UNIVERSITY OF CAMBRIDGE

Cambridge University Hospitals NHS
NHS Foundation Trust

Clinical Study Protocol

Study Title: **An open-label, multi-centre, randomised, two-period, crossover study to assess the efficacy, safety and utility of 16 week day and night automated closed-loop glucose control under free living conditions compared to sensor augmented insulin pump therapy in older adults with type 1 diabetes**

Short Title: **24/7 closed-loop in older subjects with type 1 diabetes (Dan06)**

Protocol Version: **5.0 30 July 2020**

Protocol ID: **Dan06**

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

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Funder	National Institute of Diabetes and Digestive and Kidney Diseases	

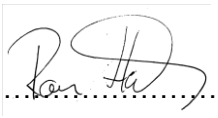
Data Safety and Monitoring Board (DSMB)

DSMB comprises

- Independent Chair
- Two independent Medical Experts

PROTOCOL SIGNATURE PAGE

The signature below documents the approval of the protocol entitled "**An open-label, multi-centre, randomised, two-period, crossover study to assess the efficacy, safety and utility of 16-week day and night automated closed-loop glucose control under free living conditions compared to sensor augmented insulin pump therapy in older adults with type 1 diabetes**" version 5.0 dated 30 July 2020 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…14 October 2020…….

Professor Roman Hovorka

Chief Investigator /Sponsor representative

SITE SIGNATURE PAGE (Cambridge, UK)

I have read the attached protocol entitled "**An open-label, multi-centre, randomised, two-period, crossover study to assess the efficacy, safety and utility of 16-week day and night automated closed-loop glucose control under free living conditions compared to sensor augmented insulin pump therapy in older adults with type 1 diabetes"** version 5.0 dated 30/07/2020, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice: The European Clinical Trials Directives 2001/20/EC and 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……..

Dr Mark Evans
Principal Clinical Investigator

SITE SIGNATURE PAGE (Manchester, UK)

I have read the attached protocol entitled "**An open-label, multi-centre, randomised, two-period, crossover study to assess the efficacy, safety and utility of 16-week day and night automated closed-loop glucose control under free living conditions compared to sensor augmented insulin pump therapy in older adults with type 1 diabetes"** version 5.0 dated 30/07/2020, and agree to abide by all provisions set forth therein.

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Signature ……. Date…….

Dr Lalantha Leelarathna
Principal Clinical Investigator

SITE SIGNATURE PAGE (Birmingham, UK)

I have read the attached protocol entitled "**An open-label, multi-centre, randomised, two-period, crossover study to assess the efficacy, safety and utility of 16-week day and night automated closed-loop glucose control under free living conditions compared to sensor augmented insulin pump therapy in older adults with type 1 diabetes"** version 5.0 dated 30/07/2020, and agree to abide by all provisions set forth therein.

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Signature …….. Date…….

Dr Parth Narendran
Principal Clinical Investigator

Table of Contents

1. List of Abbreviations and Relevant Definitions

ADA	American Diabetes Association
ADE	Adverse Device Effect
AE	Adverse Event
AP	Artificial Pancreas
AR	Adverse Reaction
ASADE	Anticipated Serious Adverse Device Effect
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 and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
IDE	US Investigational Device Exemption
ISPAD	International Society for Pediatric and Adolescent Diabetes
i.v.	Intravenous
MHRA	Medicine and Healthcare products Regulatory Agency
MPC	Model-Predictive-Control
NGP	Next generation insulin pump (Medtronic)
PSQI	Pittsburgh Sleep Quality Index
R & D	Research and Development
RCT	Randomised Control Trial
REC	Research Ethics Committee
s.c.	Subcutaneous
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Sensor Augmented Pump Therapy
SMBG	Self-Monitoring of Blood Glucose
T1D	Type 1 Diabetes Mellitus
USADE	Unanticipated Serious Adverse Device Effect
WHO	World Health Organization

2. Study Synopsis

Title of clinical trial	**An open-label, multi-centre, randomised, two-period, crossover study to assess the efficacy, safety and utility of 16 week day and night automated closed-loop glucose control under free living conditions compared to sensor augmented insulin pump therapy in older adults with type 1 diabetes**
Short Title	24/7 closed-loop in older subjects with type 1 diabetes
Sponsor name	UK - University of Cambridge and Cambridge University Hospitals NHS Foundation Trust, UK
Medical condition or disease under investigation	Type 1 diabetes
Purpose of clinical trial	To determine whether day and night automated closed-loop glucose control for 16 weeks under free living conditions is superior to sensor augmented insulin pump therapy in older subjects with type 1 diabetes
Study objectives	The study objective is to compare day and night automated closed-loop glucose control with sensor augmented insulin pump therapy under free living conditions. **1. EFFICACY:** The objective is to assess the efficacy of day and night automated closed-loop glucose control in maintaining CGM glucose levels within the target range from 3.9 to 10.0 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 in terms of episodes of severe hypoglycaemia, hyperglycaemia, and other adverse events and adverse device effects. **3. UTILITY:** The objective is to determine the percentage of time when closed-loop was operational, and usability and acceptance of the closed-loop system. 4. **HUMAN FACTORS**: Cognitive, emotional, sleep quality, and behavioural characteristics of participating subjects and their response to the closed-loop system and clinical trial will be assessed using validated surveys, focus groups, and Actiwatch. 5. **CARDIAC RHYTHM**: The objective is to evaluate cardiac arrhythmic events with concordant CGM

	glucose values during closed-loop system use and sensor augmented insulin pump therapy.
Study Design	An open-label, multi-centre, randomised, two-period crossover study, contrasting day and night automated closed-loop glucose control, 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 Endpoints	Key secondary endpoints: • Time spent above target glucose (10.0mmol/l; 180mg/dl) • Mean of glucose levels • HbA1c at 16 weeks • Time spent below target glucose (3.9mmol/l; 70mg/dl) Secondary efficacy endpoints: • standard deviation and coefficient of variation of glucose levels • Time with glucose levels <3.5 mmol/l (63 mg/dl) and <3.0 mmol/l (54mg/dl) • Time with glucose levels in significant hyperglycaemia (glucose levels >16.7 mmol/l) (300mg/dl) • Total, basal and bolus insulin dose Secondary endpoints will be based on sensor glucose data.
Exploratory endpoint(s)	Day (06:00 to 23:59) vs. night (00:00 to 05:59) glucose control.
Safety Evaluation	Frequency of severe hypoglycaemic episodes as defined by American Diabetes Association, 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 participants' perception in terms of cognitive, emotional, and behavioural characteristics and responses of participants to closed-loop system use.
Sample Size	36 adults randomised. Up to 42 subjects will be recruited to allow for dropouts.
Summary of eligibility criteria	Key inclusion criteria: 1. Age 60 years and above 2. Type 1 diabetes as defined by WHO for at least 1 year or is confirmed C-peptide negative 3. On insulin pump for at least 3 months, with good knowledge of insulin self-adjustment 4. Treated with one of the U-100 rapid acting insulin analogues only (insulin Aspart, Lispro, Faster Insulin Aspart, but not Glulisine) 5. Willing to perform regular capillary blood glucose monitoring 6. HbA1c ≤ 10 % (86mmol/mol)

