Clinical Study Protocol

Study Title: **An open-label, multi-centre, randomised, single-period, parallel design study to assess the efficacy, safety, utility and psychosocial effect of 12 week day and night automated closed loop glucose control combined with pump suspend feature compared to sensor augmented insulin pump therapy in youth and adults with type 1 diabetes with sub-optimal glucose control under free living conditions**

Short Title: **Home testing of day and night closed loop with pump suspend feature (APCam11)**

Protocol Version: **5.1** **16 June 2017**

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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 design study to assess the efficacy, safety, utility and psychosocial effect of 12 week day and night automated closed loop glucose control combined with pump suspend feature compared to sensor augmented insulin pump therapy in youth and adults with type 1 diabetes with sub-optimal glucose control under free living conditions" version 5.1 dated 16 June 2017 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

SITE SIGNATURE PAGE (Cambridge, UK)

I have read the attached protocol entitled " An open-label, multi-centre, randomised, single-period, parallel design study to assess the efficacy, safety and utility of 12 week overnight automated closed loop glucose control combined with threshold based pump interruption compared to sensor augmented insulin pump therapy in youth and adults with type 1 diabetes with sub-optimal glucose control under free living conditions" Version 5.1 dated 16 June 2017, and agree to abide by all provisions set forth therein.

I agree to comply with the conditions and principles of Good Clinical Practice as outlined in the European Clinical Trials Directives 2001/20/EC and the GCP Directive 2005/28/EC.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

Signature …….. Date…….

Professor David Dunger, Principal Clinical Investigator

SITE SIGNATURE PAGE (Cambridge, UK)

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Dr Mark Evans, Principal Clinical Investigator

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Signature …….. Date…….

Dr Daniela Elleri, Principal Clinical Investigator

SITE SIGNATURE PAGE (Leeds, UK)

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Signature …… Date…….

Dr Fiona Campbell, Principal Clinical Investigator

SITE SIGNATURE PAGE (Manchester, UK)

I have read the attached protocol entitled " An open-label, multi-centre, randomised, single-period, parallel design study to assess the efficacy, safety and utility of 12 week overnight automated closed loop glucose control combined with threshold based pump interruption compared to sensor augmented insulin pump therapy in youth and adults with type 1 diabetes with sub-optimal glucose control under free living conditions" Version 5.1 dated 16 June 2017, and agree to abide by all provisions set forth therein.

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Signature …….. Date…….

Dr Lalantha Leelarathna, Principal Clinical Investigator

Table of Contents

1 List of Abbreviations and Relevant Definitions

ADA	American Diabetes Association
ADE	Adverse Device Effect
ASADE	Anticipated Serious Adverse Device Effect
AE	Adverse Event
AP	Artificial Pancreas
AR	Adverse Reaction
AUC	Area Under the Curve
CE	Conformité Européenne (CE-mark)
CGM	Continuous Glucose Monitoring
CRF	Case Report Form
CSII	Continuous subcutaneous insulin infusion
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
IDE	US Investigational Device Exemption
IRB	Institutional Review Board
ISPAD	International Society for Pediatric and Adolescent Diabetes
MHRA	Medicine and Healthcare products Regulatory Agency
NGP	Next generation insulin pump (Medtronic)
i.v.	Intravenous
MPC	Model-Predictive-Control
R & D	Research and Development
REC	Research Ethics Committee
RF	Radio Frequency
s.c.	Subcutaneous
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Sensor Augmented Pump Therapy
T1D	Type 1 Diabetes Mellitus
USADE	Unanticipated Serious Adverse Device Effect

2 Study Synopsis

Title of clinical trial	An open-label, multi-centre, randomised, single-period, parallel design study to assess the efficacy, safety, utility and psychosocial effect of 12 week day and night automated closed loop glucose control combined with pump suspend feature compared to sensor augmented insulin pump therapy (SAP) in youth and adults with type 1 diabetes with sub-optimal glucose control under free living conditions
Short title	Day and night closed loop with pump suspend feature in sub-optimally controlled type 1 diabetes under free living conditions
Sponsors name	UK - University of Cambridge and Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK. USA - Jaeb Center for Health Research, USA
Medical condition or disease under investigation	Type 1 diabetes
Clinical trial phase	II/III
Purpose of clinical trial	To determine whether day and night automated closed loop glucose control combined with pump suspend feature will improve glucose control as measured by CGM time in range and reduce the burden of hypoglycaemia compared to sensor augmented insulin pump therapy.
Study objectives	**1. EFFICACY:** The objective is to assess efficacy of day and night automated closed loop glucose control combined with pump suspend feature in maintaining CGM glucose levels within the target range from 3.9 to 10 mmol/l (70 to 180mg/dl), as compared to sensor augmented insulin pump therapy. **2. SAFETY:** The objective is to evaluate the safety of day and night automated closed loop glucose control combined with pump suspend feature, in terms of episodes of severe hypoglycaemia and other adverse events. **3. UTILITY:** The objective is to determine the frequency and duration of the use of the automated closed loop system. **4. PSYCHOSOCIAL:** Subjects' and family members' perception in terms of life-style change, diabetes management and fear of hypoglycaemia will be assessed using validated questionnaires and semi-structured qualitative interviews.
Study design	An open-label, multi-centre, multi-national,

	randomised, single-period, parallel group study, contrasting day and night automated closed loop glucose control combined with pump suspend feature with sensor augmented insulin pump therapy.
Primary endpoint	• Time spent in the target glucose range (3.9 to 10mmol/l) (70 to 180mg/dl)
Secondary endpoint(s)	• Time spent below target glucose (3.9mmol/l)(70mg/dl) • Time spent above target glucose (10.0 mmol/l) (180 mg/dl) • HbA1c levels at 12 weeks • Average, standard deviation, and coefficient of variation of glucose levels • Time with glucose levels < 3.5 mmol/l (63 mg/dl) and <2.8 mmol/l (50 mg/dl) • Time with glucose levels in significant hyperglycaemia (glucose levels > 16.7 mmol/l) (300mg/dl) • Total, basal and bolus insulin dose • AUC of glucose below 3.5mmol/l (63mg/dl) • Number of pump suspend events (applicable to intervention arm) • Change in body weight from screening to end of study Secondary endpoint 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, monthly trends in glucose control and insulin delivery, relationships between compliance and glucose outcomes, differences between youth and adults in outcomes.
Safety evaluation	Frequency of severe hypoglycaemic episodes as defined by American Diabetes Association (adults and adolescents), and International Society for Pediatric and Adolescent Diabetes (children). Frequency of severe hyperglycaemia (>16.7 mmol/l)(>300mg/dl) with significant ketosis (plasma ketones >0.6mmol/l) and nature and severity of other adverse events.
Utility evaluation	Assessment of the frequency and duration of use of the closed loop system.
Psychosocial evaluation	Evaluation of subjects' response in terms of life-style change, daily diabetes management, fear of hypoglycaemia, and cognitive functions.
Sample size	84 participants randomised (42 youth and 42 adults). Each centre will aim to recruit between 05 and 20 participants

