the participants. If necessary, training sessions may be repeated.

9.4.2 Training Session on the Use of the Study Insulin Pump (Visit 3)

Closed-loop participants only. The training session will cover key aspects of insulin pump use with respect to the study pump, and particular attention will be paid to the following areas:

- Importance of carbohydrate counting and refresher on carbohydrate counting skills
- Understanding insulin to carb ratios and correction factors
- Correct use of bolus calculator - subjects will be required to use this bolus calculator for all insulin boluses during the study period
- Insulin cartridge and Infusion set changes and correct priming procedure
- Dealing with exercise

- Sick day rules
- Dealing with hypo and hyperglycaemia
    - Subjects will be asked to test and record blood ketones if their finger prick glucose is ≥ 16.7mmol/l (300mg/dl) upon awakening, ≥300 for more than 1 hour, or >22.2mmo/l (400mg/dL) at any time as part of the safety assessment for hyperglycaemia.

Written easy to use guidelines for the operation of the study insulin pump will be provided. Those competent in the use of the study pump will be switched to the study pump at the end of the training sessions.

UK only

This session will be conducted by a professional pump educator ± member of the study team following a written curriculum. Competency on the use of study pump will be made.

US only

This session will be conducted by a professional pump educator ± member of the study team with the subject (accompanied by a caregiver/guardian if <18years of age) following a written curriculum. Competency on the use of study pump by the subject (and caregiver/guardian if <18years of age) will be made.

9.4.2.1 Training Session on real-time Continuous Glucose Monitoring (Visit 3a)

Closed-loop participants only. This session will cover key aspects of the study real-time CGM and particular attention will be paid to the following areas:

1 Insertion and initiation of sensor session
2 Using sensor menu of the insulin pump
3 When a finger-stick BG reading needs to be taken
4 How to calibrate successfully
5 Blood glucose targets and alarm settings
6 Handling real-time CGM feedback including glucose trend arrows, reported high and low glucose
7 Use of software to upload and analyse CGM data

Written easy to use guidelines for the operation of study CGM will be provided. Competency on the use of study CGM system will be made.

9.4.3 Insulin Pump Therapy alone (Visit 3)

Insulin pump participants only. This session will cover key aspects of insulin pump use and particular attention will be paid to the following areas:

- Importance of carbohydrate counting and refresher on carbohydrate counting skills
- Understanding insulin to carb ratios and correction factors

- Correct use of bolus calculator - subjects will be required to use this bolus calculator for all insulin boluses during the study period
- Insulin cartridge and Infusion set changes and correct priming procedure
- Dealing with exercise
- Sick day rules
- Dealing with hypo and hyperglycaemia
    - Subjects will be asked to test and record blood ketones if their finger prick glucose is ≥16.7mmol/l (300mg/dl) upon awakening, ≥300 for more than 1 hour, or >22.2mmo/l (400mg/dL) at any time as part of the safety assessment for hyperglycaemia

This session will be conducted by a professional pump educator and possibly a member of the study team. As participants will continue using their own insulin pump during control intervention, above mentioned aspects will be reviewed with regard to the subject's particular insulin pump device. Competency on the use of the insulin pump will be made.

9.5 Visit 4 (Initiation of Study Treatment)

Subject will arrive at the clinical facility at the agreed time. Body weight and height measurements will be made. Additionally, any adverse events, device deficiencies, and, other medical conditions and/or medication will be captured. Subjects will receive further training according to randomisation.

At the end of the study arm initiation visits, participants of both study arms will be fitted with a blinded CGM system. The sensor will be worn at home for up to 14 days. If the sensor fails (i.e. does not provide any data) or sensor life gets interrupted prematurely (detached sensor), another sensor may be inserted. Re-insertion will be done by study staff at the clinical facility or at home. The sensor(s) will be sent back to the research team by mail or collected by the research team once the sensor life has expired and/or the sensor has detached. The sensor data may be used to optimise insulin delivery.

All subjects will be provided with 24 hour telephone helpline and will also be given written instructions about dealing with low and high glucose at home and when to contact study team. It is also possible to conduct initiation visits in subject's home.

US Only

Visit 4 must be completed in clinic.

9.5.1 Closed-loop with Low Glucose Feature

Closed-loop participants only. Subjects will receive training required for safe and effective use of the closed-loop system, low glucose suspend and predictive low glucose management. This will include training on connection and disconnection of the closed-loop system and switching between closed-

loop and usual pump therapy. Written step by step guidance will also be provided. Competency on the use of closed-loop system will be assessed by the study team. Only subjects who demonstrate competency on use of the system will be allowed to continue to the home study phase. Subject will use closed-loop system under supervision from study staff. Subjects will be allowed to go home once competency assessment has been satisfactorily completed with the study staff. Subjects are expected to use the closed-loop and low glucose feature at all times during the 6 months intervention period.

During the 6 months home closed-loop treatment, the subject is allowed to drive while adhering to usual precautions and country specific rules and regulations. Subjects will be warned about hypoglycaemia if they start regular exercise during study period. During the first 2 weeks of each study period subject will be advised against international travel. During the rest of the study period, subjects are allowed to travel internationally according to guidelines provided in the participant information sheet.

9.5.2 Insulin Pump Therapy

Insulin pump participants only. Key aspects of insulin pump use and capillary self-monitoring of blood glucose (SMBG) will be highlighted again. The glucometer and insulin pump will be downloaded, and current insulin requirements (total daily, basal and bolus insulin dose) will be recorded (average of preceding 7 days).

During the 6-month control intervention period, subjects will continue using their own insulin pump combined with SMBG and CGM if participant is a current CGM user, and will be followed up as outlined below. As per usual clinical practice glucometer, CGM data, and pump data (downloaded by the clinical team according to local clinical practice; such downloaded data are not considered to be collected for study purposes and will not be stored) and any other relevant information will be reviewed during 3 monthly follow up visits, and adjustments to settings will be made as required.

9.6 Telephone/email contacts after initiation of treatment arm

Participants and/or parents will be contacted by email or telephone within 24-48 hours and after two weeks following initiation of the respective study arm. The 24-48 hour contact will be by telephone in the US. Thereafter, participants will be contacted on a monthly basis in between 3-monthly follow up visits.

The purpose of these contacts would be to troubleshoot any problems, and to record any adverse events, device deficiencies, and changes in insulin settings, other medical conditions and/or medication.

After randomisation, subjects/parents and/or the clinical team are free to adjust insulin therapy as per usual clinical practice, but no active treatment optimisation will be undertaken by the research team.

9.7 Visit 5 (One Week after Starting Study Treatment)

The subject will be invited to attend the research centre approximately 1 week after Visit 4. The purpose of this visit will be to review the use of study device(s) and to provide any additional training required.

In the UK, the visit could be done via phone / e-mail. In the US in-person visit is mandatory if the subject is randomised to closed-loop intervention. Those in the US randomized to usual care can complete this visit via phone/email.

9.8 Visit 6 (Follow up Visit)

The subject will be invited to attend at 3 months after the initiation of study treatment visit for a routine follow up visit. Follow up visits will include the following procedures and activities:

- Blood glucose meter will be downloaded (both study arms)
- Current insulin requirements (total daily, basal and bolus insulin dose) will be recorded (preceding 7 days read from pump, no download needed) (insulin pump therapy arm only)
- Insulin pump will be downloaded (closed-loop arm only)
- A capillary blood glucose measurement will be performed.
- A urine pregnancy test will be performed on all females of child-bearing potential
- Subject and parents/guardians will be asked to complete surveys (see 12.2.1). For parents/ guardians this will again include the discrete choice experiment (see 12.2.2). If not done face-to-face during the visit, web-based versions of the surveys will be available for completion at home.
- A blood sample will be taken for measurement of HbA1c (see 12.3.3)

As per usual clinical practice glucometer downloads and pump data will be reviewed, and adjustments to settings will be made as required.

At the end of each follow up visits, participants of both study arms will be fitted with a blinded CGM system. The sensor will be worn at home for up to 14 days. If the sensor fails (i.e. does not provide any data) or sensor life gets interrupted prematurely (detached sensor), another sensor may be inserted. Re-insertion will be done by study staff at the clinical facility or at home. The sensor(s) will be sent back to the research team or collected by the research team once the sensor life has expired and/or the sensor has detached.