	7. Willingness to wear study devices 8. Literate in English 9. Having a care partner who is aware of the subject's location and is trained to administer intramuscular glucagon and able to seek emergency assistance Key exclusion criteria: 1. Non-type 1 diabetes mellitus including those secondary to chronic disease 2. Use of a closed-loop system within the last 30 days 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. Commencement of any glucose-lowering agent (such as Pramlintide, Metformin, GLP-1 analogs) in the 3 months prior to enrolment or any use of SGLT2 inhibitors 5. Untreated coeliac disease, adrenal insufficiency or hypothyroidism 6. Known or suspected allergy to insulin 7. More than one episode of severe hypoglycaemia within the last 6 months 8. Random C-peptide >200pmol/l with concomitant plasma glucose >4 mmol/l (72 mg/dl) 9. Lack of reliable telephone facility for contact 10. Total daily insulin dose ≥ 2 IU/kg/day or < 15 IU/day
Maximum duration of study for a subject	44 weeks (11 months)
Recruitment	The subjects will be recruited through the adult diabetes outpatient clinics or other established methods at participating centres.
Consent	Participants will be asked to provide written informed consent.
Baseline Assessment	Eligible subjects will undergo a baseline evaluation including a 12-lead electrocardiogram and blood sample for the measurement of HbA1c, random C-peptide, glucose, renal, liver functions, full blood count, thyroid functions and coeliac antibody screen (if not done in the previous 3 months). Additional centre specific assessments will also be undertaken. Human factors assessment to understand expectations, attitudes, and behaviours that influence the uptake and response to using a closed-loop system will be undertaken at baseline.
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 (face to face or remotely). 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 4-6 week run-in period, subjects will use study CGM and insulin pump. Subjects will be able to contact the research team for support as necessary. For compliance and to assess the ability of the subject to use the CGM and study pump safely, at least 10 days of CGM data need to be recorded during the last 14 days, 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, study CGM and closed-loop system 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 automated closed-loop glucose control or to sensor augmented insulin pump therapy, with a 4-week washout period in between the two interventions.
1. Automated day and night closed-loop insulin delivery (interventional period)	Subjects will be admitted to the Clinical Research Facility or clinical area at the agreed time. This can be done remotely if required. A blood sample (capillary/venous) will be taken for the measurement of HbA1c. Training on the use of closed-loop will be provided by the research team (face to face or remotely). Competency on the use of closed-loop system will be evaluated. Subjects will be advised to use automated closed-loop system for the next 16 weeks.
Cross-over Assessment	At the end of the first intervention, a blood sample (capillary/venous) for the measurement of HbA1c will be taken. Human factor assessment and acceptance of the system will be assessed using a validated survey. Other questionnaires to assess quality of life change, daily diabetes management and fear of hypoglycaemia will also be recorded.
Wash-out period	At the end of the first intervention, subjects will undergo a wash-out period of 4 weeks, during which they will continue to wear the study insulin pump and their standard pump settings will be applied.
2. Sensor augmented insulin pump therapy (control period)	Subjects will be admitted to the Clinical Research Facility or clinical area at the agreed time. This can be done remotely if required. A blood sample (capillary/venous) will be taken for the measurement of HbA1c. Subjects will use sensor augmented insulin pump therapy for 16 weeks.

End of study assessments	A blood sample (capillary/venous) will be taken for measurement of HbA1c. Human factor assessment will be performed to understand expectations, attitudes, and behaviours that influence the uptake and response to using a closed-loop system. The human factor assessments include both quantitative and qualitative methods which have been tested in adults in the targeted age range.
Actiwatch application at 2-month of each study period	Subjects will wear an Actiwatch for 7 days for objective sleep quality assessment.
Holter monitor application during the last month of each study period	Subjects will wear a Holter monitor for 5-7 days for retrospective analysis of cardiac rhythm during each study period. Holter monitor data will be analysed at the end of the study. Any incidental finding will be referred by the Investigator to the clinical team and be managed as per local site policy.
Procedures for safety monitoring during trial	Standard operating procedures for monitoring and reporting of all adverse events and adverse device events will be in place, including serious adverse events (SAE), serious adverse device effects (SADE) and specific adverse events (AE) such as severe hypoglycaemia. A Data Safety and Monitoring Board (DSMB) will be informed of all serious adverse events and any unanticipated adverse device/method 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 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: • Serious adverse events • Significant protocol violation or non-compliance • Failure to satisfy competency assessment • Decision by the investigator, or the sponsor, that termination is in the subject's best medical interest • Allergic reaction to insulin • Technical grounds (e.g. subject relocates)

3. Summary

The main objective of this study is to determine whether automated day and night closed-loop insulin delivery for 16 weeks under free living conditions is safer and more efficacious compared to sensor augmented insulin pump therapy in older adults with type 1 diabetes.

This is an open-label, multi-centre, randomised, crossover design study, involving a 4-6 week run-in period, followed by two 4 month study periods during which glucose levels will be controlled either by an automated closed-loop system or by sensor-augmented pump therapy in random order. A total of up to 42 adults (aiming for 36 completed subjects) aged 60 years and older with T1D on insulin pump therapy will be recruited through diabetes clinics and other established methods in participating centres. Subjects who drop out of the study within the first 6 weeks of the first intervention period will be replaced.

Subjects will receive appropriate training (face to face or remotely) in the safe use of closed-loop insulin delivery system. 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 10.0 mmol/L (70 and 180mg/dl) as recorded by CGM. Secondary outcomes are the HbA1c, time spent with glucose levels above and below target, as recorded by CGM, and other CGM-based metrics. Measures of human factor assessment, cardiac arrhythmia and objective sleep quality assessment will also be evaluated in this study.

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). The number of older people living with T1D is also increasing due to increasing life expectancy (4). This population faces unique challenges related to diabetes self-management due to long disease duration and burden of other co-morbidities compared to the younger age group (5). Hypoglycaemia (too low blood sugar) unawareness is common in the older T1D population (6) and is a recognized risk factor for severe hypoglycaemia (7; 8), predisposing to cardiac arrhythmias and cardiovascular mortality (9; 10).

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(11) but for most patients this is associated with hypoglycaemia limiting the intensification of treatment (12; 13).

Recommended treatment goals specific for various age groups of people with T1D have been published (14), but achieving it in clinical practice is still challenging due to hypoglycaemia risk associated with insulin therapy (15). This is pertinent in the older patient group, due to multiple burden of co-morbidities. 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 (16). Even in patients with good control, as judged by average HbA1c, significant

glucose excursions occur with periods of silent hyper- and hypoglycaemia (17; 18). Further older patients with T1D have impaired defence mechanisms (counter-regulatory responses) to low glucose, thus impairing recovery and increasing the threat of future episodes (19). 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 (20).

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.(21-24).

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 (25). 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 (26).

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 (27).

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 (28). Two relatively small out-patient studies of short duration (21 children for 6 weeks (29) and 31 adults (30) 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 (31).

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 (32).

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 (33). The simulations suggested a reduced risk of nocturnal hypoglycaemia and hyperglycaemia with the use of the MPC algorithm (34).

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 (35) 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 (36).

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 (37). Closed-loop was activated over at least 4 hours on 269 nights (80%); sensor data were collected over at least 4 hours 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 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 (38). 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].

A multicentre crossover RCT comparing 12 week overnight closed-loop with 12 week sensor augmented pump therapy in 24 children and adolescents aged 6 to 18 years has been completed recently; data analysis is underway.