Summary of eligibility criteria	Key inclusion criteria: 1. The subject is at least 6 years or older with equal proportion of youth (6 to 21 years) and adults (22 years and older) 2. The subject has type 1 diabetes, as defined by WHO for at least 1 year or is confirmed C-peptide negative 3. The subject/carer will have been an insulin pump user for at least 3 months, with good knowledge of insulin self-adjustment as judged by the investigator 4. The subject is treated with one of the U-100 rapid acting insulin analogues only (insulin Aspart, Lispro but not Glulisine) 5. The subject/carer is willing to perform regular finger-prick blood glucose monitoring, with at least 4 blood glucose measurements taken every day 6. HbA1c ≥ 7.5% (58.5mmol/mol) and ≤ 10 % (86mmol/mol) based on analysis from local laboratory with equal proportion of subjects above and below HbA1c 8.5% (69mmol/mol) 7. The subject is literate in English 8. The subject lives with someone who is trained to administer intramuscular glucagon and is able to seek emergency assistance Key exclusion criteria: 1. Non-type 1 diabetes mellitus including those secondary to chronic disease 2. Subject is using real-time CGM on regular basis 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 hypothyroidism 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. Subjects with clinical significant nephropathy, neuropathy or proliferative retinopathy as judged by the investigator 8. Total daily insulin dose ≥ 2 IU/kg/day 9. Total daily insulin dose < 15 IU/day 10. Pregnancy, planned pregnancy, or breast feeding 11. Severe visual impairment 12. Severe hearing impairment

	13. Significantly reduced hypoglycaemia awareness in subjects 18 year and older (Gold score > 4) 14. Any episode of severe hypoglycaemia within the last 6 months 15. Subjects using implanted internal pace-maker 16. Random C-peptide > 100pmol/l with concomitant blood glucose >4 mmol/l (72 mg/dl) 17. Regular use of acetaminophen
Maximum duration of study for a subject	18 weeks
Recruitment	The subjects will be recruited through the paediatric and adult diabetes outpatient clinics at each centre.
Consent	Written consent/assent will be obtained from participants and/or guardians according to REC/IRB requirements.
Screening assessment	Eligible participants will undergo a screening evaluation where blood samples for full blood count, renal, liver, thyroid function and anti-transglutaminase antibodies with IgA levels will be taken (if not done in the previous 3 months). Random C-peptide, glucose and HbA1c will also be measured, and a urine pregnancy test in females of child-bearing potential. Questionnaires investigating participants' quality of life, psychosocial functioning and response to their current treatment will be distributed.
Study Training	Training sessions on the use of study CGM, insulin pump (and closed loop system for those randomised to the intervention group) will be provided by the research team. Training session on the use of real-time CGM and on how to interpret real-time and retrospective stored data will be provided to all subjects/carers using written material.
Run-in Period	During a 4 week run-in period, subjects will use study CGM and insulin pump. The research team will contact subject once weekly during the run-in period, and subjects will also be able to contact the research team for support and treatment optimisation as necessary. For compliance and to assess the ability of the subject to use the CGM and study pump safely, at least 12 days of CGM data need to be recorded and safe use of study insulin pump demonstrated during the last 14 days of run-in period.
Competency assessment	Competency on the use of study insulin pump and study CGM will be evaluated using a competency assessment tool developed by the research team. Further training may be delivered as required.

Randomisation	Eligible subjects will be randomised using randomisation software to the use of real-time CGM and pump suspend feature combined with day and night closed loop or to sensor augmented insulin pump therapy.
1. Automated day and night closed loop insulin delivery (intervention arm) combined with pump suspend feature (interventional arm)	At the start, a blood sample will be taken for the measurement of HbA1c and a urine pregnancy test in females of child-bearing potential. A subset of participants will be interviewed to enable their historical diabetes management practices, everyday work and family lives, and their initial expectations of using closed loop technology to be captured and explored in-depth. Subjects will be admitted to the clinical facility on Day 1. Training on the use of closed loop and pump suspend feature will be provided by the research team. During the next 2-4 hours patient will operate the system under the supervision of the clinical team. Competency on the use of closed loop system will be evaluated. Subjects will use closed loop and pump suspend feature for 12 weeks.
2. Sensor augmented insulin pump therapy **(control arm)**	A blood sample will be taken for the measurement of HbA1c and a urine pregnancy test in females of child-bearing potential. Subjects will use sensor augmented insulin pump therapy without pump suspend feature for 12 weeks.
End of study assessments	- A blood sample will be taken for measurement of HbA1c. - Validated questionnaires evaluating the impact of the devices employed on life change, diabetes management will be completed. - Follow-up interviews will be undertaken with the subset of participants/family members at the end of the closed loop intervention.
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 or urine ketones if their finger prick glucose is above 14.0mmol/l (250mg/dl) in the morning on waking, as part of the safety assessment for hyperglycaemia. 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 participation of a subject 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 7. Technical grounds (e.g. subject relocates)

3 Summary

The main study objective is to determine whether day and night automated closed loop glucose control combined with pump suspend feature will improve glucose control and reduce the burden of hypoglycaemia compared to sensor augmented insulin pump therapy alone.

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

It is expected that up to 100 subjects, aiming for 84 randomised subjects [42 youth (6 to 21 years), and 42 adults (22 years and older)], with type 1 diabetes will be recruited through paediatric and adult outpatient diabetes clinics in each of the investigation centres. Subjects who drop out within the first four weeks of the intervention may be replaced. Subjects who dropout prior to the final visit will receive an exit survey. Participants will all be on subcutaneous insulin pump therapy and will have proven competencies both in the use of the study insulin pump and the study CGM device.

Subjects in the intervention group will receive appropriate training in the safe use of closed loop insulin delivery system and pump suspend 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 time spent in target range between 3.9 and 10.0mmol/l as recorded by CGM. Secondary outcomes are between group differences in HbA1c levels at the end of treatment period, 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.

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, 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).

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 that are compliant with using the device (14-17).

4.1 Sensor-Augmented Insulin Pump Therapy

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 (18). 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 (19).

4.2 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 (20).

4.3 Threshold Based Pump Interruption

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 (21). Two relatively small out-patient studies of short duration (21 children for 6 weeks (22) and 31 adults (23) 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 (24).

4.4 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 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 (25).

The closed loop model predictive control (MPC) algorithm has been studied extensively using *in silico* testing utilising a simulator developed by members of the study team (26). The simulations suggested a reduced risk of nocturnal hypoglycaemia and hyperglycaemia with the use of the MPC algorithm (27).

4.5 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. 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 (28) 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.

4.6 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 a MPC 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 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 (29).

4.7 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 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 (Appendix 1) (30). Closed loop was activated over at least 4hours 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.

4.8 Overnight Closed loop Study in Adults with Type 1 Diabetes in Home Setting

We have recently 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. (Appendix 2) (31) . 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].

4.9 Day and Night Closed loop Studies in Adults and Adolescents with Type 1 Diabetes in Home Setting

We have completed a seven day, day and night home study in 17 adults in a multicentre, multi-national crossover study design (Appendix 3) (32). 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). A one week single centre study in children and adolescents is underway (N = 12).

4.10 Automated Closed loop System (FlorenceM) to be used in the Present Study

The automated closed loop system (FlorenceM) will consist of:

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

- An Android smartphone containing the Cambridge model predictive algorithm and communicating wirelessly with the insulin pump using a proprietary translator device.

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

Figure 1: Representative design of the proposed FlorenceM automated closed loop system

4.11 Rationale for the Current Study

No study thus far has combined the pump suspend feature 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 pump suspend 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 multiple weeks in a relatively large group of adults and children with type 1 diabetes in a multi-centre and multi-national setting to demonstrate the generalisability of results.

5 Objectives

5.1 Efficacy

The objective is to assess efficacy of day and night automated closed loop glucose control combined with pump suspend feature in maintaining glucose levels within the target range from 3.9 to 10.0mmol/l based on subcutaneous continuous glucose monitoring (CGM), as compared with sensor augmented insulin pump therapy alone.