9.9 Visit 7 (Fitting blinded CGM)

For assessment of glycaemic control during the final 3-month period of the trial, participants of both study arms will be asked to attend the clinical facility 2 to 4 weeks weeks before the end of study *Visit 8*. Alternatively, this visit could take place in the subject's home.

Participants will be fitted with a blinded CGM sensor. The sensor will be worn at home for up to 14 days. If the sensor fails (i.e. does not provide any data) or sensor life gets interrupted prematurely (detached sensor), another sensor may be inserted. Re-insertion will be done by study staff at the clinical facility or at home. The sensor(s) will be sent back to the research team by mail or collected by the research team once the sensor life has expired and/or the sensor has detached, or at the end of study Visit 8.

9.10 Visit 8 (End of Study Visit)

The subject will be invited to attend the research centre approximately 6 months after the initiation of study treatment visit (Visit 4) and 7 months after randomisation (Visit 3). The following procedures will be followed:

- Blood glucose meter will be downloaded (both study arms)
- Current insulin requirements (total daily, basal and bolus insulin dose) will be recorded (average of preceding 7 days, verified by pump download)(both study arms)
- CGM device and closed-loop data will be downloaded (closed-loop arm only)
- A blood sample will be taken for measurement of HbA1c (see 12.3.3)
- Body weight, height and blood pressure measurements will be made.
- A capillary blood glucose measurement will be performed.
- Subject and parents/guardians will be asked to complete surveys (see 12.2.1). Parents/ guardians will repeat the discrete choice experiment (see 12.2.2). If not done face-to-face during the visit, web-based versions of the surveys will be available for completion at home.
- Subjects will be asked to join a focus group as outlined in section 12.2.3.

Subjects randomised to closed-loop will be asked to return all study devices, and will revert to conventional insulin therapy by switching back to the insulin pump they were using before entering the study. Subjects of the control intervention will continue with standard insulin pump therapy as before.

US only: The end of study visit may be completed in-person in clinic or in an alternate location such as the participant's home. If this is not possible, the study visit may occur remotely via phone or videoconferencing. Certain procedures such as measurement of body weight, height, and blood pressure in addition to the central laboratory HbA1c sample collection or cognitive testing may be missed if the visit is not completed in-person. A clinician will be available to discuss/direct transition of the study subject back to the subject's conventional insulin therapy.

9.11 Participant Withdrawal Criteria

The following pre-randomisation withdrawal criteria will apply:

1. Subject/caregiver is unable to demonstrate safe use of study insulin pump as judged by the investigator
2. Subject/caregiver fails to demonstrate compliance with insulin pump and SMBG during run-in

The following pre- and post-randomisation withdrawal criteria will apply:

3. Subjects/Caregivers may terminate participation in the study at any time without necessarily giving a reason and without any personal disadvantage
4. Significant protocol violation or non-compliance
5. Two distinct episodes of severe hypoglycaemia related to the use of the closed-loop system
6. Two severe hypoglycaemia events not related to the use of the closed-loop system
7. Two distinct episodes of DKA unrelated to infusion site failure and related to the use of the closed-loop system
8. Decision by the investigator or the sponsor that termination is in the subject's best medical interest
9. Allergic reaction to insulin
10. Allergic reaction to adhesive surface of infusion set or glucose sensor
11. Subject becomes pregnant during the study period

Efforts will be made to retain subjects in follow up for the final primary outcome assessment even if the intervention is discontinued, unless the investigator believes that it will be harmful for the subject to continue in the trial. Subjects who are withdrawn for reasons stated in (4) to (11) will be invited to provide blood sample at the end of the planned study intervention for the assessment of HbA1c.

Subjects who dropout or discontinue study intervention prior to the final visit will receive an exit survey.

9.11.1 Criteria for Stopping Study

The study may be stopped if three consecutive participants withdraw on the safety grounds listed in 9.11 or on the advice from the DSMB.

9.12 Co-enrolment Guidelines

To avoid potentially confounding issues, ideally participants should not be recruited into other trials. Where recruitment into another study is considered to be appropriate and without having any detrimental effect on the present study, this must first be discussed with the Chief Investigator, or the Sponsor or its representative.

9.13 Support Telephone Line

There will be a 24-hour telephone helpline to the local research teams for subjects in case of any technical device or problems related to diabetes management such as hypo- or hyperglycaemia. The local research team will have access to central 24 hour advice on technical issues.

9.14 Subject Reimbursement

The study will provide the CGM device, insulin pump, closed-loop components, related consumables, glucose meters, and glucose test strips to the closed-loop group. Ketone meters and ketone test strips will be provided to both groups. A study fee will be paid to reflect local practice. The amount paid will be specified in the participant information sheet/informed consent form and REC/IRB application form. Reasonable travel expenses will also be reimbursed. After completing the study, subjects will not keep the study devices. They will revert to their conventional insulin pump therapy.

10 Endpoints

10.1 Primary Endpoint

The primary endpoint is HbA1c level at the end of treatment period.

10.2 Other Key Endpoints

- Time spent in the target glucose range from 3.9 to 10.0 mmol/l (70 to 180mg/dl)
- Mean sensor glucose
- Time spent above target glucose (10.0 mmol/l) (180 mg/dl)
- Time spent below target glucose (3.9mmol/l) (70mg/dl)

10.3 Secondary Endpoints

Secondary endpoints regarding between treatment group comparisons include:

- CGM derived indices based on 3-monthly sensor glucose data (blinded CGM)
    - Standard deviation and coefficient of variation of glucose levels
    - The time with glucose levels < 3.5 mmol/l (63mg/dl) and <3.0 mmol/l (54mg/dl)
    - AUC of glucose below 3.5mmol/l (63mg/dl)
    - The time with glucose levels in the significant hyperglycaemia (glucose levels > 16.7 mmol/l) (300mg/dl)
    - AUC of glucose above 10.0 mmol/l (180mg/dl)
- Binary metrics for HbA1c
    - HbA1c <7.0%
    - HbA1c <7.5%
    - Relative reduction ≥10% from baseline
    - Absolute reduction ≥0.5% from baseline
    - Absolute reduction ≥1% from baseline

- Absolute reduction ≥1% from baseline or HbA1c <7.0%

- Total, basal and bolus insulin dose
- Body weight (BMI z-score)
- Blood pressure

10.4 Safety Evaluation

Safety evaluation will comprise the number of episodes of severe hypoglycaemia as well as the number of subjects experiencing severe hypoglycaemia, frequency of diabetic ketoacidosis, and other adverse events or serious adverse events.

10.5 System Use Evaluation

System use evaluation includes the duration of use of the CGM and closed-loop system combined with low glucose feature.

10.6 Human Factors Evaluation

Cognitive, emotional, and behavioural characteristics of participating subjects and family members and their response to the closed-loop system and clinical trial will be assessed using validated surveys and focus groups.

11 Assessment and Reporting of Adverse Events

11.1 Definitions

11.1.1 Reportable Adverse Events

A reportable Adverse Event is any untoward medical occurrence that meets criteria for a serious adverse event or any unanticipated medical occurrence in a study subject that is study or device-related. Device deficiencies that could have led to a serious adverse device effect will also be reported.

11.1.2 Adverse Events

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in a subject who has received an investigational device, whether or not related to the investigational medical device. This definition includes events related to the device under investigation or the comparator or to the study procedures.

The following anticipated adverse events will not be recorded:

- Non clinically significant skin reactions as judged by investigator
- Pre-existing medical conditions
- New illnesses or conditions not requiring concomitant medication or medical intervention/procedures

- Non severe hypoglycaemia
- Hyperglycaemia without significant ketonaemia (>0.6mmol/l)

11.1.3 Adverse Device Effect

An Adverse Device Effect (ADE) is an adverse event related to the use of an investigational medical device. This includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition also includes any adverse event resulting from use error or from intentional misuse of the device under investigation.

11.1.4 Serious Adverse Event

A serious adverse event (SAE) is an adverse event that:

- led to a death
- led to a serious deterioration in the health of the subject, that either resulted in:
  - a life threatening illness or injury
  - a permanent impairment of a body structure or function
  - in-patient hospitalisation or prolonged hospitalisation
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- led to foetal distress, foetal death or a congenital abnormality or birth defect

A planned hospitalization for pre-existing condition, or a procedure required by the study protocol, without a serious deterioration in health, is not considered to be a serious adverse event.