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

We completed a seven day, day and night home study in 17 suboptimally controlled (HbA1c>7.5%) adults with type 1 diabetes in a multicentre, multi-national crossover study design (39). 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 two centre multinational crossover study comparing day and night closed-loop with usual pump therapy during free-living settings was completed in 29 adults with well-controlled (HbA1c<7.5%) type 1 diabetes (40). The proportion of time when sensor glucose concentration was in target range was significantly increased during closed-loop delivery compared with usual pump therapy (65·6±8.1 vs 76·2±6·4%, p<0.0001). Compared with usual pump therapy, closed-loop delivery also reduced the proportion of time spent in hypoglycaemia: the proportion of time with glucose concentration below 3·5 mmol/L was reduced by 65% (53 to 74, p<0·0001) and below 2·8 mmol/L by 76% (59 to 86, p<0·0001). No episodes of serious hypoglycaemia or other serious adverse events occurred.

We completed a 12-week day and night multicentre, multi-national crossover design home study in 33 adults with T1D (18 male, age 40.0±9.4years, duration of diabetes 20.9±9.3years)(41). The proportion of time when sensor glucose was in target range between 3.9 and 10.0mmol/l was significantly increased during closed-loop compared to sensor augmented pump therapy (67.7±10.6 vs. 56.8±14.2%, p<0.001). Mean glucose (8.7 vs. 9.3 mmol/l, p<0.001) and time spent above (p<0.001) and below target range (p=0.02) were significantly reduced during closed-loop. Hypoglycaemia exposure measured by AUC <3.5 mmol/l was reduced during closed-loop (p<0.001). Reduction in mean glucose and time spent above target range during closed-loop was brought about without changing the total daily insulin delivery (p=0.57).

4.10. Automated Closed-Loop System (CamAPS FX) to be used in the Present Study

The automated closed-loop system (CamAPS FX) will consist of:

- Dexcom G6 (Dexcom, San Diego, CA, USA) or similar Continuous Glucose Monitoring (CGM) System
- Dana R Diabecare (Sooil Corp. Seoul, South Korea) or similar subcutaneous insulin infusion pump
- An Android smartphone hosting CamAPS FX Application with the Cambridge model predictive control algorithm and communicating wirelessly with the insulin pump

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

Figure 1. CamAPS FX comprises Samsung Galaxy phone (or similar) running Cambridge control algorithm, Dana insulin pump (Sooil), G6 real-time CGM sensor (Dexcom).

4.11. Rationale for the Current Study

No study thus far has specifically evaluated use of closed-loop insulin delivery in older adults with type 1 diabetes. The current study will provide further evidence on the effect of consecutive closed-loop day and nights over 4 months in a group of older subjects with type 1 diabetes in a multicentre and multi-national setting to demonstrate the generalisability of results.

5. Objectives

5.1. Efficacy

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

5.2. Safety

To evaluate the safety of automated closed-loop glucose control in terms of episodes and severity of hypoglycaemia and nature and severity of other adverse events.

5.3. Utility

To determine the percentage of time when closed-loop was operational.

5.4. Human Factors

To evaluate the expectations, attitudes and behaviours that influence the uptake and response to using a closed-loop system, and sleep quality.

5.5. Cardiac Rhythm

To evaluate cardiac arrhythmic events with concordant CGM sensor glucose values during closed-loop system use and sensor-augmented pump therapy.

6. Study Design

An open-label, multi-centre randomised, two-period crossover study comparing day and night automated closed-loop glucose control with sensor-augmented pump therapy.

It is expected that up to 42 older subjects with type 1 diabetes with T1D will be recruited, aiming for 36 randomised subjects. Subjects who drop out within the first six weeks of the intervention may be replaced. The study flow chart is outlined in Figure 2.

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7. Study Subjects

7.1. Study population

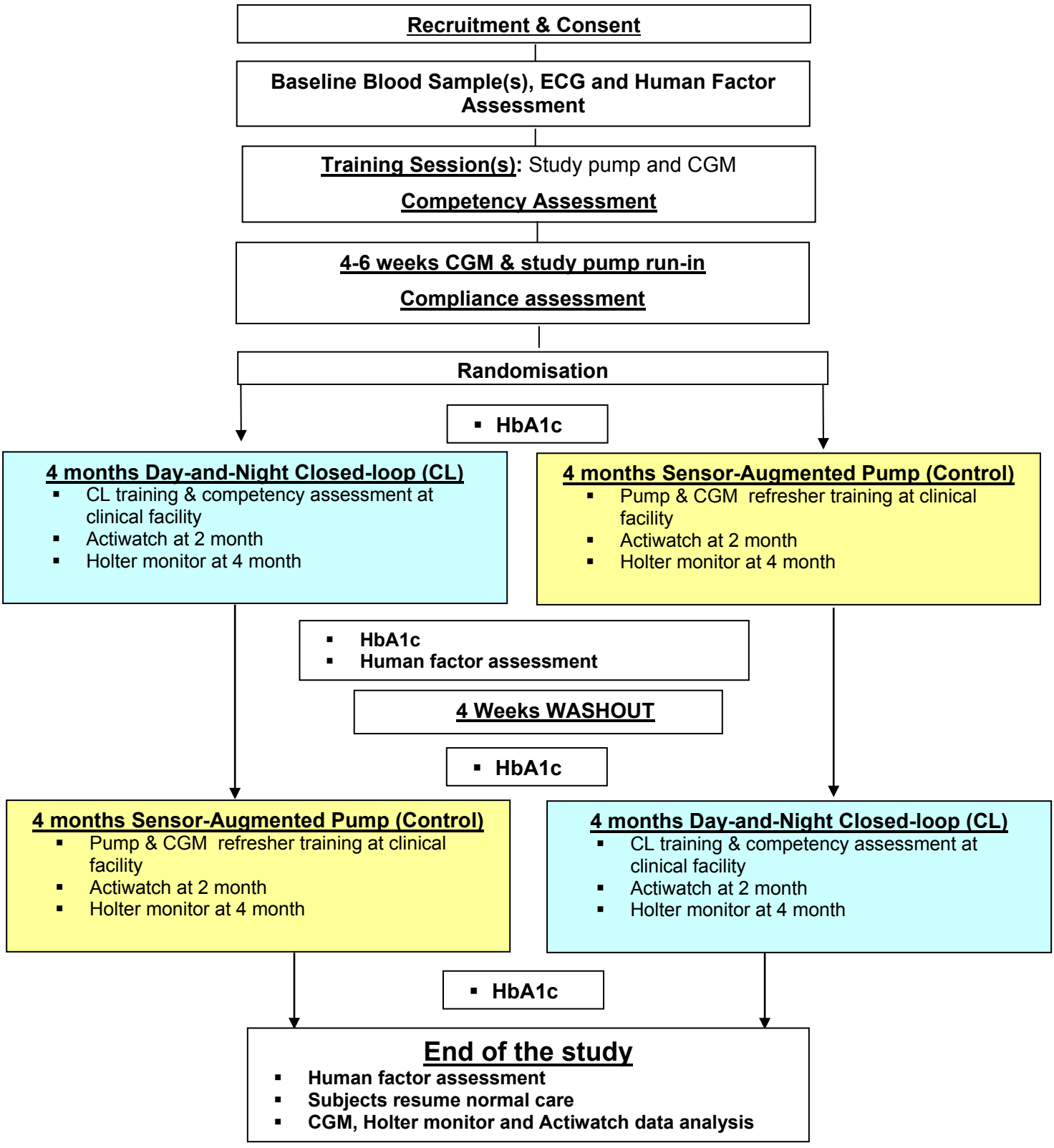
This is a multicentre and multinational study and recruitment will take place at the following centres:

1. Addenbrooke's Hospital, Cambridge, UK
2. Manchester Royal Infirmary, Manchester, UK
3. Queen Elizabeth Hospital, Birmingham, UK
4. Medical University of Graz, Graz, Austria

Adults aged 60 years or over with type 1 diabetes on insulin pump therapy will be recruited. The study will aim for 36 completed subjects. Recruitment will target up to 42 subjects (8 - 20 subjects per centre) to allow for drop-outs. Methods of patient recruitment will follow well established practice at each centre.