5.2 Safety

The objective is to evaluate the safety of day and night automated closed loop glucose control combined with pump suspend feature in terms of episodes of severe hypoglycaemia and other adverse events.

5.3 Utility

The objective is to determine the frequency and duration of use of the automated closed loop system.

5.4 Psychosocial

Subjects' and family members' perception in terms of life-style change, diabetes management will be assessed using validated questionnaires and semi-structured qualitative interviews.

6 Study Design

An open-label, multi-centre, multi-national, randomised, single-period parallel study, in youth (6 to 21 years) and adults (22 years and older) with type 1 diabetes on insulin pump treatment will contrast day and night automated closed loop glucose control combined with pump suspend feature with sensor augmented insulin pump therapy alone.

It is expected that up to 100 youths and adults with type 1 diabetes with T1D will be recruited, aiming for 84 randomised subjects. Subjects who drop out within the first four weeks of the intervention may be replaced. Subjects who dropout prior to the final visit will receive an exit survey. The study flow chart is outlined in Figure 2.

7 Study Subjects

7.1 Study Population

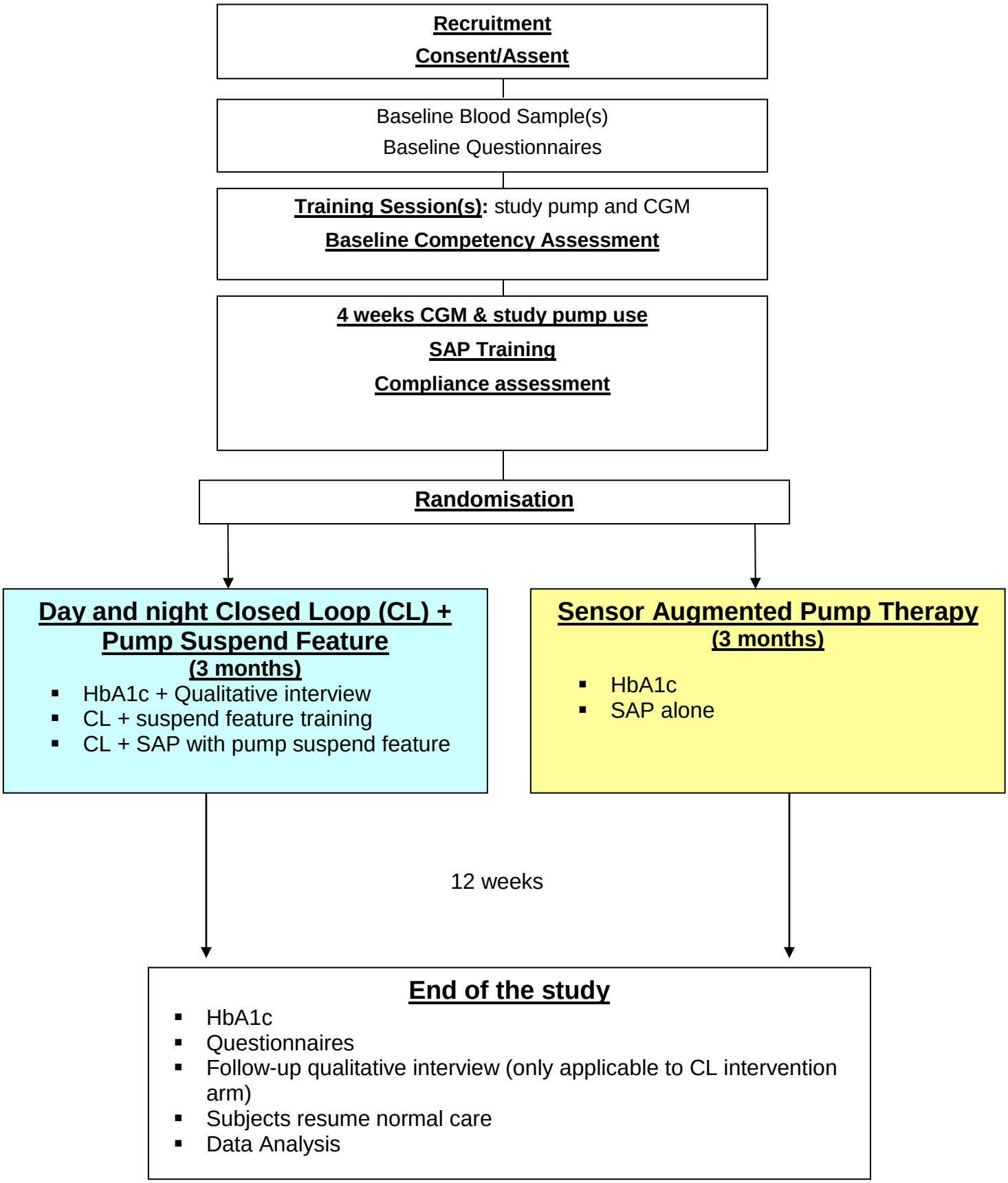
This is a multicentre and multinational study and recruitment will take place at the following centres:

1. Addenbrooke's Hospital, Cambridge, UK (adults and youth)
2. Royal Hospital for Sick Children, Edinburgh, UK (youth)
3. Leeds Teaching Hospital, Leeds, UK (youth)
4. Manchester Royal Infirmary, Manchester, UK (adults)
5. International Diabetes Center at Park Nicollet, Minneapolis, USA (adults and youth)
6. Barbara Davis Center for Childhood Diabetes, Aurora, USA (adults)

Up to a total of 50 youths aged 6 to 21 years and 50 adults aged 22 years and older with type 1 diabetes on insulin pump therapy will be recruited. Each centre will aim to recruit between 10 to 20 participants but may recruit more if needed

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.

Figure 2. Study flow chart



7.2 Inclusion Criteria

1. The subject is at least 6 years or older [with equal proportion of youth (6 to 21 years) and adults (22 years and older)]
2. The subject has type 1 diabetes, as defined by WHO for at least 1 year or is confirmed C-peptide negative
3. The subject will have been an insulin pump user for at least 3 months, with good knowledge of insulin self-adjustment as judged by the investigator
4. The subject is treated with one of the U-100 rapid acting insulin analogues only (insulin Aspart, Lispro but not Glulisine)
5. The subject/carer is willing to perform regular capillary blood glucose monitoring, with at least 4 blood glucose measurements taken every day
6. Screening HbA1c ≥ 7.5% (58.5mmol/mol) and ≤ 10 % (86mmol/mol) based on analysis from local laboratory or equivalent [with equal proportion of subjects above and below HbA1c 8.5% (69mmol/mol)]
7. The subject is literate in English
8. The subject is willing to wear glucose sensor
9. The subject is willing to wear closed loop system at home
10. The subject is willing to follow study specific instructions
11. The subject is willing to upload pump and CGM data at regular intervals
12. The subject is willing to restrict alcohol consumption to ≤ 2 units per day throughout the study period
13. Female subjects of child bearing age should be on effective contraception and must have a negative urine-HCG pregnancy test at screening.
14. The subject lives with someone who is trained to administer intramuscular glucagon and is able to seek emergency assistance.
15. The subject has access to WiFi at home.