More than one of the above criteria can be applicable to one event. Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. Medical judgement should be exercised in deciding whether an adverse event or reaction is serious in other situations.

Important adverse events or reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

The following serious adverse events, should they occur, will be classified as anticipated:

- Severe hypoglycaemia
- DKA

11.1.5 Serious Adverse Device Effect

A Serious Adverse Device Effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

11.1.6 Unanticipated Serious Adverse Device Effect

An Unanticipated Serious Adverse Device Effect (USADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the protocol.

An Anticipated Serious Adverse Device Effect (ASADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the protocol.

11.1.7 Device Deficiencies

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labelling. A device deficiency may lead to an Adverse Device Effect or Serious Adverse Device Effect.

The following anticipated device deficiencies and device issues will not be recorded:

- Infusion set occlusion/leakage not leading to ketonaemia
- Sensor failure due to miscalibration/detachment
- Premature interruption of sensor-life
- Battery lifespan deficiency due to inadequate charging or extensive wireless communication
- CAD error messages not needing system replacement
- Intermittent device communication failure not leading to system replacement

11.1.8 Adverse Event Intensity

Intensity	Definition
Mild	Patient is aware of signs and symptoms but they are easily tolerated
Moderate	Signs / symptoms cause sufficient discomfort to interfere with usual activities
Severe	Patient is incapable to work or perform usual activities

NB. The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as ‘serious’, which is based on patient/event outcome or action criteria (see definition 11.1.4). For example, itching for several days may be rated as severe, but may not be clinically serious.

11.1.9 Adverse Event Causality

Intensity	Definition
Not assessable	A report suggesting an adverse event, which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship, which makes a causal relationship improbable, and in which other drugs/treatments, chemicals or underlying disease(s) provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment/use of investigational treatment/device, but which also could be explained by concomitant diseases or other drugs/treatments or chemicals.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the treatment/use of medical method/device, unlikely to be attributable to concomitant disease(s) or other drugs/treatments or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
Definite/certain	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to study treatment/use of medical method/device and which cannot be explained by concomitant disease(s), other drugs/treatments or chemicals. The response to withdrawal of the treatment (dechallenge) should be clinically plausible. The event must be unambiguous, either pharmacologically or as phenomenon, using satisfactory rechallenge procedures if necessary.

(Reference: WHO-UMC Causality Categories)

11.2 Recording and Reporting of Adverse Events, Serious Adverse Events and Device Deficiencies

11.2.1 Monitoring Period of Adverse Events

The period during which adverse events will be reported is defined as the period from the beginning of the study (obtaining informed consent) until 3 weeks after the end of the study participation. Adverse events that continue after the subject's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected. The follow up of AEs may therefore extend after the end of the clinical investigation; however no new AEs will be reported after the trial reporting period unless it is associated with an ongoing AE.

11.2.2 Recording and Reporting of Adverse Events

Throughout the course of the study, all efforts will be made to remain alert to possible adverse events or untoward findings. The first concern will be the safety of the subject, and appropriate medical

intervention will be taken. The investigator will elicit reports of adverse events from the subject at each visit and complete adverse event forms. All AEs, including those the subject reports spontaneously, those the investigators observe, and those the subject reports in response to questions will be recorded on paper or electronic AE forms at each site within seven days of discovering the event.

The study investigator will assess the relationship of any adverse event to be device-related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by the study device or study procedures. The individual investigator at each site will be responsible for managing all adverse events according to local protocols, and decide if reporting is required.

11.2.3 Severe Hypoglycaemia

In adolescents, severe hypoglycaemia will be defined as an event requiring assistance, which means that assistance of another person is needed to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopaenia to induce seizure or coma.

In paediatric subjects hypoglycaemic events will be considered severe if the event requires assistance of another person due to altered consciousness to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the subject is impaired cognitively to the point that he/she is unable to treat him- or herself, is unable to verbalize his or her needs, is incoherent, disoriented, and/or combative, or experiences seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Severe hypoglycaemia will be regarded as a foreseeable serious adverse event and a serious adverse event form will be completed. Non-severe hypoglycaemia will not be reported or considered an adverse event.

11.2.4 Diabetic Ketoacidosis

Diabetic Ketoacidosis (DKA) is defined as: hyperglycemia (blood glucose >250 mg/dl or >13.9 mmol/l) with either low serum bicarbonate (<15 mEq/l) and/or low pH (<7.24), anion gap (> 12) and either ketonemia or ketonuria and requiring treatment within a health-care facility (American Diabetes Association Workgroup on Hypoglycemia, Diabetes Care 28:1245-1249, 2005).

DKA will be regarded as a foreseeable serious adverse event and a severe adverse event form will be completed.

11.2.5 Treatment provided in a health care facility Reporting of Serious Adverse Events and Serious Adverse Device Effects

When reporting adverse events, all pertinent data protection legislation must be adhered to.

The relationship of the SAE to the investigational treatment / medical device should be assessed by the investigator at site, as should the anticipated or unanticipated nature of any SAEs and SADEs. All SAEs whether or not deemed investigational method/device related and whether anticipated or unanticipated must be reported to the Sponsor by email or fax within 24 hours (one working day) of the Investigator learning of its occurrence.

UK specific reporting instructions:

SAEs should be reported to:

Stephen Kelleher
Cambridge University Hospitals
NHS Foundation Trust
Box 277, Addenbrooke's Hospital
Hills Road, Cambridge, CB2 0QQ, UK
Phone: +44 (0) 1223 217418
Fax: +44 (0) 1223 348494
E-mail: r&denquiries@addenbrookes.nhs.uk

A written report must follow within five working days and is to include a full description of the event and sequelae, in the format detailed on the Serious Adverse Event reporting form. If applicable, the Sponsor will notify the competent authority of all Serious Adverse Events in line with pertinent legal requirements.

The Investigator will notify the Research Ethics Committee (REC) in UK of all Serious Adverse Events in line with pertinent legal requirements. The Investigator will inform the Sponsor about all reports sent to the reporting organisation including follow-up information and answers by the reporting organisation. The local investigator is responsible for informing other site principal investigators and the CI of all SAEs.

The regulatory authority (MHRA) will be notified of all SAEs as soon as possible within ten days of the event occurring during the study. The main REC/IRB will be notified of all unexpected and related SAEs within 15 days of the occurrence of the event.

USA specific reporting instructions:

SAEs should be reported to:

Judy Sibayan
Jaeb Center for Health Research
15310 Amberly Drive, Suite 350
Tampa, FL 33647, USA
Phone: 813-975-8690

APP Fax: 888-795-2859
E-mail: jsibayan@Jaeb.org

It is the responsibility of the local investigator to follow the SAE and SADE reporting requirements stipulated by the Investigational Centre's reviewing IRB and the Sponsor.

11.2.6 Recording and Reporting of Device Deficiencies

All device deficiencies will be documented throughout the study. The investigator at each site will be responsible for managing all device deficiencies and determine and document in writing whether they could have led to a serious adverse device effect.

All device deficiencies that might have led to a serious adverse device effect(s) if suitable action had not been taken; intervention had not been made; or if circumstances had been less fortunate, must be reported to the Sponsor (see section 11.2.5) as for SAEs/SADEs.

11.2.7 Reporting of Pregnancy

Urine pregnancy testing will be performed as part of the trial screening process, prior to randomization and repeated no less frequently than every 3 months during follow-up for all female study participants of child-bearing potential. Any pregnancy which does occur during the course of the study should be reported to the Sponsor as indicated in section 11.2.5 immediately. Participants who become pregnant will stop study treatment and their care will be transferred to a team experienced in diabetes care during pregnancy according to local practice. Participants who become pregnant will be invited to provide blood sample at the end of the planned study intervention for the assessment of HbA1c. All pregnancies that occur during trial treatment, or within seven days of finishing treatment, need to be followed up until completion and reported separately.

11.2.8 Healthcare Arrangements and Compensation for Adverse Events

Healthcare arrangements for subjects who suffer an adverse event as a result of participating in the study may include advice from clinical members of the study team or the patient's treating diabetes team, or use of emergency health services.

If an adverse event occurs, there are no special compensation arrangements unless this was due to the negligence of one of the clinical investigators or due to harm resulting from study protocol design. In this case subjects may have grounds for legal action for compensation. The normal national complaints mechanism will be available. In addition, any harm arising due to study design (both negligent and non-negligent) will be covered under Sponsor's insurance policy as applicable.