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.



7.1.1. Inclusion criteria

1. Age 60 years and above
2. Type 1 diabetes as defined by WHO for at least 1 year or is confirmed C-peptide negative
3. On insulin pump for at least 3 months with good knowledge of insulin self-adjustment
4. Treated with one of the U-100 rapid acting insulin analogues only (insulin Aspart, Lispro, Faster insulin Aspart but not Glulisine)
5. Willing to perform regular capillary blood glucose monitoring
6. HbA1c ≤ 10% (86 mmol/mmol) based on analysis from central laboratory or equivalent
7. Literate in English
8. Having a care partner who is aware of the subject's location and is trained to administer intramuscular glucagon and able to seek emergency assistance
9. Willing to wear closed-loop system at home and at work place
10. Willing to follow study specific instructions
11. Willing to upload pump and CGM data at regular intervals
12. Has access to WiFi

7.1.2. Exclusion criteria for all countries

1. Non-type 1 diabetes mellitus
2. Use of a closed-loop system within the last 30 days
3. Any other physical or psychological disease or condition likely to interfere with the normal conduct of the study and interpretation of the study results
4. Commencement of any glucose-lowering agent (such as Pramlintide, Metformin, GLP-1 analogs) in the 3 months prior to enrolment or any use of SGLT2 inhibitors
5. Untreated coeliac disease, adrenal insufficiency or hypothyroidism
6. Known or suspected allergy against insulin
7. More than one episodes of severe hypoglycaemia as defined by American Diabetes Association (42) in preceding 6 months
8. Random C-peptide > 200pmol/l with concomitant plasma glucose >4 mmol/l (72 mg/dl)
9. Lack of reliable telephone facility for contact
10. Total daily insulin dose ≥ 2 IU/kg/day

11. Total daily insulin dose < 15 IU/day
12. Severe visual impairment
13. Severe hearing impairment
14. Medically documented allergy towards the adhesive (glue) of plasters or unable to tolerate tape adhesive in the area of sensor placement
15. Serious skin diseases (e.g. psoriasis vulgaris, bacterial skin diseases) located at places of the body, which could potentially be used for localisation of the glucose sensor)
16. Subject is currently abusing illicit drugs
17. Subject is currently abusing prescription drugs
18. Subject is currently abusing alcohol
19. Subject has elective surgery planned that requires general anaesthesia during the course of the study
20. Subject is a shift worker with working hours between 10pm and 8am
21. Subject has a sickle cell disease, haemoglobinopathy; or has received red blood cell transfusion or erythropoietin within 3 months prior to time of screening
22. Subject plans to receive red blood cell transfusion or erythropoietin over the course of study participation
23. Subject diagnosed with current eating disorder such as anorexia or bulimia
24. 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
25. Subject not proficient in English (UK), or German (Austria)

7.1.3. Additional exclusion criteria specific for Austria

1. Positive results on urine drug screen (amphetamines/metamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates).
2. Positive alcohol breath test.
3. Positive reaction to any of the following tests: hepatitis B surface (HBs) antigen, anti-hepatitis C virus (anti-HCV) antibodies, anti-human immunodeficiency virus (HIV) 1 antibodies, anti-HIV2 antibodies.

7.2. Randomisation

The order of closed-loop or sensor-augmented pump therapy will be randomly allocated using block randomisation within a centrally administered randomisation programme. Randomisation will take place within 1 week before the start of first home study phase.

8. Methods under Investigation

8.1. Name and description of the method of investigation

The investigational treatment is the CamAPS FX, 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. Component versions will be identified during regulatory submission to the MHRA and relevant authority in Austria.

8.2. Intended purpose

The intended purpose of the investigational treatment is automated day and night closed-loop insulin delivery.

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.

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. This can be done face to face or remotely as required. 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 sensor-augmented pump treatment.

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 coordinated from the Institute of Metabolic Science, University of Cambridge, and performed at the following sites

1. Addenbrooke's Hospital, Cambridge, UK
2. Manchester Royal Infirmary, Manchester, UK
3. Queen Elizabeth Hospital, Birmingham, UK
4. Medical University of Graz, Graz, Austria

The study will consist of up to 19 visits or pre-planned telephone/email contacts including two study periods (closed-loop vs. sensor-augmented pump therapy). The study periods will last 4 months each. The order of the two interventions will be in random order.

The visit to set up automated closed-loop for the first time may take place in the study or clinical facility or can be done remotely. All other visits can take place at the hospital clinic, home or other suitable meeting place or remotely, according to participants' convenience. Two 16-week study periods will be performed within four weeks of each other. Maximum time in study is 12 months.

Table 1 outlines study activities when CL intervention precedes sensor-augmented pump therapy.
Table 2 outlines study activities when sensor-augmented pump therapy precedes CL intervention.

Table 1. Schedule of study visits when closed-loop intervention precedes sensor-augmented pump therapy.

	Visit/ contact	Description	Start relative to previous / next Visit / Activity	Duration
	*Visit 1	Recruitment visit: Consent HbA1c, baseline bloods, 12-lead ECG, human factor assessment	-	1-3 hours
Study Pump & CGM Training /Run-In	*Visit 2	Insulin pump training and initiation of study pump Competency assessment	Can be combined with Visit 1, or within 1 to 3 weeks of Visit 1	3-4 hours
	*Visit 3	CGM training Initiation of CGM Competency assessment	Within 7 days of Visit 2. Can coincide with Visit 2	1 hour
	*Visit 4	Review pump and CGM data & compliance assessment & Randomisation	After 3 - 4 weeks of Visit 3	1-2 hours
CL Intervention (4 months)	*Visit 5	CL initiation at CRC or remotely - CL training & competency assessment - HbA1c	Can be combined with Visit 4, or within 2 week of Visit 4	Up to 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 4 weeks of Visit 5	<1 hour
	*Visit 10	End of second month; Review pump and CGM data. Actiwatch sleep monitor	After 4 weeks of Visit 9	<1 hour
	*Visit 11	End of third month; Review pump and CGM data.	After 4 weeks of Visit 10	<1 hour
	*Visit 12	12-lead Holter monitor applied for 5-7 days.	Within 14 days after Visit 11.	<1 hour

			Can coincide with Visit 11	
	*Visit 13	End of closed-loop treatment period (4 months). HbA1c. Collect algorithm device. Revert back to usual diabetes therapy. Human factor assessment.	After 4 weeks of Visit 11	1-2 hours
	-	**Washout period**	Immediately after Visit 13	4 weeks
Control Intervention (4 months)	*Visit 14	Control therapy initiation at CRC or remotely - Sensor-augmented pump refresher training & competency assessment - HbA1c	After 4 weeks of end of Visit 13	Up to 6 hours
	*Visit 15	End of first month. Review of home data.	After 4 weeks of Visit 14	<1 hour
	*Visit 16	End of second month. Review of home data. Actiwatch sleep monitor	After 4 weeks of Visit 15	<1 hour
	*Visit 17	End of third month. Review of home data.	After 4 weeks of Visit 16	<1 hour
	*Visit 18	12-lead Holter monitor applied for 5-7 days.	Within 14 days after Visit 17. Can coincide with Visit 17	<1 hour
	*Visit 19	End of open-loop treatment period (4 months) HbA1c. Human factor assessment	After 4 weeks of Visit 17	1-2 hours

*Could be done via phone / e-mail in UK.