7.3 Exclusion Criteria

1. Non-type 1 diabetes mellitus including those secondary to chronic disease
2. Subject using real-time CGM on regular basis in preceding 3 months
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 hypothyroidism
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. Adults: one or more episodes of severe hypoglycaemia as defined by American Diabetes Association (33) in preceding 6 months; Youth: one or more episodes of of severe hypoglycaemia during the previous 6 months (Adults and 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. Random C-peptide > 100pmol/l with concomitant blood glucose >4 mmol/l (72 mg/dl)
10. 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. Significantly reduced hypoglycaemia awareness in subjects 18 year and older (screening Gold score > 4)
18. Subjects using implanted internal pace-maker
19. Patients with medically documented allergy towards the adhesive (glue) of plasters or Subject is unable to tolerate tape adhesive in the area of sensor placement
20. 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)
21. Subject is currently abusing illicit drugs
22. Subject is currently abusing prescription drugs
23. Subject is currently abusing alcohol
24. Subject is using pramlintide (Symlin) or other commonly used hypoglycaemic agents including sulphonylureas, biguanides, DPP4-inhibitors, GLP-1 agonists, SGLT-2 inhibitors at time of screening
25. Subject has elective surgery planned that requires general anaesthesia during the course of the study
26. Subject is a shift worker with working hours between 10pm and 8am
27. Subject has a sickle cell disease, haemoglobinopathy; or has received red blood cell transfusion or erythropoietin within 3 months prior to time of screening

28. Subject plans to receive red blood cell transfusion or erythropoietin over the course of study participation
29. Subject diagnosed with current eating disorder such as anorexia or bulimia
30. Subject plans to use significant quantity of herbal preparations (use of over the counter herbal preparation for 30 consecutive days or longer period during the study) or significant quantity of vitamin supplements (four times the recommended daily allowance used for 30 consecutive days or longer period during the study) known to affect glucose metabolism and/or blood glucose levels during the course of their participation in the study

7.4 Randomisation

Eligible subjects will be randomised using central randomisation software to the use of day and night closed loop combined with pump suspend feature or to sensor augmented insulin pump therapy. The randomisation will be stratified at each centre by HbA1c groups [equal proportion of below and above 8.5% (69mmol/mol)]. Each site will recruit only in one of the two age groups [youth (6 to 21 years) or adults (22 years and older)].

8 Methods under Investigation

8.1 Name and Description of the Method of Investigation

The investigational treatment is the FlorenceM, see section 4.10, 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 pump suspend feature.

8.3 Method of Administration

The closed loop system consists of components directly attached to the patient, which are the CGM 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.

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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 study CGM device, the study pump and where appropriate the closed loop system. Competency assessments of the participants' capability to use study devices and 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 pump suspend 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, and performed at following sites:

1. Addenbrooke's Hospital, Cambridge, UK
2. Royal Hospital for Sick Children, Edinburgh, UK
3. Leeds Teaching Hospital, Leeds, UK
4. Manchester Royal Infirmary, Manchester, UK
5. International Diabetes Center at Park Nicollet, Minneapolis, USA
6. Barbara Davis Center for Childhood Diabetes, Aurora, USA

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

The study includes up to 11 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 an in-patient 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 18 weeks.

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 sensor augmented pump therapy alone (control group).

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

	Visit/ contact	Description	Start relative to previous / next Visit / Activity	Duration
	Visit 1	Recruitment visit: Consent, HbA1c, screening bloods & questionnaires, urine pregnancy test	-	1-4 hours
Training & Run-in (4 wks)	Visit 2	Insulin pump training and the initiation study pump Competency assessment	Within 1 to 3 weeks of Visit 1	3-4 hours
	Visit 3	CGM training Initiation of CGM Weekly contact via phone/email Competency assessment	Within 3 to 7 days of Visit 2	2-3 hours
	*Visit 4	Review pump and CGM data & optimisation of treatment & compliance assessment & randomisation	After 4 weeks of Visit 3	<1 hour
	Contact	Qualitative interview (with a subset of participants/family members)	After randomisation but before Visit 5	<1 hour
CL + LGS Intervention (3 months)	Visit 5	CL initiation at clinic/home - urine pregnancy test - CL and suspend feature training - competency assessment - HbA1c	Within 1 week of Visit 3	2-6 hours
	* Visit 6	Review use of study devices	After 24-48 hours of Visit 5	<1 hour
	**Visit 7	Review use of study devices	After 1 week of Visit 5	<1 hour
	*Visit 8	Review pump and CGM data	After 1 week of Visit 7	<1 hour
	*Visit 9	End of first month: Review pump and CGM data	After 2 weeks of Visit 8	<1 hour
	*Visit 10	End of second month: Review pump and CGM data	After 4 weeks of Visit 9	<1 hour
	Visit 11	End of closed loop treatment arm (3 months): HbA1c, Complete questionnaires, and follow-up qualitative interviews	After 4 weeks of Visit 10	1-3 hours

*Could be done via phone / e-mail in UK. Follow-up by phone is mandatory in US only.
** Could be done via phone / e-mail in UK. In-person visit mandatory in US only.

Table 2. Schedule of study visits / phone contacts when the participant is randomised to sensor augmented pump.

	Visit/ contact	Description	Start relative to previous / next Visit / Activity	Duration
	Visit 1	Recruitment visit: Consent HbA1c, screening bloods & questionnaires, , urine pregnancy test	-	1-4 hours
Training & Run-in (4 wks)	Visit 2	Insulin pump training and the initiation study pump Competency assessment	Within 1 to 3 weeks of Visit 1	3-4 hours
	Visit 3	CGM training Initiation of CGM Weekly contact via phone/email Competency assessment	Within 3 to 7 days of Visit 2	2-3 hours
	*Visit 4	Review pump and CGM data & optimisation of treatment & compliance assessment & randomisation	After 4 weeks of Visit 3	<1 hour
SAP Intervention (3 months)	Visit 5	SAP initiation at clinic/home - urine pregnancy test - SAP training - competency assessment - HbA1c	Within 1 week of Visit 4	2-6 hours
	*Visit 6	Review use of study devices	After 24-48 hours of Visit 5	<1 hour
	**Visit 7	Review use of study devices	After 1 week of Visit 5	<1 hour
	*Visit 8	Review pump and CGM data	After 1 week of Visit 7	<1 hour
	*Visit 9	End of first month: Review pump and CGM data	After 2 weeks of Visit 8	<1 hour
	*Visit 10	End of second month: Review pump and CGM data	After 4 weeks of Visit 9	<1 hour
	Visit 11	End of SAP treatment arm (3 months): HbA1c, Complete questionnaires.	After 4 weeks of Visit 10	1-3 hours

*Could be done via phone / e-mail in UK. Follow-up by phone is mandatory in US only.
** Could be done via phone / e-mail in UK. In-person visit mandatory in US only.

9.2 Recruitment Visit and Screening Assessment (Visit 1)

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
- record of current insulin therapy
- urine pregnancy test (females of child-bearing potential)
- record of occupation and educational attainment

9.2.1 Screening Blood Sampling

Blood samples will be taken for the screening measurement of random C-peptide, glucose, and HbA1c (measured at a local laboratory). Liver, renal, thyroid function, full blood count, anti-tranglutaminase antibodies and IgA will also be evaluated (if not done in previous 3 months). Less than 15 ml of whole blood will be taken from each participant.

9.2.2 Questionnaires at Screening

Validated questionnaires will be distributed to assess quality of life before entering the study.

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9.3 Training Session on the use of the Study Insulin Pump (Visit 2)

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
- Sick day rules
- Dealing with hypo and hyperglycaemia
- Uploading pump data

Written easy to use guidelines for the operation of insulin pump will be provided.