11.3 Anticipated Adverse Events, Risks and Benefits

11.3.1 Risks and anticipated adverse events

Known risks represent hazardous situations which may result in anticipated adverse events. In the following text, where appropriate, the term “risk” and “anticipated adverse events” are used interchangeably without affecting meaning.

11.3.2 Hypoglycaemia and Hyperglycaemia

Subjects with type 1 diabetes have a pre-existing risk for hypoglycaemia and hyperglycaemia. Potential risks are:

- Risk of mild to moderate hypoglycaemia and associated symptoms such as sweating, trembling, difficulty thinking and dizziness. There is also a rare risk of severe hypoglycaemia when conscious level is altered, needing help from a third party to correct the hypoglycaemia. These risks are pre-existent in any patient with type 1 diabetes and the study objective is to develop systems to minimise these risks
- Risk of possible mild to moderate hyperglycaemia similar to the risk that a subject with type 1 diabetic experiences on a daily basis
- Risk of hyperglycaemia leading to diabetic ketoacidosis (DKA). This risk is pre-existent in any patient with type 1 diabetes.

Although the objective of the use of the closed loop system is to reduce hypoglycaemia and hyperglycaemia, use of the system could increase the risk if the system does not perform properly.

11.3.3 Blood Sampling

Subjects will be required to have 3-4 blood tests (venipuncture) during the whole study. Venipuncture is required annually as part of the annual review for people with diabetes, and in some places venipuncture is required every 3 to 6 months for assessment of HbA1c. Potential risks include:

- Slight discomfort or bruising at the site (common)
- Excess bleeding at the site (unlikely)
- Infection at the site (rare)
- Fainting (rare)

Local anaesthetic cream or spray may be used to minimise the discomfort.

11.3.4 Finger-prick Blood Glucose Measurements

Finger-prick tests may produce pain and/or bruising at the site.

11.3.5 Insulin Pump Therapy

Patients participating in this study are already using an insulin pump. Potential risks associated with insulin pump therapy include:

- Slight discomfort at the time of insertion of the insulin delivery cannula (common)
- Slight bruising at the site of insertion (common)
- Infusion set and cannula occlusions (common)
- Insulin pump malfunction and mechanical problems (common)
- Lipodystrophy / lypoatrophy (common)
- Bleeding at insertion site (rare)
- Infection at the site of insertion (rare)
- Allergy to the insulin delivery cannula or adhesive (rare)
- Allergy to insulin (very rare)

11.3.6 Continuous Glucose Monitoring

Potential risks associated with CGM:

- Slight discomfort at the time of insertion of CGM (common)
- Slight bruising at the site of insertion (unlikely)
- Bleeding at insertion site (rare)
- Infection at the site of insertion (rare)
- Allergic reaction to the CGM sensor material (rare)

If a skin reaction is classified as severe (the observation is noticeable and bothersome to subject and may indicate infection or risk of infection or potentially life-threatening allergic reaction), an adverse event form will be completed.

11.3.7 Surveys and Focus Groups

As part of the study, subjects will participate in focus groups and will complete surveys which include questions about their private attitudes, feelings and behaviour related to diabetes. It is possible that some people may find these surveys to be mildly upsetting. Similar surveys have been used in previous research and these reactions are uncommon.

The study team takes the safeguarding of children very seriously and should any concerns be raised during the course of the study, including during the surveys and focus group sessions, these concerns will be dealt with in accordance to local policy. Participants and caregivers will be made aware of this in the participant information sheets.

11.3.8 Risk Analysis and Residual Risk Associated with the Investigational Device

A detailed risk analysis for the closed-loop system was conducted, according to Cambridge University Hospitals NHS Foundation Trust's standard Risk Assessment Tool. The risk analysis is presented in a separate risk analysis report

The hazard analysis has led to two hazardous situations in which the residual risk identified exceed a predefined score after all practicable control measures have been applied. Risk/benefit analyses concerning these hazardous situations have been conducted by experienced and knowledgeable multidisciplinary members of the research team.

The risks/benefit analysis concluded that day and night closed-loop is expected to reduce substantially but not to eliminate the risk of plasma glucose levels below 2.0 mmol/l (36mg/dl). This is supported by clinical data recorded over more than 100 nights at the clinical research facility, by simulations, and is further enhanced by the requirement for a calibration check to be performed each day before breakfast and an evening meal.

It is also the assessment of the investigators that this protocol is a minor increase over minimal risk. In addition, it is the belief of the investigators that this study also presents prospect of direct benefit to the subjects and general benefit to others with diabetes.

11.4 Benefits

It is expected that day and night closed-loop system in combination with low glucose feature or insulin pump therapy alone may have an important role in the management of diabetes. Therefore, the results of this study are likely to be beneficial for subjects with diabetes.

It is possible that subjects will not directly benefit from being a part of this study. However, it is also possible that the blood sugar information from the CGM devices along with the information about insulin dosing during day and night closed-loop will be useful for subjects' diabetes self-management.

12 Methods and Assessments

12.1 Procedures

12.1.1 Height, Weight and Blood Pressure

Height and weight will be recorded at screening, at the start and the end of the study interventions. Blood pressure will be measured at screening and at the end of the study. Height will be measured in centimetres using a calibrated stadiometer. Weight will be measured in kilograms using a calibrated electronic scale. Blood pressure readings will be obtained using automated calibrated BP monitors with the patient seated comfortably for 5 minutes prior to the measurements.

12.1.2 Insulin Pump Data

Data from the study insulin pump (closed-loop arm) will be downloaded periodically during each intervention by the participant and during study visits.

In the control group, insulin requirements (total daily, basal and bolus insulin dose) will be read from participant's pump (preceding 7 days, no separate download needed) during respective study visits/contacts, and will be recorded on the case report forms.

12.1.3 Blood Glucose Meter Data

The study blood glucose meter (Bayer Contour™ Next) will be downloaded periodically during both intervention arms.

12.1.4 Continuous Subcutaneous Glucose Monitoring

Two different continuous glucose monitoring systems (CGM) will be used throughout this trial: a blinded CGM with retrospective sensor glucose data read out, and a real-time system providing a contemporaneous display of sensor readings.

12.1.5 Blinded Continuous Subcutaneous Glucose Monitoring

Blinded CGM will be intermittently applied during run-in and at three-monthly throughout the trial. During run-in, blinded CGM will serve to gain knowledge of the specific subject's glucose control characteristics before the beginning of any intervention arm. Post-randomisation, blinded CGM will be periodically used following initiation visit and 3-monthly follow up visits. Participants of both intervention arms will be fitted with a blinded sensor during the study visits and will wear the sensors until expiry or detachment. Sensors will be returned to the research team thereafter. Secondary glucose endpoints will be based on glucose data derived from data captured during these up to 14 day periods. Moreover, these data may be used to facilitate insulin dose adjustment during control intervention.

12.1.6 Real-time Continuous Subcutaneous Glucose Monitoring

Real-time CGM will be applied during closed-loop intervention only. The control algorithm will use the real-time CGM's continuous stream of glucose data to control insulin titration. Data from the real-time CGM system will be downloaded periodically during study visits as part of pump download.

12.2 Assessment of Human Factors

We are broadly referring to human factors as the cognitive, emotional, and behavioural characteristics of the participants in the study. The human factors assessment battery is grounded in two principles: 1) it is critical to use evidence-based methods that are reliable, valid, and have parallel forms for youth and their caregivers, and 2) both quantitative (i.e., surveys) and qualitative (i.e., focus groups) data need to be gathered to provide the richest, most comprehensive characterization of the sample and their response to the closed-loop system and clinical trial. Selected surveys will also be used as inputs into the cost utility analyses.

12.2.1 Surveys

Surveys are listed in Table 3 along with information about who completes the survey (youth versus caregiver, or both). All surveys will be administered online so there is no requirement for completion

face-to-face. It is estimated that youth will take 45-50 minutes to complete their surveys; parents will take 25-30 minutes. The Measure column lists the construct of interest in bold. Surveys will be completed at the time of major assessments in the clinical trial – 0 weeks (prior to randomisation), 3 months, and 6 months.

Table 3. Human Factors Assessment (all completed at Visit 1, 6, and 8).