Table 2. Schedule of study visits when sensor-augmented pump therapy precedes closed-loop intervention.

	Visit/ contact	Description	Start relative to previous / next Visit / Activity	Duration
	*Visit 1	Recruitment visit: Consent HbA1c, baseline bloods, 12-lead ECG, human factor assessment	-	1-3 hours
Study Pump & CGM Training /Run-In	*Visit 2	Insulin pump training and initiation of study pump Competency assessment	Can be combined with Visit 1, or within 1 to 3 weeks of Visit 1	3-4 hours
	*Visit 3	CGM training Initiation of CGM Competency assessment	Within 7 days of Visit 2. Can coincide with Visit 2	1 hour
	*Visit 4	Review pump and CGM data & compliance assessment & Randomisation	After 4 weeks of Visit 3	1-2 hours
Control Intervention (4 months)	*Visit 14	Control therapy initiation at CRC or remotely - Sensor-augmented pump refresher training & competency assessment - HbA1c	After 8 week of end of Visit 13	Up to 6 hours
	*Visit 15	End of first month. Review of home data.	After 4 weeks of Visit 14	<1 hour
	*Visit 16	End of second month; Review of home data. Actiwatch sleep monitor	After 4 weeks of Visit 15	<1 hour
	*Visit 17	End of third month. Review of home data.	After 4 weeks of Visit 16	<1 hour
	*Visit 18	12-lead Holter monitor applied for 5 days.	Within 14 days after Visit 17. Can coincide with Visit 17	<1 hour
	*Visit 19	End of open-loop treatment period (4 months) HbA1c. Revert back to usual pump therapy. Human factor assessment	After 4 weeks of Visit 17	1-2 hours
	-	**Washout period**	Immediately after Visit 19	4 weeks

CL Intervention (4 months)	*Visit 5	CL initiation at CRC or remotely - CL training & competency assessment - HbA1c	After 4 weeks of end of Visit 19	Up to 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 4 weeks of Visit 8	<1 hour
	*Visit 10	End of second month; Review pump and CGM data. Actiwatch sleep monitor	After 4 weeks of Visit 9	<1 hour
	*Visit 11	End of third month; Review pump and CGM data.	After 4 weeks of Visit 10	<1 hour
	*Visit 12	12-lead Holter monitor applied for 5 days.	Within 14 days after Visit 11. Can coincide with Visit 11	<1 hour
	*Visit 13	End of closed-loop treatment period (4 months). HbA1c. Collect algorithm device. Revert back to usual pump therapy. Human factor assessment.	After 4 weeks of Visit 11	1-2 hours

*Could be done via phone / e-mail in UK.

9.2. Recruitment Visit (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
- blood pressure measurement
- 12-lead electrocardiogram recording
- record of current insulin therapy
- record of occupation and educational attainment

Austria only - At the recruitment visit, the subject will have a breath alcohol test, a urine drug screen, and blood test for serology (HIV/Hepatitis B, C).

9.2.1. Screening blood sampling

Blood samples will be taken for the screening measurement of random C-peptide, glucose, and HbA1c. 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. Human factor assessments

Human factors assessment to understand expectations, attitudes, and behaviours that influence the uptake and response to using a closed-loop system will be undertaken at baseline. This will include surveys listed in Table 3. It is estimated that participants will take 20-25 minutes to complete surveys.

Table 3. Human Factors Assessment Battery.

Measure	***Construct Measured / Relevant Points***
WHO-5 quality of life measure*	All participants complete this 5 item measure from the World Health Organization (WHO) that assesses health related quality of life. (5 items; 3 mins)

Diabetes Distress Scale*	Gold standard measure for understanding distress symptoms related to diabetes. A recently validated version for adults with T1D includes 28 items and takes 6 minutes to complete.
Glucose Monitoring Satisfaction Survey*	This recently validated survey is an outgrowth of DirecNet and JDRF CGM surveys. It has been reduced to 15 items and evaluates treatment satisfaction and burden. (4 mins)
Hypoglycemia Confidence*	Includes 8 different common situations where hypoglycemia occurs (e.g., physical activity, driving) and evaluates level of confidence it can be managed in those situations. (8 items; 3 mins)
INSPIRE Survey	Newly developed measure of the psychosocial impact of closed-loop. Include 31 items and takes 5 - 7 minutes to complete.
Pittsburgh Sleep Quality Index (PSQI)	The PSQI is a validated 19 item questionnaire that holistically assesses sleep quality and sleep duration.
Cognitive Functioning	Computerised assessment of attention, executive functioning, and processing speed using standardised tools from CogState (10 – 12 minutes)

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.

This session will be conducted by a member of the study team and/or a professional pump educator following a written curriculum. Competency in the use of study pump will be assessed.

9.4. Training session on the 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
- Use of handheld CGM receiver & sensor calibrations
- Use of software to analyse CGM data
- Use of CGM data to optimise treatment
- Uploading CGM data using software

Written guidelines for the operation and use of CGM device will be provided. If necessary, training sessions may be repeated.

This session will be conducted by a member of the study team. Competency in the use of CGM will be assessed.

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 three weeks run-in period for all subjects (end of Visit 3 to end of Visit 4). Subjects will be able to contact the research team during the run-in period via phone/email to troubleshoot any problems and to ask for any additional training on the devices if required.

At the end of the run-in period (Visit 4), the subject's compliance in 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 10 days' worth of CGM data during last 14 days of run-in period.

9.6. Randomisation

Subject will be randomised in Visit 4 if no extension of the run-in period is needed. Eligible subjects will be randomised centrally using a randomisation based on a

computer-generated random code. Randomisation will take place centrally. Subjects will be allocated to either closed-loop intervention preceding sensor augmented insulin pump therapy, or vice versa.

The next section describes the situation when closed-loop precedes the sensor augmented insulin pump therapy.

9.7. Closed-loop visit; within 2 weeks of Visit 4 (Visit 5)

Subject will arrive at the clinical research facility or clinical area at the agreed time. If required this visit can be done remotely by telephone. A blood sample for HbA1c (capillary/venous) will be taken. Subjects will receive training required for safe and effective use of the closed-loop system. This will include training on connection and disconnection of the closed-loop system, and switching between closed-loop and usual pump therapy. Subjects will be advised to use closed-loop 24/7 for the next 4 months with bolus wizard integrated with control algorithm adapted insulin carb ratio for prandial insulin delivery. Written step by step guidance will also be provided, including how to deal with low and high glucose at home. Subjects will be provided with 24 hour telephone helpline and information on when to contact study team. Competency in the use of closed-loop system will be assessed by the study team. Only subjects who demonstrate competency in use of the system will be allowed to continue to the home study phase.

The subject is allowed to drive while adhering to usual precautions and country specific rules and regulations. Subjects will be warned about hypoglycaemia if they start regular exercise during study period.

9.8. 24-48 hours after Starting Study Treatment (Visit 6)

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. The purpose of this visit will be to review the use of study devices and to provide any additional training required.

9.9. 1 Week after Starting Study Treatment (Visit 7)

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.

9.10. 2 Weeks after Starting Study Treatment (Visit 8)

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.