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 Training Session on Continuous Glucose Monitoring (Visit 3)

This session will cover key aspects of the study CGM and particular attention will be paid to the following areas:

- Insertion and initiation of sensor session
- Using sensor menu of the insulin pump & sensor calibrations
- Use of software to analyse CGM data
- Use of CGM data to optimise treatment
- Uploading CGM data using Carelink or similar software

Written guidelines for the operation and use of CGM device will be provided.

UK only

This session will be conducted by a professional pump educator and possibly a member of the study team. Competency on the use of CGM will be made.

US only

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

9.5 Run-in Period (ends at Visit 4)

The subject will use study insulin pump and study CGM over the run-in period. The subject will be invited to attend the research centre or contacted via e-mail / telephone at the end of the run-in period. Study insulin pump and CGM device will be downloaded and data may be used for treatment optimisations. There should be a minimum of four weeks run-in period for all subjects (end of Visit 3 to end of Visit 4). Subjects will be contacted once weekly during the run-in period via phone/email to troubleshoot any problems. Subjects will also be able to contact the research team in between these weekly contacts for support or to provide any additional training on the devices as required.

9.5.1 Compliance Assessment

During Visit 4, participant's compliance of using the study CGM and study pump over preceding 14 days will be assessed. To proceed with the study subject needs to demonstrate correct use of study insulin pump including use of bolus calculator over 75% of meal boluses and at least 12 days' worth of CGM data during last 14 days of run-in period. In addition, subject should carry out upload of CGM and pump data at weekly intervals. If subject fails to demonstrate compliance, the study will be terminated and subject will be removed from the study.

Subject randomisation for the treatment intervention will take place during the week following Visit 4. Maximum period allowed between Visit 3 and Visits 5 is six weeks with a minimum of four weeks.

9.6 Randomisation

Eligible subjects who have gained confidence in the use of the study insulin pump and the study CGM system, as assessed by the research team, will be randomised centrally using a randomisation based on a computer-generated random code. Randomisation will take place centrally, with an independent person being responsible for the randomisation sequence. Subjects will be allocated to one of the two intervention arms: three months use of day and night closed loop combined with pump suspend feature or three months use of sensor augmented insulin pump therapy without pump suspend feature.

9.7 Baseline Qualitative Interview

A subset of subjects/guardians randomised to the use of day and night closed loop with pump suspend feature will be invited for a qualitative interview (face to face or telephone interview) at a mutually convenient time, see section 12.2.2. Whenever possible, the interview will occur before Visit 8.

9.8 Visit 5 (Initiation of Study Treatment; within 1 Week of Visit 4 and at least 4 Weeks after Visit 3)

Subject will arrive at the clinical facility at the agreed time. Urine pregnancy test will be performed on arrival for all females of child bearing age and all subjects will have a blood test for HbA1c. Body weight measurement will be made. Subjects will be provided with necessary training on use of study devices according to randomisation. Competency assessment will be made. During the three months home treatment period, the subject will be asked to upload the study insulin pump and CGM at weekly intervals.

During the three months home closed loop treatment, the subject is allowed to drive while adhering to usual precautions and country specific rules and regulations.

During the first 2 weeks of each study period subject will be advised against international travel. During the rest of the study period, participants are allowed to travel internationally according to guidelines provided in the participant information sheet.

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 Visit 8 in subject's home.

9.8.1 Day and Night Closed loop with Pump Suspend Feature

Those subjects randomised to closed loop intervention with pump suspend feature will receive training required for safe and effective use of the closed loop system and pump suspend feature. This will include training on connection and disconnection of the closed loop system, use of pump suspend feature 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 provided with a meal according to participant's choice and will be required to deliver meal bolus for the given meal. Subjects will be allowed to go home once competency assessment has been satisfactorily completed with the study staff. Participants are expected to use the closed loop and pump suspend feature at all times during the three months intervention period.

9.8.2 Sensor-Augmented Pump Therapy

Those subjects randomised to sensor augmented insulin pump therapy will receive training on the effective use of real-time CGM for optimisation of insulin therapy. Rest of the visit is identical to closed loop group as described in section 9.8.1.

9.9 Visit 6 – 24-48 hours after Starting Study Treatment

The subject will be contacted via telephone/e-mail or invited to attend the research centre approximately 24-48 hours after Visit 5 once study treatment has begun. US site must complete the contact by phone at minimum. The purpose of this visit will be to review the use of study devices and to provide any additional training required.

9.10 Visit 7 – 1 Week after Starting Study Treatment

The subject will be invited to attend the research centre approximately 1 week after Visit 5. The purpose of this visit will be to review the use of study devices 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.

9.11 Visit 8 – 2 Weeks after Starting Study Treatment

The subject will either be contacted via telephone/e-mail or seen in the clinic 1 week after Visit 7. The purpose of this visit would be to troubleshoot any problems. The subject is free to optimise further treatment but no active treatment optimisation will be undertaken by the study team.

9.12 Visit 9 – End of first month on Study Treatment

The subject will be contacted via telephone/e-mail or invited to attend the research centre approximately 1 month after start of study treatment to review the use of study devices. Any additional device training required will be provided. The subject is free to optimise further treatment but no active treatment optimisation will be undertaken by the study team.

9.13 Visit 10 – End of Second Month on Study Treatment

The subject will be contacted via telephone/e-mail or invited to attend the research centre approximately 1 month after Visit 9 to review the use of study devices. The subject is free to optimise further treatment but no active treatment optimisation will be undertaken by the study team.

9.14 Visit 11 – End of Study (3 months)

The subject will be invited to attend the research centre approximately 1 month after Visit 10. This would be the end of three months home study period and subjects will return to their normal diabetes care. Insulin pump and CGM device data will be downloaded. The subject will have a blood test for the HbA1c. Body weight measurement will be made. Subject will be asked to complete questionnaires as outlined in section 12.2. Subset of subjects/family members who completed CL intervention arm will be invited to perform a qualitative interview with the trained personnel. Subjects will be asked to return the study devices used, and will revert to their conventional insulin therapy by switching back to the insulin pump they were using before entering the study.

9.15 Participant Withdrawal Criteria

The following pre-randomisation withdrawal criteria will apply:

1. Subject is unable to demonstrate safe use of study insulin pump and / or CGM during run-in period as judged by the investigator
2. Subject fails to demonstrate compliance as mentioned in section 9.5.1 with study insulin pump and / or CGM during run-in period

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

3. Subjects 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. Any severe hypoglycaemia event related to use of the closed loop system
6. Two severe hypoglycaemia events unrelated to the use of the closed loop system
7. 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. Subject becomes pregnant during the study period
10. Allergic reaction to insulin
11. Allergic reaction to adhesive surface of infusion set or glucose sensor
12. If patient continues to use pump suspend feature in the control group despite advice to the contrary

Subjects who are withdrawn for reasons stated in (4) to (12) will be invited to provide blood sample at the end of the planned study intervention for the assessment of HbA1c.

9.16 Study Stopping Criteria

The study may be stopped if three consecutive participants withdraw on safety grounds or on the advice of an independent Data Safety and Monitoring Board (DSMB).

9.17 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.

9.18 Subject reimbursement

The study will provide the CGM device, insulin pump, closed loop components, related consumables, and glucose test strips. A study fee will be paid to reflect local practice. The amount

paid will be specified in the participant information sheet 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 outcome is the time spent in the target glucose range from 3.9 to 10.0 mmol/l (70 to 180mg/dl) based on CGM glucose levels during the 12 week free living phase.