Measure	*Respondent*	*Construct Measured / Relevant Points*
Paediatric **Quality of Life** Inventory (PedsQL) Diabetes	All youth and All parents	**YOUTH** - All youth ages 6-18 will complete age-appropriate PedsQL Diabetes module. Versions are included for 6-7 year-olds, 8-12 year-olds, and 13-18 year-olds. **PARENTS** – All parents complete a proxy version reporting on their child's quality of life. Versions of the parent proxy correspond to age of child.
Child Health Utility-9D (CHU-9D)	All youth	**YOUTH** – All youth ages 6-18 complete this widely used survey that will be administered so that Quality adjusted life years (QALYs) can be calculated. Accepted by the FDA and NICE.
EQ-5D-Y	Youth 8-18	**YOUTH** – Youth ages 8-18 complete this survey to evaluate quality of life and further calculate QALYs accepted by NICE.
Cognition	All youth	**YOUTH** – All youth ages 6-18 will complete 4 computerized tests included in the Brief Battery produced by CogState. The 4 tests measure processing speed, attention, visual learning, and working memory. They take 12-15 minutes to complete.
Glucose Monitoring System Survey (GMSS-T1D)	Youth ≥11, All parents	**YOUTH** – Youth ages 11-18 will complete this survey on satisfaction with glucose monitoring device. **PARENT** – All parents complete a shortened version on their own satisfaction with this device.
Diabetes **Self Management** Profile – Self Report	Youth ≥11 All parents	**YOUTH** – Youth ages 11-18 will complete this survey on diabetes management tasks. **PARENT** – All parents complete a version of how their family completes diabetes management.
Centre for Epidemiologic Studies – **Depression (CES-D)**	Youth ≥11, All parents	**YOUTH** – Youth ages 11-18 will complete this survey on symptoms of depression. **PARENT** – All parents complete the version of the CESD on their own depressive symptoms.
Problem Areas in Diabetes – Teen (**Diabetes Burden**)	Youth ≥ 11	**YOUTH** – Youth ages 11-18 will complete this survey on psychological distress and burden associated with taking care of diabetes.
Diabetes Distress Scale	All parents	**PARENTS** – All parents will complete this survey on psychological distress and burden associated with taking care of diabetes that they perceive in their children.

Use of and Comfort with Technology	Youth ≥11, All parents	**YOUTH** – Youth ages 11-18 will complete this survey on use of and comfort with general technology and diabetes devices. **PARENT** – All parents complete the same questions on technology and devices.
Physical Activity Questionnaire (PAQ)	Youth ≥11, All parents	**YOUTH** – Youth ages 11-18 will complete the PAQ to document physical activity. **PARENT** – All parents complete a proxy version of the PAQ on their child's physical activity.
Clarke **Hypoglycaemia Unawareness** Scale	All youth	**YOUTH –** All youth ages 6-18 complete this brief survey on the recognition of symptoms of hypoglycaemia.
Hypoglycemia Confidence & Worries	Youth ≥11	**YOUTH** – Youth ages 11-18 will complete the worry subscale of the Hypoglycemia Fear Survey (17 items) and 8 items of the Hypoglycemia Confidence Scale.
INSPIRE Surveys	All Youth All Parent	Measures the psychological side of automated insulin delivery. Child version (6-12) has 27 items; Adolescent version (13-18) has 28 items; Parent version has 30 items.

12.2.2 Discrete Choice Experiment

In order to assess how strongly participants value both the anticipated and actually experienced potential benefits of the closed loop system (compared with the default insulin pump), we will also conduct a discrete choice experiment (DCE). In the DCE, respondents will be asked to answer a series of binary choice questions (e.g., "Given a choice between option A or B, which would you prefer...") where those two options offer differing strengths and weaknesses. For example, one hypothetical alternative “A” might dramatically reduce the risk of hypoglycemic events, but also be much less convenient to use, whereas the alternative “B” might be less effective in reducing hypoglycemic events, but also more convenient. By varying the performance levels of these different desirable characteristics, we can assess their relative importance. Included with the other human factors assessments performed at 0, 3, and 6 months, the parents (or guardians) of study participants (in both the treatment and control groups) will be asked to answer a series of no more than 10 such binary choice questions. The estimated time required per administration should be approximately 3-5 minutes. Design of the specific questions will employ well-established DCE methodologies.

The specific performance characteristics that respondents will be asked about have not been finalized, but will likely include how well the system: reduces hypoglycemic event frequency/severity; improves overall average lifetime HgA1c level/blood glucose control; reduces worry/stress about blood glucose complications; offers convenience of use for daily blood glucose management; and imposes no more than a specified maximum associated out of pocket cost per month. The precise attributes tested, appropriate performance levels for each attribute, and the wording of their descriptions will be refined before fielding the study using data from published literature and focus groups recently conducted with parents of children with T1DM. Preliminary pilot testing will also be conducted by administering the resulting questions to study personnel to assess their readability, usability, and logical consistency. Selection of the alternatives for each DCE question and assembling optimal sets of approximately 10 questions for each respondent will be made using a D-Efficient design algorithm. Questions with dominated alternatives (i.e., where one option is unequivocally better than the other) may be included in the question sets in order to test respondents' rational consistency. The final question sets will be randomly assigned to participants.

12.2.3 Focus Groups

Focus groups will be completed at the end of the study (6 months). We will conduct virtual focus groups using HIPAA-approved software supported by Stanford University. Focus groups will be run with 3-6 participants and we will work from a script of open-ended questions used to gather feedback and reactions to the closed-loop system/insulin pump therapy, the clinical trial, and quality of life changes. There will also be time for discussion of content raised by participants. Use of a moderator

with advanced training will ensure consistency across groups. Trained study coordinators will observe the focus groups and take field notes. The study coordinator will keep time and manage group logistics. Sessions will be audio- and video-taped and transcribed by a professional transcription service.

12.3 Laboratory Methods

12.3.1 Screening Sample

Liver function (AST, ALT, GGT, albumin, total bilirubin), thyroid function (TSH, fT4), anti-transglutaminase antibodies (and IgA levels if not done in the previous 12 months), and full blood count will be measured locally.

12.3.2 C-peptide and Glucose

Blood sample for the measurement of C-peptide with simultaneous exclusion of biochemical hypoglycaemia (plasma glucose <4.0 mmol/l (72mg/dl)) by laboratory glucose analysis on a sample at the same time point, will be taken at screening. A fingerprick will be taken prior to central lab sample collection to confirm normoglycaemia. If subject is hypoglycaemic, the glucose will be treated and fingerprick glucose checked again. Repeat until normoglycaemic.

Plasma C-peptide will be measured at a central laboratory. Plasma glucose will be measured locally.

12.3.3 HbA1c

Blood samples for the measurement of HbA1c levels will be taken at three different time points: Visit 1 (Screening), Visits 6(three monthly follow up visit), and Visit 8 (End of study intervention). If Visit 1 (Screening) and Visit 3 (Randomisation) are >28 days apart, an additional HbA1c sample will be taken at Visit 3 (Randomisation).

At each time point, HbA1c will be measured locally for patient care, and centrally for analysis of primary and secondary endpoints. HbA1c eligibility criterion will be based on local measurement at screening. HbA1c analysis at the central laboratory will be performed using an International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) aligned method. All HbA1c testing must follow National Glycohemoglobin Standardization Program (NGSP) standards.

12.4 Total Blood Loss

The total blood volume for blood draws will be less than 35 ml.

13 Study Materials and Products

13.1 Insulin

U-100 rapid acting insulin will be used in the insulin pumps. This includes either Aspart (Novorapid; Novo Nordisk, Bagsvaerd, Denmark) or Lispro (Humalog; Eli Lily, Indianapolis, USA).

13.2 Insulin Pumps

13.2.1 Run-in and Insulin Pump Therapy alone Intervention

During Run-in and control intervention, rapid acting insulin will be administered using the subject's own insulin pump in accordance with the manufacturer's instructions for their intended purpose.

Insulin requirements (total daily, basal and bolus insulin dose) will be read from the pump (preceding 7 days) during respective study visits/contacts, and will be recorded on the case report forms. No separate pump downloads will be carried out for the purpose of the study but may be done by the clinical team for the purposes of standard clinical practice and adjustments to settings will be made as required.