9.11. Visits 9, 10 and 11 – 4 week, 8 week and 12 week after starting closed-loop therapy

The subject will be invited to attend the research centre approximately 4 (Visit 9), 8 (Visit 10) and 12 (Visit 11) weeks after Visit 5. These visits could be done via telephone/e-mail. The purpose of these visits will be to review the use of study devices and data from study devices will be downloaded. The subject is free to adjust further treatment but no active treatment optimisation will be undertaken by the study team. An Actiwatch sleep monitor will be applied at Visit 10 and worn for 7 days at home. Participants will be asked to complete a sleep diary while they wear the Actiwatch and will be provided with a stamped addressed envelope to return/post the Actiwatch and sleep diary to investigators for further analysis.

9.12. Holter monitor application (Visit 12)

The subject will be invited to attend the research centre within 7 days after Visit 11 to have a Holter monitor applied by the investigator. This procedure may also coincide with Visit 11. If required this visit can be done remotely by telephone once the Holter monitor has been delivered to the participant. The Holter monitor device will be collected at Visit 13, or at an agreed time and place with the investigator or returned via post/courier. Holter monitor data will be retrospectively evaluated and analysed at the end of the study. Any incidental finding will be referred by the Investigator to the clinical team and be managed as per local site policy for incidental findings.

9.13. End of CL treatment (Visit 13)

The subject will be invited to attend the research centre approximately 4 weeks after visit 11. If required this visit can be done remotely by telephone. This would be the end of 4 month 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 (capillary/venous) for the HbA1c. Human factors survey assessment (Table 3) will be performed. Subjects will be asked to return the CGM and control algorithm devices, and will revert to their usual diabetes care with their usual home devices during the 1-month washout period.

9.14. Washout

A minimum washout period of four weeks must be ensured between treatment periods. Duration of the wash out period has been chosen to minimise any carry over effect between the two interventions. This duration was decided pragmatically based on experience of the study team as there are no published studies investigating an optimal washout period for closed-loop studies. The subject may continue to use the study CGM and study insulin pump during the washout period if he or she wishes. Otherwise the subject will continue to use their usual diabetes care with their usual home devices during the washout period. Then the subject will cross over to alternative intervention.

9.15. Control therapy (Visit 14)

The order of Visit 5 and Visit 14 will be in random order. Visit 14 is similar to Visit 5 except that in Visit 14 there is no closed-loop insulin training and application, and subjects will initiate sensor augmented insulin pump therapy. If required this visit can be done remotely by telephone. Subjects will follow usual treatment guidelines for driving, exercise, hyperglycaemia and hypoglycaemia.

9.16. Visits 15, 16 and 17 – 4 week, 8 week and 12 week after starting sensor augmented pump treatment

The subject will be invited to attend the research centre approximately 4 (Visit 15), 8 (Visit 16) and 12 (Visit 17) weeks after Visit 14. If required these visits can be done remotely via telephone/e-mail. The purpose of this visit will be to review the use of study devices and data from study devices will be downloaded. The subject is free to adjust further treatment but no active treatment optimisation will be undertaken by the study team. At Visit 16, an Actiwatch sleep monitor will be applied and worn for 7 days at home. Participants will be asked to complete a sleep diary and will be provided with a stamped addressed envelope to return/post the Actiwatch to investigators for further analysis.

9.17. Holter monitor application (Visit 18)

The subject will be invited to attend the research centre within 14 days after Visit 17 to have a Holter monitor applied by the investigator. If required this visit can be done remotely by telephone once the Holter monitor has been delivered to the participant. This procedure may also coincide with Visit 17. The Holter monitor device will be collected at Visit 19, or at an agreed time and place with the investigator or returned via post/courier. Holter monitor data will be retrospectively evaluated and analysed at the end of the study. Any incidental finding will be referred by the Investigator to the clinical team, to be managed as per local site policy for incidental findings.

9.18. End of control treatment (Visit 19)

The subject will be invited to attend the research centre approximately 4 weeks after Visit 17. If required this visit can be done remotely by telephone. This would be the end of the study period and subjects will return to their normal diabetes care. Insulin pump will be downloaded. The subject will have a blood test (capillary/venous) for the HbA1c. A human factors survey assessment (Table 3) will be performed. Participants will be invited to a focus group for investigators to gather feedback and reactions to the closed-loop system, the clinical trial, and quality of life changes.

9.19. 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 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. Allergic reaction to insulin
10. Severe allergic reaction to adhesive surface of infusion set or glucose sensor

Subjects who are withdrawn for reasons stated in (4) to (10) will be invited to provide a blood sample at the end of the planned study intervention for the assessment of HbA1c.

9.20. 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).

9.21. Support telephone line

There will be a 24-hour telephone helpline to the research team for subjects in case of any technical device or problems related to diabetes management such as hypo- or hyperglycaemia.

9.22. Subject reimbursement

The study will provide the CGM device, insulin pump, closed-loop components, related consumables, and glucose test strips. A recompense payment to participants will be paid to reflect local practice. The amount paid will be specified in the participant information sheet and REC 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. Efficacy endpoints

10.1.1. Primary efficacy 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) throughout the 16 week study periods based on continuous glucose monitoring (CGM).

10.1.2. Secondary efficacy endpoints

Key secondary outcomes include:

- Time spent above target glucose (10.0 mmol/l) (180 mg/dl)
- Average of glucose levels
- HbA1c at 16 weeks
- Time spent below target glucose (3.9mmol/l) (70mg/dl)

Other secondary endpoints

- standard deviation and coefficient of variation of glucose levels
- The time with glucose levels <3.5 mmol/l (63mg/dl), and <3.0 mmol/l (54mg/dl)
- The time with glucose levels in the significant hyperglycaemia (glucose levels >16.7 mmol/l) (300mg/dl)
- Total, basal and bolus insulin dose

Glucose endpoints will be based on sensor glucose.

10.2. 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.

All subjects including those who withdraw will be included in the safety evaluation.

10.3. Utility evaluation

Utility evaluation is the frequency and duration of use of the closed-loop system at home.

10.4. Human factors evaluation

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

10.5. Cardiac arrhythmia analysis

Holter monitor data at the fourth month in the two treatment groups will be retrospectively evaluated by a cardiologist masked to other study data at the end of the study. Any incidental finding will be referred by the Investigator to the clinical team and be managed as per local incidental findings site policy.

10.6. Sleep quality assessment

Quality, duration and fragmentation of sleep will be assessed subjectively (using the Pittsburgh Sleep Quality Index (PSQI), and a daily sleep diary) and objectively (by actigraphy) in participants.

The PSQI is a validated 19 item questionnaire that holistically assesses sleep quality and sleep duration. The sleep diary will record time of going to bed and waking, plus time of, and reason for any nocturnal awakenings.

An Actiwatch (Philips Respironics, Bend, Oregon, USA) worn on the non-dominant wrist will provide objective measures of sleep and wakefulness based on motor activity - a low cost, non-invasive and objective method for evaluating sleep in free-living participants. Actiwatches will record time in bed and actual sleep time, as well as changes in sleep quality from measures of sleep maintenance, sleep efficiency, sleep latency, fragmentation index, total nocturnal activity, and percentage moving time. Light exposure will be measured by the Actiwatch's photovoltaic sensor.