10.2 Secondary Endpoints

Secondary endpoints include:

- HbA1c at 12 weeks
- Time spent below target glucose (3.9mmol/l) (70mg/dl)
- Time spent above target glucose (10.0 mmol/l) (180 mg/dl)
- Average, standard deviation, and coefficient of variation of glucose levels
- The time with glucose levels < 3.5 mmol/l (63mg/dl) and <2.8 mmol/l (50mg/dl)
- The time with glucose levels in the significant hyperglycaemia (glucose levels > 16.7 mmol/l) (300mg/dl)
- Total, basal and bolus insulin dose
- AUC of glucose below 3.5mmol/l (63mg/dl)
- Number of pump suspend events (applicable to intervention arm)
- Change in body weight from screening to end of study

Glucose endpoints will be based on sensor glucose.

10.3 Safety Evaluation

Safety evaluation will comprise number of episodes of severe hypoglycaemia as well as the number of subjects experiencing severe hypoglycaemia, severe hyperglycaemia (fingerprick glucose >16.7 mmol/l) (>300mg/dl) and plasma ketones >0.6mmol/l), diabetic ketoacidosis, and other adverse events. Subjects will be asked to measure blood or urine ketone levels on waking in the morning if their finger prick glucose is above 14mmol/l (250mg/dl), as part of the safety evaluation for hyperglycaemia.

10.4 Utility Evaluation

Utility evaluation is the frequency and duration of use of the closed loop system combined with pump suspend feature in the closed-loop treatment arm as well as CGM use in both treatment arms.

10.5 Psychosocial Evaluation

The subjects' response will be assessed in terms of life-style change and daily diabetes management, as evaluated by questionnaires and a semi-structured qualitative interview (only applicable to CL intervention arm and also including family members).

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 included events related to the device under investigation or the comparator or to the study procedures. For users or other persons, this definition is restricted to events related to the investigational device.

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 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.

This includes unanticipated procedure related serious adverse events; that is, serious adverse events occurring during the study procedure that are unrelated to any malfunction or misuse of the investigational medical device.

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. A device deficiency may lead to an Adverse Device Effect or Serious Adverse Device Effect. The following anticipated device deficiencies and device-related 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.

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 adult subjects, 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 Hyperglycaemia, Ketonaemia and 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.

Severe hyperglycaemic events (fingerprick glucose >300 mg/dl/16.7mmol/l and blood ketones >0.6mmol/l) will be recorded as Adverse Events. Non-severe hyperglycaemia events will not be reported or considered as adverse events.

11.2.5 Reporting of Serious Adverse Events and Serious Adverse Device Effects

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

The serious adverse event report should contain the following information*:

1. Study identifier (EudraCT number if applicable)
2. Participant's unique study number
3. Date of birth
4. Event description
5. Start date of event
6. Laboratory tests used and medical interventions used to treat the SAE
7. Planned actions relating to the event, including whether the study device was discontinued
8. Statement on the patient's current state of health
9. Reason for seriousness (i.e. death, life threatening, hospitalisation, disability/incapacity or other)
10. Evaluation of causality (including grade of relatedness) with the following (more than one may apply):
    a. the investigational treatment/medical device
    b. the clinical study/a study specific procedure
    c. other: e. g. concomitant treatment, underlying disease
11. Reporter's name, date and signature

*In the case of incomplete information at the time of initial reporting, all appropriate information should be provided as soon as this becomes available.

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:

John Lum
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: jlum@Jaeb.org

It is the responsibility of the local investigator to follow the SAE and SADE reporting requirements stipulated by the Investigational Center'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 as for SAEs/SADEs.

11.2.7 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.

11.3.3 Blood Sampling

Subjects will be required to have three blood tests (venepuncture) during the whole study. Venepuncture is required annually as part of the annual review for people with diabetes, and in some places venepuncture 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)

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

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

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 night before closed loop is initiated.

11.4 Benefits

It is expected that day and night closed loop system in combination pump suspend feature or sensor augmented 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.

11.5 Data Safety Monitoring Board (DSMB)

An independent Data Safety Monitoring Board (DSMB) will be informed of all serious adverse events and any unanticipated adverse device effects that occur during the study and will review compiled adverse event data at periodic intervals.

12 Methods and Assessments

12.1 Procedures

12.1.1 Height and Weight

These will be recorded at the study initiation visit at screening. Weight will be also measured at the start and the end the study interventions. Height will be measured in centimetres using a calibrated stadiometer. Weight will be measured in kilograms using a calibrated electronic scale.

12.1.2 Continuous Subcutaneous Glucose Monitoring

At least 12 days of study CGM data will be collected prior to the beginning of the study with the aim of gaining knowledge of the specific subject's glucose control characteristics at screening and assessing compliance before the beginning of any intervention arm. During the pre-study training session on the use of CGM, the CGM receiver may be masked to the study participant.

Data from the study CGM system will be downloaded periodically at least every four weeks during each intervention by the participant.

12.1.3 Insulin Pump Data

Data from the study insulin pump will be downloaded periodically during each intervention by the participant.

12.2 Questionnaires and Interviews

12.2.1 Questionnaires

Psychosocial data will be collected using a mixed methods approach. Quantitative data on health-related quality of life will be assessed using validated questionnaires. Participants/guardians will complete the questionnaires at screening and at the end of the study intervention. Additionally, feedback questionnaires on closed loop specific experience will be distributed to participants/guardians who had been randomised to the closed loop intervention arm. All results will be evaluated at the end of the study.

12.2.2 Qualitative Interview

A subset of participants randomized to a closed loop system will be interviewed at baseline (post-randomization) to enable their historical diabetes management practices, everyday work and family lives, and their initial expectations of using this technology to be captured and explored in-depth. The same participants will be followed-up 3 months later to look at whether, in what ways, and why, use of a closed loop system has impacted on their diabetes self-management practices, their attitudes towards hypoglycaemia; and, their work and family lives. These follow-up interviews will also explore how participants think the technology could be refined and improved in light of their

experiences of using it. A subset of family members will be interviewed at 3 months to capture the benefits of using a closed loop system from their perspectives, including how this technology has impacted on their own lives and on their role in supporting diabetes management practices. A family member recruitment pack will be given to participants/guardians at Visit 8 to pass onto a partner/adult family member in order to recruit the subset of family members for the interviews at 3 months. The family member recruitment pack can also be mailed or emailed after Visit 8 to participants/guardians.

Approximately 25 people with diabetes will be interviewed. This sample size will be large enough for a full range of issues relating to use of closed loop systems to be identified and explored in-depth and for data saturation to occur (i.e. for no new findings to emerge from any new data collected). If possible, participants will be purposively sampled so there is diversity in the final sample in terms of age, gender, occupation/education and geographical location. Approximately 20 family members will be interviewed.

Interviews will be informed by topic guides developed in light of literature reviews, initial research questions, inputs from the trial team and lay/patient advisors, and revised in light of emerging findings (see above). UK based interviews will take place at a time and location chosen by participants (most likely their own homes) and possibly by phone; US interviews will need to be undertaken by telephone. Interviews will be digitally recorded with consent and will average an hour.