13.2.2 Closed-loop with Low Glucose Feature Intervention

During day-and-night automated closed-loop glucose control combined with low glucose feature, the next generation Medtronic subcutaneous insulin infusion pump Medtronic 640G (Medtronic Minimed, Northridge, CA, USA) will be used. Low glucose suspend/predictive low glucose management will be initially set to suspend insulin delivery at sensor glucose values of 3.9 mmol/l (70 mg/dl) or less, after which the setting could range from 2.8 to 5.0 mmol/l (50 mg/dl to 90 mg/dl).

To download insulin and sensor data, Medtronic CareLink® Therapy Management Software or similar will be used.

13.3 Blood Glucose Meter

For self-monitoring of capillary blood glucose (SMBG) during both intervention arms, Bayer CONTOUR™ Next Link blood glucose meters will be used exclusively.

During the closed-loop intervention, capillary meter readings are used to calibrate the study pump. The study pumps use the calibration point in the real-time algorithm which calculates the sensor glucose values that are displayed to the subject.

13.4 Continuous Subcutaneous Glucose Monitor

13.4.1 Blinded Continuous Subcutaneous Glucose Monitor

FreeStyle Libre Pro sensor (Abbott Diabetes Care, Alameda, CA) or similar blinded CGM devices will be used. Insertions will be done by the research team according to manufacturer's instruction.

FreeStyle Libre Pro automatically stores up to 14 days worth of glucose data and requires no calibration.

To download blinded sensor data during run-in, interventional and control periods, Abbott's software or similar will be used.

13.4.2 Real-time Continuous Subcutaneous Glucose Monitor

The next generation Medtronic Enlite 3 family real-time sensor with Enlite serter (Medtronic Minimed, Northridge, CA, USA) will be used during closed-loop intervention of the study. The sensor will be calibrated according to manufacturer's instructions with additional calibration checks in the morning and evening.

The use of real-time continuous glucose monitoring systems will not be promoted during control intervention.

13.5 CareLink USB

The Medtronic CareLink™ USB is indicated for use commercially by patients at home and for clinicians in a medical office setting as a means of facilitating communication between Medtronic diabetes therapy management devices that use Paradigm-compatible RF telemetry and a personal computer that uses data management application software. The CareLink USB device will enable data from study insulin pumps to be uploaded to CareLink database.

13.6 Computer-Based Algorithm

The Cambridge closed-loop controller has been used safely and effectively in the closed-loop studies in both children and adults with T1D **(study REC Ref. 06/Q0108/350, REC Ref. 07/H0306/116, REC Ref. 08/H0304/75, REC Ref. 08/H0308/297, REC Ref. 09/H0306/44, REC Ref. 10/H0304/87, REC Ref. 12/EE/0155, REC Ref. 12/EE/0034, and REC Ref. 12/EE/0424).**

Section 4.4.6 documents safe and efficacious use of the closed-loop algorithm over 1 to 3 week application in unsupervised home settings. Section 4.4.7 documents a similar performance in adults over up to 3 month use in unsupervised home settings.

14 Data Analysis

14.1 Primary Outcome Analysis

The primary analysis will evaluate between group differences in HbA1c levels at the end of treatment period. A 5% significance level will be used to declare statistical significance for the primary outcome comparison.

The primary analysis will follow the intention-to-treat principle. It will include all randomized subjects, the data from whom will be analysed in the group to which the subjects were assigned through randomisation regardless of the actual treatment received. Data will not be truncated due to protocol deviations.

In the primary analysis, missing data will be handled using multiple imputation with pattern mixture models assuming the dropout trajectory of the treatment subjects was that of the control arm. It is worth noting that all statistical methods for handling missing data rely on untestable assumptions and there is no one correct way to handle missing data. Our goal is to minimize the amount of missing data so that the results will not be sensitive to which statistical method is used.

Means ± SD values or percentiles appropriate to the distribution will be reported for the primary outcome by treatment group. The two treatment groups will be compared using a linear regression model adjusting for HbA1c at baseline, age, and clinical centre as random effect. A 95% confidence interval will be reported for the difference between the randomisation groups based on the linear regression model. Residual values will be examined for an approximate normal distribution. If values are highly skewed then a transformation or robust statistical methods (e.g., non-parametric or MM estimation) will be used instead. A detailed analysis plan will be provided separately.

14.2 Other Key Endpoints

For following key endpoints at 6 months, the familywise type I error rate (FWER) will be controlled at two-sided $\alpha = 0.05$. A gatekeeping strategy will be used, where the primary endpoint will be tested first, if passing the significance testing, other key endpoints will be tested in the order listed below using the fixed-sequence method at $\alpha = 0.05$.

- HbA1c (primary endpoint)
- Time spent in the target glucose range from 3.9 to 10.0 mmol/l (70 to 180 mg/dl)
- Mean glucose
- Time spent above target glucose 10.0 mmol/l (180 mg/dl)
- Time spent below target glucose 3.9 mmol/l (70 mg/dl)

If a non-significant ($p > 0.05$) result is obtained for any outcome on this list, then no further hypothesis testing will be done for any metrics further down on the list.

14.3 Secondary Efficacy Analyses

The following endpoints will be considered exploratory. For these analyses, the false discovery rate (FDR) will be used to account for multiple comparisons.

CGM derived indices

- SD of sensor glucose

- sensor glucose variability measured with the coefficient of variation
- The time with glucose levels < 3.5 mmol/l (63mg/dl)
- The time with glucose levels <3.0 mmol/l (54mg/dl)
- AUC of glucose below 3.5mmol/l (63mg/dl)
- The time with glucose levels in the significant hyperglycaemia (glucose levels > 16.7 mmol/l) (300mg/dl)
- AUC glucose above 10.0 mmol/L (180mg/dl)

Following CGM metrics will also be calculated separately for day-time period (06:00-23:59) and night-time period (00:00-05:59):

- The time with CGM glucose from 3.9 to 10.0 mmol/l (70-180 mg/dl)
- Mean glucose
- Glucose variability as measured by standard deviation
- The time with CGM glucose values <3.5 mmol/l (63 mg/dl)

Binary metrics for HbA1c

- HbA1c <7.0%
- HbA1c <7.5%
- Relative reduction ≥10% from baseline
- Absolute reduction ≥0.5% from baseline
- Absolute reduction ≥1% from baseline
- Absolute reduction ≥1% from baseline or HbA1c <7.0%

Insulin and Other Endpoints

- Total, basal and bolus insulin dose
- Body weight (BMI z-score)
- Blood pressure

Above described glycaemic metrics will be based on CGM glucose levels collected during post-randomisation periods of blinded CGM sensors wear. Up to 2 weeks of sensor data prior to randomisation will be used to define the baseline.

Based on the distribution, summary statistics (mean and SD or percentiles) will be reported for each glycaemic and insulin metric at 3 months and 6 months by treatment group. Linear regression models will be used to compare above continuous outcomes at 6 months between the two treatment groups by adjusting for the corresponding metric calculated at baseline, baseline HbA1c, clinical centre, and age. Residual values will be examined for an approximate normal distribution. If values are highly skewed then an alternate transformation (log(x+0.005), square-root, or rank transformation) or robust statistical methods will be used instead. Logistic regression models will be used to compare above binary HbA1c outcomes at 6 months between the two treatment groups by adjusting for baseline HbA1c as a continuous variable, clinical centre, and age.

Longitudinal analyses of HbA1c values (baseline, 3, and 6months) along with selected sensor glucose and insulin outcomes will also be performed. For 3-monthly longitudinal glycaemic outcomes, a minimum of 5 days (120 hours) of data is required in order to calculate the metrics. The secondary analyses mentioned above will be repeated for the longitudinal HbA1c, sensor glucose and insulin outcomes while using a repeated measures regressions instead. Missing values will not be imputed for the longitudinal analyses.