11. Assessing and Reporting of Adverse Events

11.1. Definitions

11.1.1. Reportable Adverse Events

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

11.1.2. Adverse Events

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

The following anticipated adverse events will not be recorded:

- Non clinically significant skin reactions as judged by investigator
- Pre-existing medical conditions

- New illnesses or conditions not requiring concomitant medication or medical intervention/procedures
- Non severe hypoglycaemia
- Hyperglycaemia without significant ketonaemia (>0.6mmol/l)

11.1.3. Adverse Device Effect

An Adverse Device Effect (ADE) is an adverse event related to the use of an investigational medical device. This includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition also includes any 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 hospitalization
    - 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 hospitalisation 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 current 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 of working or performing 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.
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 second intervention. 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

Severe hypoglycaemia will be defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopaenia to induce 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 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 will be notified of all unexpected and related SAEs within 15 days of the occurrence of the event.

Austria specific reporting instructions:

All SAEs have to be documented by the sponsor and immediately reported according to § 42 (8) of the Austrian Medical Device Directive (StF: BGBl. Nr. 657/1996, BGBl. I Nr. 143/2009) to the competent authority (AGES) and the competent authorities of other countries within the European Union where the study is conducted. All SAEs must be reported using the templates provided by AGES.

It is the responsibility of the local investigator to follow the SAE and SADE reporting requirements stipulated by the Investigational Centre's reviewing REC 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. Risks and discomforts and potential / anticipated adverse events and adverse device events/effects

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 diabetes 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 screening blood tests at baseline (venepuncture). 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. HbA1c samples collected during the study can be capillary (NOT point of care) or venous samples. Capillary samples can be collected by the participant using their own blood glucose testing apparatus and delivered to the local investigator if required.

Potential risks of venepuncture include:

- Localised infection – an infection in the tissue around the site
- Phlebitis – inflammation of the wall of the vein
- Haematoma – an accumulation of blood within the tissues that clots to form a solid swelling

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

11.3.4. 12-lead electrocardiogram

Potential risks and adverse device effects associated with electrocardiogram recording:

- Slight discomfort at the time of electrode adhesives placement (rare)
- Mild skin irritation to electrode adhesives (rare)

If an incidental finding is found during the electrocardiogram recording at the Recruitment Visit, this will be referred by the Investigator to the clinical team, to be managed as per local site policy.

11.3.5. Finger-prick blood glucose measurements

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

11.3.6. Insulin pump therapy

Subjects participating in this study are already using an insulin pump. Potential risks and adverse device effects 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)
- Priming mechanism failure
- Pump screen damage
- Fast battery drainage

11.3.7. Continuous glucose monitoring

Potential risks and adverse device effects 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 (very rare)
- Intermittent CGM failure (common)

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

11.3.8. Holter monitor

Potential risks and adverse device effects associated with Holter monitor:

- Slight discomfort at the time of electrode adhesives placement (rare)
- Mild skin irritation to electrode adhesives (rare)

If an incidental finding is found during analysis of the Holter monitor data at the end of the study period, this will be referred by the Investigator to the clinical team, to be managed as per local site policy.

11.3.9. Actiwatch

Potential risks and adverse device effects associated with Actiwatch include:

- Mild irritation at skin surface in contact with Actiwatch (rare)

11.3.10. Human factor assessment

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

11.3.11. Burdens

The study will involve up to 19 visits but all of these visits could be done via e-mail/ telephone. The study also includes two up to 6 hour visits to the clinical research facility (which can be done via telephone if required) and four months home study period.

At home, subjects will wear the closed-loop system for a 4 month period. The subject is required to carry the closed-loop system for work and when going outside home. During the night, the closed-loop system will be located on a bedside table.

The subjects will be required to perform regular finger stick measurements (4 - 6 hourly) during day time.

11.3.12. Risk analysis and residual risk associated with the investigational device

After in-depth analysis and consideration of all the potential hazards in relation to use of the CamAPS FX system in the home environment, it is concluded that the CamAPS FX system is safe, if used as intended.

Risk Assessment of the CamAPS FX system has been carried out in accordance with ISO 14971:2012. A preliminary Hazard Determination has been carried out including consideration of the questions in Annex C of ISO 14971:2012.

One hazard 'Hazard S7: Incorrect Calibration of Blood Glucose Sensor due to error of reading resulting in overestimation of blood glucose' is the only hazard identified that could not be reduced to an acceptable risk level, post mitigation. Our in-detail risk/benefit assessment concluded that the benefits of the system outweigh the risk with respect to this specific hazard.

As per our risk management process, further risk analysis shall be undertaken post production and release as to ensure any issues raised are acted upon to ensure the CamAPS FX system continues to improve and develop.

11.4. Benefits

It is expected that day and night closed-loop system or sensor-augmented pump therapy 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 and Safety Monitoring Board

An independent Data and 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 baseline. Height will be measured in centimetres using calibrated measuring devices. Weight will be measured in kilograms using a calibrated electronic scale.

12.1.2. Continuous subcutaneous glucose monitoring

At least 10 days of CGM data will be collected before visit 4. During the study subject is required to upload the CGM data via internet using secure website.

12.1.3. Insulin pump data

During the study subject is required to upload insulin pump data via internet using secure website.

12.1.4. 12-lead electrocardiogram

During the Recruitment Visit, a 12-lead electrocardiogram recording will be collected. Any incidental finding will be referred by the Investigator to the clinical team and be managed as per local site policy.

12.1.5. Holter monitor

At least 5 days of Holter monitor data will be collected during the fourth month in the two treatment groups and analysed at the end of the study period. Any incidental finding will be referred by the Investigator to the clinical team and be managed as per local site policy.

An incidental finding may be defined as ‘a finding that has potential health or reproductive importance, unknown to the participant, which is discovered unexpectedly in the course of conducting research, but is unrelated to the purpose and beyond the aims of the study’. This study will adopt the following framework for handling incidental findings:

- To respect the research participant's right to know or, alternatively, their right not to know about incidental findings. Explicit consent must have always been given by the participant for incidental findings to be returned.
- Incidental findings should only be returned where they are of significant clinical importance.
- Incidental findings should be clinically and analytically validated before being returned to participants by their treating clinician.
- Feedback to individual participants should be conducted by a trained professional.

12.2. Surveys and focus groups

Human factors assessments in closed-loop trials are made up of tests and procedures that taps in to the “human side” of these systems. Human factor assessments cut across the acceptability, usability, and efficacy of the system from the perspective of the user. Further, human factor assessments help to understand expectations, attitudes, and behaviours that influence the uptake and response to using a closed-loop system. The human factor assessments in research include both quantitative and qualitative methods and have been tested in adults in the targeted age range. They reflect the most methodologically sound and clinically informed tools available. Surveys are listed in Table 3 and all surveys will be administered in-person. It is estimated that participants will take 20-25 minutes to complete surveys. Surveys will be completed at the time of major assessments in the trial – baseline (after run-in, but prior to randomisation) and at the end of each study period.

In addition, focus groups will be convened during the study trial. Focus groups will meet when each study group completes each study period. We will aim to conduct focus groups in-person and will utilise local facilitators who have worked with the research team on similar projects. Focus groups will include 3-6 participants and a script of open-ended questions will be used to gather feedback and reactions to the closed-loop system, the clinical trial, and quality of life changes. There will also be time for discussion of content raised by participants. Use of a moderator with advanced training (PhD level) will ensure consistency across groups. Sessions will be audio- and video-taped and transcribed by a professional transcription service.

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

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

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

12.3.3. HbA1c

HbA1c will be measured at a local laboratory compliant with IFCC reference HbA1c method. This sample can be capillary or venous.

12.4. Total Blood Loss

The total blood loss will be approximately 50 to 100 ml.