To maximise rigour two experienced qualitative researchers will be involved in data analysis. A thematic analysis will be undertaken by these two individuals who will independently review all data before attending regular meetings to compare their interpretations and reach agreement on recurrent themes and findings. Each individual's baseline and three month interview will be compared, and attention paid to any continuities and changes in their attitudes, experiences and use of closed loop systems over time, and the reasons for these. Participants' accounts will also be cross-compared, enabling the identification of overarching themes which cut across different people's experiences. A final coding frame, reflecting the initial research questions and emergent themes, will be developed once all data have been reviewed and consensus reached on key themes and findings. NVivo9, a qualitative software package, will be used to facilitate data coding/retrieval.

12.3 Laboratory Methods

12.3.1 Screening Sample

Renal, liver and thyroid function and anti-transglutaminase antibodies with IgA levels (to exclude diagnosis of coeliac disease) and full blood count will be measured locally if not done within the previous 3 months.

12.3.2 C-peptide and Glucose

Random blood sample for the measurement of C-peptide with simultaneous exclusion of biochemical hypoglycaemia (blood glucose <4.0 mmol/l (72mg/dl)) by laboratory glucose analysis on a sample at the same time point, will be taken at screening.

Plasma C-peptide will be measured at a local laboratory.

12.3.3 HbA1c

Blood samples for the measurement of HbA1c levels will be taken at three different time points: screening, beginning[1] and end[2] of study intervention. An additional HbA1c sample will be taken at the beginning and end of study intervention for storage purposes.

Screening HbA1c will be measured locally. HbA1c taken at beginning and end of study intervention will be measured at a central laboratory in each country using an International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) aligned method. HbA1c testing must follow National Glycohemoglobin Standardization Program (NGSP) standards.

12.4 Total Blood Loss

The total blood loss will be approximately 35 ml.

[1] An extra blood sample will be taken and frozen, to be stored as a spare HbA1c sample

[2] An extra blood sample will be taken and frozen, to be stored as a spare HbA1c sample

13 Study Materials and Products

13.1 Insulin

U-100 rapid acting insulin analogue will be used in the insulin pumps. This includes either Aspart (Novorapid; Novo Nordisk, Bagsvaerd, Denmark) or Lispro (Humalog; Eli Lily, Indianapolis, USA) but not Glulisine (Apidra; Sanofi-Aventis, Paris, France)

13.2 Insulin Pump with Pump Suspend Feature

During day and night automated closed loop glucose control combined with threshold based pump interruption, the next generation Medtronic subcutaneous insulin infusion pump Medtronic 640G (Medtronic Minimed, Northridge, CA, USA) will be used. Threshold-suspend feature 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).

13.3 Insulin Pump used during Run-in and Control Intervention

During sensor augmented insulin pump therapy, similar insulin pump device will be used (Medtronic 640G) but pump suspend feature will be turned off.

During run-in and to download insulin and sensor data during the interventional and control periods, Medtronic CareLink® Therapy Management Software or similar will be used.

13.4 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 in the study. The sensor will be calibrated according to manufacturer's instructions with additional calibration checks in the morning and evening.

13.5 Carelink USB link

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 Clinical.

13.6 Bayer CONTOUR™ Next Link Blood Glucose Meter

A Bayer Contour Next Link RF enabled BG Meter (Study Meter) will be provided to study participants for use with the study pumps. The meter measures a subject's capillary blood glucose level, which is then used to calibrate the 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.

13.7 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).**

14 Data Analysis

14.1 Primary Analysis

The primary analysis will evaluate between group difference in the time (midnight to midnight) spent in the target glucose range from 3.9 to 10 mmol/l (70 to 180mg/dl) based on CGM glucose levels during the 12 week free living phase.

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.

Mean (SD) for % time spent in the target range will be tabulated by treatment group. A linear model will be used to compare the difference between the two intervention arms, while adjusting for baseline % time spent in the target glucose range and random site effect. A 95% confidence interval will be reported for the difference between the treatment groups based on the linear model. Normality of the residuals will be assessed. If the residuals have highly skewed distribution, then ranked normal score transformation of outcome data will be applied in the regression model. However, previous experience suggests that % time in target glucose range will follow an approximately normal distribution. A detailed analysis plan will be provided separately.

14.2 Secondary Analysis

If primary endpoint is not met, secondary endpoint findings will be considered exploratory. The secondary efficacy analyses will include a comparison between the two treatment arms for outcomes given in section 10.2.

Glycaemic metrics will be based on CGM glucose levels collected during the 12 week intervention period. Similar linear models as the primary outcome will be used to compare the between treatment difference. For those metrics which have highly skewed distribution, a ranked normal

score transformation of outcome data will be applied in the regression model. P-value <0.05 will be used to define statistical significance for selected secondary outcomes (HbA1c, glucose CV, %time below 3.9 mmol/l, %time above 10.0 mmol/l, total daily insulin and change in body weight). For other outcomes, in order to reduce the inflation of type I error caused by multiple comparisons, p-value <0.01 will be used to define statistical significance.

A subset of CGM and insulin metrics will also be tabulated separately for daytime period (8AM-12PM) and nighttime period (12PM-8AM).

- Percent time with glucose in target range of 3.9 to 10.0 mmol/l (70-180 mg/dl)
- Mean glucose
- Glucose variability as measured by standard deviation
- Percent time with glucose level <3.5 mmol/l (63 mg/dl)
- Amount of delivered insulin

Trends in CGM data collected within intervention arms will be evaluated on a 4-weekly basis.

14.3 Safety Analysis

Below safety outcomes will be tabulated by treatment group:

- Number of subjects with any diabetic ketoacidosis events
- Number of episodes of diabetic ketoacidosis events per subject and incidence rate per 100-person years
- Number of subjects with any severe hypoglycaemia events
- Number of episodes of severe hypoglycaemia events per subject and incidence rate per 100-person years
- Number of subjects with any severe hyperglycaemia events as defined by fingerprick glucose >16.7 mmol/l (>300 mg/dl) and plasma ketones >0.6 mmol/l
- Number of episodes of severe hyperglycaemia events per subject and incidence rate per 100-person years

Above safety data will be tabulated for all subjects in the two intervention periods, including drop-outs and withdrawals, irrespective of whether CGM data are available and irrespective of whether closed loop was operational. All adverse events will be listed for the entire study duration.

If there are enough observed events to allow formal statistical modelling for above safety outcomes, the following analyses will be conducted. The event rates will be compared using a Poisson regression model adjusting for random site effect. If outliers exist, a robust Poisson regression model will be used instead. Binary variables will be compared using a logistic regression model

adjusting for random site effect. Models involve severe hypoglycaemia events will also adjust for severe hypoglycaemia in the previous 6 months before enrolment.

14.4 Utility Evaluation

The amount of CGM use will be calculated for both intervention arms, and the amount of closed-loop system used will be calculated for the closed-loop treatment arm only over the 12 week intervention and by 4-weekly period. The difference in CGM use between treatment groups will be compared using similar linear model as described for primary outcome.

14.5 Subgroup Analysis

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: (1) age (6 to 12 years, 13 to 21 years, 22 years and older), (2) gender, (3) race-ethnicity, (4) clinical centre, and (5) baseline HbA1c (<8.5% and ≥8.5%).

14.6 Per-protocol Analysis

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

- CL + LGS arm
  - Closed loop active for at least 80% of the time when CGM data were available
  - CGM data available for at least 50% of the 84 day study period
- SAP arm
  - CGM data available for at least 50% of the 84 day study period.