14.4 Safety Evaluation

The following events will be tabulated and statistically compared by treatment group:

- Number of SH events per subject and SH event rate per 100 person-years
- Number of DKA events per subject and DKA event rate per 100 person-years
- CGM-measured hypoglycemic events per week (>15 minutes with glucose concentration <54 mg/dL)
- CGM-measured hyperglycemic events per week (>15 minutes with glucose concentration >300 mg/dL
- Proportion of subjects with worsening of HbA1c from baseline to 6 months by >0.5%

In addition the following will be tabulated without formal statistical testing between groups

- Proportion of subjects with 1 or more SH events
- Proportion of subjects with 1 or more DKA events
- Any ketonemia event
- Any hyperglycemia event other than DKA and ketonemia
- Any adverse event other than hypoglycemia, hyperglycemia, DKA, and ketonemia which have been reported separately
- Any serious adverse events (SAE) other than hypoglycemia, hyperglycemia, DKA, and ketonemia which have been reported separately
- Adverse device effects (ADE)
- Unanticipated adverse device effects (UADE)

If there are enough observed events to allow formal statistical modelling the following analyses will be conducted. For comparing event rates, Poisson regression models will be constructed to compare the treatment group difference for event rates by adjusting for age, baseline HbA1c and random site effect. If any outlier exist, a robust Poisson regression model will be used instead. For binary HbA1c outcome, logistic regression models will be used to compare the treatment group difference by adjusting for age, baseline HbA1c and random site effect. No adjustment of p-values will be made on above safety outcomes.

14.5 System Use/Function

Following system use/function outcomes among the closed-loop treatment arm will be tabulated for the intervention period:

- Number of LGS events
- %time when CL system use is functioning
- %time when CGM is used

14.6 Additional Tabulations

The following tabulations and analyses will be performed without any statistical test: (1) baseline demographics and clinical characteristics, (2) flow chart accounting for all subjects according to treatment group and study group for all visits, (3) visit completion rates for each follow-up visit according to treatment group, (4) protocol deviations according to treatment group, (5) device issues, (6) Number and reasons for unscheduled visits and phone calls.

14.7 Sensitivity Analyses

Missing Data

Following alternative approaches will be used for handling missing HbA1c data as sensitivity analyses for the primary outcome:

- Only subjects who completed the 6-month HbA1c exam will be included (this will include any subjects who withdraw early but subsequently return to take HbA1c sample at 6 months)
- Direct likelihood method (MMRM model)
- Rubin's multiple imputation with treatment group in the imputation model
- Rubin's multiple imputation separately by treatment group

Confounding

Repeat primary analysis by including other potential confounding factors beyond age, baseline HbA1c and site at enrolment. Following potential confounding factors at baseline will be assessed for imbalance between groups: (1) gender, (2) race/ethnicity, (3) diabetes duration, (4) BMI, (5) baseline C-peptide, (6) total daily insulin, (7) blood glucose, (8) number of SH and DKA in last 12 months, (9) pump use, and (10) CGM use. Unlike the list of covariates in the primary analysis which is pre-specified, the inclusion of covariates here maybe data-driven based on observed imbalances between treatment arms. The imbalance will be assessed based on clinical judgement reviewing the distributions in the two treatment arms, not on a p-value.

14.8 Subgroup Analyses

No subgroups were considered during the power calculations. Interpretation of any subgroup analyses will depend on whether the overall analysis demonstrates a significant treatment group

difference. In the absence of such an overall difference and if performed, the following subgroup analyses will be interpreted with caution.

Following subgroup analyses will be performed for HbA1c at 6 months: (1) baseline HbA1c, (2) baseline/run-in time spent in hypoglycaemia, and (3) age (6 to 12 years vs. 13 to 18 years). Additional analyses may also be performed by following subgroups: (4) gender, (5) race-ethnicity, (6) clinical centre, and (7) baseline C-peptide.

The planned subgroup analyses for CGM endpoints include age subgroup analyses for (1) the time with glucose levels 3.9-10.0 mmol/l (70-180 mg/dl), and (2) the time with glucose levels < 3.5 mmol/l (63mg/dl).

14.9 Per-Protocol Analysis

A per-protocol analysis will be performed to replicate the primary analysis limited to subjects who meet the following criteria:

- Did not withdraw from the study (withdrawals excluded even if they return for a 6 month HbA1c measurement)
- Intervention arm: Closed loop active for at least 70% of the time

14.10 Analysis of Human Factors Data

Quantitative data on usability and satisfaction will be analysed using simple descriptive statistics. In addition, we will analyse scores from the measures in the human factors assessment battery to determine if changes occur over time and between groups. We will construct predictive models in the general linear framework to examine each set of human factors (e.g., QOL, fear of hypoglycaemia) and its association with our outcomes. Treatment group will be the primary covariate. For the discrete choice experiment (DCE), the strength of preference (importance) of each performance attribute will be estimated from the pooled DCE responses using standard regression analysis techniques.

Qualitative data will be analysed using Atlas.ti (release 6.0; Scientific Software Development GmbH, Berlin, Germany) to organize and manage the entire corpus of focus group data. Analysis begins with an initial coding procedure to capture and describe the range of responses to the intervention. A second, more focused and detailed level of coding will be applied to major categories of findings in the initial review to determine themes in response to the clinical trial, use of the closed-loop system, and quality of life changes.

14.11 Cost Utility Analyses

To inform reimbursement decision-making, we will conduct a cost utility analysis on the benefits of closed-loop insulin delivery. The analysis timeframe for both costs and benefits will include not just the study period, but also anticipated future impacts. Costs will be denominated in U.S. Dollars. They will be framed to include both health related expenditures and any realized or projected incremental

health cost savings. Utility will be quantified in quality adjusted life years (QALYS). We will elicit health related quality of life (HRQOL) during the study period using one or both of the following preference based measures (PBM) of health status: the Child Health Utility 9D (CHU-9D)(53) and the EuroQol 5D-Y (EQ-5D-Y) (54). Both measures are validated and child specific (55-57). The PBMs will be incorporated into the human factors assessment battery (Table 3) -- participants' health status will be elicited routinely during each scheduled psychosocial assessment. We also anticipate that a major HRQOL benefit of closed-loop insulin delivery will derive from improved HbA1c levels over the long term. Starting from the HbA1c levels achieved at the study endpoint, those health benefits will be modelled forward in time using capabilities developed for the Future Americans Model and other published work (58; 59).

14.12 Interim analysis

No interim efficacy analyses will be performed.

14.13 Sample Size and Power Calculations

Data from the JDRF Continuous Glucose Monitoring Randomized Clinical Trial (CGM RCT) from subjects meeting the eligibility criteria for the current trial were used to project the distribution of baseline and 6-month HbA1c. A detailed document detailing the approach of sample size is in the protocol Appendix.

Among N=53 subjects meeting the eligibility criteria in the JDRF CGM RCT (N=20 subjects 8 to 12 years of age and N=33 subjects 13 to 18 years of age), the upper limit of the confidence interval for the effective SD of HbA1c is 0.71%. With this effective SD, for a true 0.4% reduction in HbA1c, power = 85%, 2-sided type 1 error = 5%, 1:1 randomisation, total sample size is estimated to be 116.

Adding 10% for potential dropout/non-compliance results in a final total sample size of approximately 128 (64 in each treatment group).

15 Case Report Forms

The Case Report Form (CRF) is the printed, optical, or electronic document designed to record all the protocol required information to be reported to the Chief Investigator for each study participant.

CRFs will be completed in accordance with Good Clinical Practice (GCP) and ISO 15197;2013 Guidelines. The electronic CRF system provides an edit feature that records the identity of the person making the change and retains a record of the before and after values of the data field(s) in question. In addition, all eCRF changes require electronic review and signoff by the investigator associated with the visit.

If any amendments to the protocol or other study documents are made, CRFs will be reviewed to determine if an amendment to these forms is also necessary.

16 Data Management

Confidentiality of subject data shall be observed at all times during the study. Personal details for each subject taking part in the research study and linking them to a unique identification number will be held locally on a study screening log in the Trial Master File at each of the investigation centres. These details will not be revealed at any other stage during the study, and all results will remain anonymous. The study identification number will be used on the case report forms and on all the blood and serum samples that are collected throughout the study. Names and addresses will not be used. Collected samples will be stored securely and locked away. Only researchers directly involved in the study will have access to the samples.

Electronic data will be stored on password-protected computers. All paper records will be kept in locked filing cabinets, in a secure office at each of the investigation centres. Only members of the research team and collaborating institutions will have password access to the anonymised electronic data. Only members of the research teams will have access to the filing cabinet. Paper copies of the data will be stored for 15 years.

Direct access to the source data will be provided for monitoring, audits, REC/IRB review and regulatory authority inspections during and after the study. The fully anonymised data may be shared with third parties (EU or non-EU based) for the purposes of advancing management and treatment of diabetes.

Appropriate procedures agreed by the Chief Investigator and Principal Clinical Investigators will be put in place for data review, database cleaning and issuing and resolving data queries.