14.7 Psychosocial Evaluation

Questionnaires for diabetes related quality of life assessment (PedsQL v3.2) will be collected at screening and at the end of the study intervention. For subjects ≥18 years of age, only answers from the participants themselves will be collected; for subjects ≤17 years of age, answers will be collected from both parent version and child version. The items scores in diabetes module of PedsQL v3.2 can be summarized into a total score and 5 dimensions: (1) diabetes, (2) treatment I, (3) treatment II, (4) worry, and (5) communication.

At each assessment time point, mean ± SD score for each dimension and the total score will be tabulated by intervention arm for both parent version and participant version. The between group difference of each score at end of study will be assessed using similar linear model as described previously by adjusting for corresponding score at baseline.

14.8 Interim analysis

No interim analysis will be performed.

14.9 Statistical Methods

The respective values obtained during the 12-week randomised interventions contrasting the closed loop combined with pump suspend feature against the sensor augmented pump therapy will be compared using independent samples statistical techniques. For non-normally distributed parameters transformation or nonparametric analyses will be used.

Primary analysis will be a single comparison and no attempt will be formally made to control the overall type I error rate for the secondary outcomes. A 5% significance level will be used to declare statistical significance for the primary comparison.

Severe hypoglycaemic events and ketone-positive hyperglycaemia will be tabulated in each treatment group, which will be compared using repeated measures logistic regression (generalised estimator equation).

Safety data including severe hypoglycaemia events and ketone-positive hyperglycaemia will be tabulated for all subjects, including drop-outs and withdrawals, irrespective of whether CGM data are available and irrespective of whether closed loop was operational.

14.10 Sample Size and Power Calculations

Based on our previous day-and-night closed loop studies and a conservative estimate of 10 percentage points improvement in time when glucose is in target glucose range with a SD of 14.5 percentage points, 76 subjects are required to achieve 85% power and an alpha level of 0.05 (two-tailed). 84 are planned to be randomised to allow for dropouts. It is expected that 95 or more subjects will be recruited; recruitment will continue until it is anticipated that a sufficient number have been enrolled to meet the randomisation goal. Randomisation target may be exceeded since all of the subjects who have initiated the run-in phase will be permitted to continue into the intervention.

14.11 Deviations from the statistical plan

Any deviations from the original statistical plan will be recorded and agreed by the Investigators.

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 GCP and ISO 15197;2013 Guidelines. Corrections to the CRF will be performed by striking through the incorrect entry and by writing the correct value next to the data that has been crossed out; each correction will be initialled and explained (if necessary) by the Investigator or the Investigator's authorised staff.

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 Clinical Principal 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 comprise a chairperson and two experts. The DSMB will be informed of all serious adverse events and any unanticipated adverse device effects/events that occur during the study. The DSMB will review compiled adverse event data at periodic intervals. The DSMB will report to the Study Management Committee any safety concerns and recommendations for suspension or early termination of the investigation.

17.2 Study Management Committee

A study management committee consisting of the Chief Investigator, Study Coordinators, and Study Data Manager will meet quarterly to discuss the operational aspects of the study. The Principal Clinical Investigators may also participate.

17.3 Study Monitoring

The Study Coordinators on behalf of the Sponsor will ensure that the study is conducted in accordance with GCP standards through site monitoring visits. A monitoring plan will be written and agreed prior to randomisation.

18 Responsibilities

18.1 Chief Investigator

The Chief Investigator (CI) is the person with overall responsibility for the research and all UK 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 or Institutional Review Board 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

Inclusion of the first subject in the study is planned to take place in June 2015, with an enrolment period of up to 6 months. The expected completion of the last subject is May 2016 and the planned completion of the Clinical Study Report is October 2016.

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.

26 Appendices

26.1 Appendix 1

Three-Week Unsupervised Home Use of Overnight Closed loop Insulin Delivery in adolescents with Type 1 Diabetes: Crossover Randomised Controlled Study

Background

Closed loop systems deliver insulin in glucose responsive fashion. Overnight application focuses on reducing the risk of nocturnal hypoglycaemia and achieving consistent overnight glucose levels.

Methods

We evaluated unsupervised home use of overnight closed loop in 16 pump-treated adolescents with type 1 diabetes aged 12 to 18years who, after training on study devices, underwent two three-week periods of sensor augmented insulin pump therapy separated by one to three week washout. During one period, randomly assigned, overnight insulin delivery was automatically modulated by an adaptive model predictive controller. The primary endpoint was the time when conservatively adjusted sensor glucose was in target range between 3.9 and 8.0mmol/l from 23:00 to 07:00.

Results

Closed loop worked over at least 4hours on 269nights (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(standard deviation 3.2)mmol/l, P<0.001. The time when glucose was below 3.9mmmol/l was low and comparable between treatment but nights with glucose less than 3.5mmol/l for at least 20min were less frequent during closed loop (10% vs. 17%, P=0.01). Benefits of overnight closed loop were observed over the 24hour period. Total daily insulin amount was reduced despite increased overnight insulin delivery (P=0.009).

Conclusions

Home application of overnight closed loop is feasible reducing mean glucose with fewer episodes of nocturnal hypoglycaemia in adolescents with type 1 diabetes.

26.2 Appendix 2

Home use of closed loop insulin delivery improves overnight glucose control in adults with type 1 diabetes: A four-week multicentre randomised crossover study

Background: Closed loop systems (artificial pancreas) modulate insulin delivery according to real-time glucose measurements**.** We assessed whether home use of automated closed loop insulin delivery improves overnight glucose control in adults with type 1 diabetes.

Methods: We studied 24 adults aged 18 years and older with type 1 diabetes on insulin pump therapy in a multicentre crossover study design. We compared four weeks of overnight automated closed loop using a model predictive control algorithm to direct insulin delivery, with four weeks of sensor-augmented pump therapy (SAP) as control. The order of interventions was random according to computer-generated code. During SAP, participants used real-time sensor glucose alone. Primary efficacy outcome was time when sensor glucose was in the target range between 3.9 and 8.0mmol/l from midnight to 07:00. All analyses were by intention to treat. Trial registration ClinicalTrials.gov NCT01440140.

Findings: Closed loop was utilised over median 8.3 (interquartile range 6.0, 9.6) hours on 555 nights (86%). Proportion of time when overnight glucose was in target range was significantly higher during closed loop compared to SAP (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]. Lower mean overnight glucose was brought about by increased overnight insulin delivery [6.4 (4.5, 8.1) vs. 4.9 (3.7, 6.3) units, p<0.001) without changing the total daily insulin amount (p=0.32).

Interpretation: Unsupervised overnight closed loop at home is feasible and may improve glucose control in adults with type 1 diabetes.

26.3 Appendix 3

Day and Night Home Closed loop Insulin Delivery in Adults with Type 1 Diabetes: Three Centre Randomised Crossover Study

Objective

To evaluate the feasibility of day and night closed loop insulin delivery in adults with type 1 diabetes under free-living conditions.

Methods

Seventeen adults with type 1 diabetes on insulin pump therapy [age 34±9years; HbA1c 7.6±0.8%; duration of diabetes 19±9years; mean±SD] participated in an open-label multinational three-centre cross-over study. In a random order participants underwent two eight day periods (first day at the clinical research facility followed by seven days at home) of sensor augmented insulin pump therapy or automated closed loop insulin delivery. The primary endpoint was the time when sensor glucose was in target range between 3.9 and 10.0 mmol/l during the seven day home phase.

Results

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).

Conclusions

Compared to sensor augmented pump therapy, one week closed loop insulin delivery at home reduces mean glucose and increases time in target without increasing the risk of hypoglycaemia in relatively well controlled adults with type 1 diabetes.

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