17 Study Management

17.1 Data Safety Monitoring Board (DSMB)

An independent Data Safety Monitoring Board (DSMB) will be established. The DSMB will be informed of all serious adverse events, including severe hypoglycaemia and DKA, and any unanticipated adverse device effects/events as they occur during the study. The DSMB will review compiled adverse event data at periodic intervals. The DSMB will report to the NIDDK any safety concerns and recommendations for suspension or early termination of the investigation. Details regarding review will be documented in separate DSMB procedural documentation.

17.2 Study Management Committee

A study management committee consisting of the Chief Investigator, Study Coordinators, and Study Data Manager will meet monthly to discuss the operational aspects of the study. The Principal Clinical Investigators may also participate. Meetings could be conducted via phone/teleconference.

17.3 Study Monitoring

Designated personnel from the Coordinating Centre will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements. Adverse events will be prioritized for monitoring.

A risk-based monitoring (RBM) plan will be developed and revised as needed during the course of the study. The data of most importance for monitoring at the site are participant eligibility and adverse events. Therefore, the RBM plan will focus on these areas. As much as possible, remote monitoring will be performed in real-time with on-site monitoring performed to evaluate the verity and completeness of the key site data. Elements of the RBM may include:

- Qualification assessment, training, and certification for sites and site personnel
- Oversight of Institutional Review Board (IRB) coverage and informed consent procedures
- Central (remote) data monitoring: validation of data entry, data edits/audit trail, protocol review of entered data and edits, statistical monitoring, study closeout
- On-site monitoring (site visits): source data verification, site visit report
- Device accountability
- Communications with site staff
- Patient retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

JCHR representatives or their designees may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study.

18 Responsibilities

18.1 Chief Investigator

The Chief Investigator (CI) is the person with overall responsibility for the research and all ethical applications will be submitted by the CI. The CI is accountable for the conduct of the study and will ensure that all study personnel are adequately qualified and informed about the protocol, any

amendments to the protocol, the study treatments and procedures and their study related duties. The CI should maintain a list of appropriately qualified persons to whom he/she has delegated specified significant study-related duties.

18.2 Principal Clinical Investigators

The Principal Clinical Investigators at each investigation centre will be responsible for the day-to-day conduct of the clinical aspects of the study.

18.3 Study Coordinators

The Study Coordinators will provide day-to-day support for the sites and provide training through Principal Investigator meetings, site initiation and routine monitoring visits.

19 Ethics

The study will be conducted in accordance with the Declaration of Helsinki Ethical Principles for Medical Research involving Human Subjects (October 2000).

19.1 Research Ethics Committee and Institutional Review Board

Prior to commencement of the study, the protocol, any amendments, subject information and informed consent and assent forms, any other written information to be provided to the subject, subject recruitment procedures, current investigator CVs, and any other documents as required by the Research Ethics Committee (REC) or Institutional Review Board (IRB) will be submitted. Written approval will be obtained from the REC/IRB prior to the commencement of the study. Any additional requirements imposed by the REC/IRB or regulatory authority shall be followed.

19.2 Informed Consent of Study Subjects

In obtaining and documenting informed consent, the investigator will comply with the applicable regulatory requirements and will adhere to GCP standards and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the start of the study, the Investigator will obtain favourable ethical opinion of the written informed consent form, assent form and any other written information to be provided to subjects.

Subjects will be given full verbal and written information regarding the objectives and procedures of the study and the possible risks involved. The study team will avoid any coercion or undue improper inducement of the subject to participate and subjects will be given ample time to consider participation in the study. Subjects will be informed about their right to withdraw from the study at any time.

The subject and/or their legal representative will be informed in a timely manner should any new information become available during the course of the study that may affect their well-being, safety and willingness to participate in the study.

Written consent/assent will be obtained from participants and/or guardians/family members according to REC/IRB requirements. The signed informed consent forms will be photocopied, originals filed in the Investigator's Site File, and a copy placed in the patient's notes and a copy given to the subjects.

20 Amendments to the Protocol

Any substantial amendments to the protocol and other documents shall be notified to, and approved by, the Research Ethics Committee or Institutional Review Board, and the regulatory authority, prior to implementation as per nationally agreed guidelines.

21 Deviations from the Protocol

Deviations from the protocol should not occur without prior approval of the REC/IRB or sponsor except under emergency circumstances, to protect the rights, safety and well-being of subjects. If deviations do occur, they will be documented, stating the reason and the date, the action taken, and the impact for the subject and for the study. The documentation will be kept in the Investigator's Site File. Deviations will be logged electronically and will require chief investigator or local principal investigator acknowledgement and sign-off.

Deviations affecting the subject's rights, safety and well-being or the scientific integrity of the study will be reported to the REC/IRB and sponsor as soon as possible/ in a timely manner, following nationally-agreed guidelines.

22 Timetable

The study is expected to start enrolling participants in June 2017, complete clinical follow up in September 2019, and report results in December 2019.

23 Reports and Publications

Data will be submitted for publication in internationally peer-reviewed scientific journals; members of the investigator group will all be co-authors. The privacy of each subject and confidentiality of their information shall be preserved in reports and publication of data.

24 Retention of Study Documentation

Subject notes must be kept for the maximum time period as permitted by each individual site. Other source documents and the Investigator's Site File must be retained for at least 15 years, in line with the Data Protection Act 1998. The Principal Investigator will archive the documentation pertaining to the study after completion or discontinuation of the study.

25 Indemnity Statements

The clinical investigators are indemnified to cover negligent harm to patients participating in the study by their membership of medical defence organisations.

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Appendix A. Sample Size Calculations

The planned study will be two parallel groups with HbA1c at 6 months as the primary outcome. The enrolled subjects would meet the following inclusion criteria:

- 6[1] to 18 years of age
- Insulin pump users with type 1 diabetes
- Time since diagnosis > 6 months
- Insulin therapy > 6 months
- Baseline HbA1c between 7.5%[2] and 10%.

A 2 to 8 week run-in period will precede randomization in order to document a minimum amount of system use.

To estimate the total sample size, data from the JDRF CGM RCT were used. There were N=53 subjects (N=20 subjects 8 to 12 years of age and N=33 subjects 13 to 18 years of age) at enrollment who met the criteria listed above and were randomized to the control group (no CGM use).

Power is increased by including baseline HbA1c as a covariate in the analysis, which results in a lower effective estimated standard deviation as can be seen in Table A1.

Table A1. JDRF CGM Trial – Mean and SD of HbA1c at 6[a] months in the control group (N=53).

Parameter	Estimate	95% Confidence Limits	
Mean	7.80%	7.60%	8.00%
SD	0.73%	0.61%	0.90%
Correlation[b]	0.63	0.43	0.77
Effective SD[c]	0.57%	0.48%	0.71%

a – The data at 6 months are being used as a proxy for 12 months because the control group initiated CGM at 6 months.
b – Estimated correlation between baseline HbA1c and HbA1c at 6 months.
c – For a model adjusting for baseline as a covariate.

Sample size estimates were calculated under various scenarios for the treatment effect and SD. The range for the SD was taken from the confidence interval for the effective SD in Table A1.

Table A2. Required total sample size[a,b] assuming parallel groups, normal distribution for the treatment effect, a 2-tailed test, and a type I error = 5%.

SD	Power	Treatment Effect		
		0.3%	**0.4%**	**0.5%**
0.48%[c]	**80%**	N=82	N=48	N=32
	85%	N=94	N=54	N=36
	90%	N=110	N=64	N=42
0.57%[d]	**80%**	N=116	N=66	N=44

[1] Eligibility for the JDRF CGM RCT was >8 years old at enrolment

[2] The original sample size was based on HbA1c of 7.5-10%. Protocol v7.0 lowered the HbA1c range to 7.0% to broaden the population being studied

	85%	N=134	N=76	N=50
	90%	N=156	N=88	N=58
0.71%[e]	**80%**	N=178	N=102	N=66
	85%	N=204	N=116	N=76
	90%	N=238	N=134	N=88

a – Total sample size for both treatment groups. Half would be randomized to each group.
b – Does not account for dropout or noncompliance. Would typically add 10% - 15% to these numbers.
c – Lower limit of the confidence interval for the effective SD after adjusting for baseline (see Table A1).
d – Point estimate for the effective SD after adjusting for baseline (see Table A1).
e – Upper limit of the confidence interval for the effective SD after adjusting for baseline (see Table A1).