13. Study Materials

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), Faster Insulin Aspart (Fiasp; Novo Nordisk, Bagsvaerd, Denmark), or Lispro (Humalog; Eli Lily, Indianapolis, USA) but not Glulisine (Apidra; Sanofi-Aventis, Paris, France).

13.2. Insulin Pump

During the run-in period and both study arms, the Dana insulin pump (SOOIL) will be used. Glooko/Diasend software or similar will be used to download insulin pump data at regular intervals.

13.3. Continuous Subcutaneous Glucose Monitor

The Dexcom G6 real-time sensor with sensor applicator (Dexcom, Northridge, CA, USA) will be the study CGM. The sensor will be calibrated according to manufacturer's instructions.

13.4. Blood Glucose Meter

Study participants will use their own approved glucose meter for self-monitoring of capillary blood glucose (SMBG) during the study. The capillary glucose meter readings may be used to calibrate the sensor according to manufacturer's instructions.

13.5. Computer-based Algorithm

The model predictive computer-based controller will be used. The controller has been used safely and effectively in the closed-loop studies in both children and adults with T1D **(studies 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).**

13.6. Actiwatch

An Actiwatch (Philips Respironics, Bend, Oregon, USA), worn on the non-dominant wrist, will be used to measure sleep.

13.7. Holter Monitor

A Holter monitor (Lifecard 12; Spacelabs Healthcare, Hertford, UK, or similar) will be applied.

14. Data Analysis

14.1. Primary Analysis

The primary analysis will evaluate 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 16 week interventions.

14.2. Secondary Analysis

14.2.1. Biochemical evaluation

Key secondary endpoints include the between group differences in time spent above target glucose (>10.0 mmol/l) (>180mg/dl), average glucose levels, HbA1c levels at the end of treatment period and time spent below target glucose (<3.9mmol/l) (<70mg/dl), Other secondary efficacy endpoints include the between group differences in standard deviation, and the coefficient of variation of glucose levels, the time with glucose levels < 3.5 mmol/l (63mg/dl) and <3.0 mmol/l (54mg/dl), the time with glucose levels in the significant hyperglycaemia (glucose levels > 16.7 mmol/l) (300mg/dl), total, basal and bolus insulin dose.

All analyses will be by intention to treat.

Summary statistics for the following outcome metrics will also be tabulated separately for daytime (defined as 6am to less than 12am) and nighttime (defined as 12am to less than 6am) over the four month period:

- Percent time with glucose levels spent in the target range (3.9 to 10.0 mmol/L)
- Mean of glucose levels
- Standard deviation of glucose levels
- Percent time with glucose levels below 3.9 mmol/L
- Total insulin dose

Per-protocol analysis will also be performed which will evaluate glucose sensor based outcomes with a minimum of 60% of available CGM readings during the control period and 60% CL system use during the CL period. Descriptive tabulations of questionnaires will be carried out.

14.2.2. Analysis of Human Factors Data

Quantitative data on usability and satisfaction will be analysed using simple descriptive statistics. In addition, we will analyse scores from the measures in the human factors assessment battery to determine if changes occur over time and between groups. Using SAS v9.4, we will construct predictive models in the general linear framework to examine each set of human factors (e.g., QOL, fear of hypoglycaemia) and its association with our outcomes. Group assignment will be the primary covariate.

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

14.2.3. Cardiac Arrhythmia Analysis

Holter monitor data at the fourth month in the two treatment groups will be analysed at the end of the study period. Arrhythmic events analysed will include atrial fibrillation, atrial ectopic beats, bradycardia, ventricular premature beats, complex ventricular premature beats, non-sustained ventricular tachycardia and measures of heart rate variability and QT interval. All identified arrhythmic events will be manually verified for accuracy.

Investigators will be blinded to glucose values during arrhythmia analysis. The frequency of arrhythmic events during periods of hypoglycaemia (sensor glucose ≤3.9 mmol/L and 3.0 mmol/L), will be compared to the frequency of arrhythmic events during normoglycaemia (3.9-10 mmol/L) within each study arm. Analyses will be calculated for daytime and night-time periods to take into account diurnal variation. Any incidental finding will be referred by the Investigator to the clinical team and be managed as per local site policy.

14.2.4. Quality of Sleep Assessment using Actiwatch

Sleep will be automatically scored by Actiware software using previously described and validated algorithms. Sleep duration will be calculated as the sum of all epochs scored as sleep during the time in bed. Variability across nights in a participant's sleep duration will be summarised using the coefficient of variation. Sleep data will be averaged across nights in each participant for each study period.

14.3. Exploratory Analysis

No exploratory analyses will be performed.

14.4. Interim Analysis

No interim analysis will be performed.

14.5. Statistical Methods

The respective values obtained during the 4 month randomised interventions contrasting the closed-loop system against the sensor augmented insulin pump therapy will be compared using a linear mixed model adjusting for period as a fixed effect and site as a random effect. The analysis dataset will be three records per subject (one for baseline and one for each period). Inclusion of the pre-randomization baseline value as a third observation for each subject in the model gives a variance reduction analogous to adjusting for it as a covariate. Residual values from the regression model will be examined for an approximate normal distribution. If values are highly skewed a transformation or nonparametric analyses will be used. The statistical analysis will include the assessment of the period effect.

The primary analysis will follow the intention-to-treat principle and will be a single comparison. 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.

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

- Time spent with sensor glucose levels between 3.9 to 10.0 mmol/l

- Time spent above target glucose (10.0 mmol/l)
- Average of glucose levels
- HbA1c
- Time spent below target glucose (3.9 mmol/l)

This process continues iteratively moving to the next variable down on the list until a non-significant result ($p \geq 0.05$) is observed, or all five variables have been tested. If a non-significant result is encountered, then formal statistical hypothesis testing is terminated and any variables below on the list are not formally tested and analysis of these variables becomes exploratory.

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

- Intervention period: Closed loop active for at least 60% of the time
- Control period: Sensor used for at least 60% of the time

Consistency of treatment effect across sites will be investigated by testing for interaction between study intervention and study site.

Severe hypoglycaemic events and ketone-positive hyperglycaemia will be tabulated in each treatment group, which will be compared (if enough events) using repeated measures logistic regression adjusting for period and whether the subject has ever had a prior event. We will also apply a repeated measures regression model as for the primary analysis to assess treatment differences in absolute terms.

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.

14.6. Sample Size and Power Calculations

Power calculation is based on improvements in time in target. Assuming a standard deviation of 18% at baseline and average improvement of time in target of 10% (41), 31 subjects are required at the desired 80% power and an alpha level of 0.05 (two-tailed).

Up to 40 subjects could be recruited aiming for 36 completed subjects to allow for drop-outs. Subjects who drop out of the study during optimisation period and within the first 4 weeks of the first intervention period may be replaced.

14.7. 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.

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 in line with the General Data Protection Regulation (GDPR) (EU) 2016/679.

Direct access to the source data will be provided for monitoring, audits, REC 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

The study will be undertaken in accordance with Good Clinical Practice (GCP). All staff will receive appropriate Good Clinical Practice Training. A Study Management Committee, and Data and Safety and Monitoring Board will be appointed for the study. Each recruiting site will have a designated Principal Investigator. Obtaining consent and recruitment to the study, CGM training, insulin pump training and closed-loop system training will be undertaken by appropriately trained members of the local teams. A delegation log will be held at each site listing the responsibilities of staff members.

17.1. Data and Safety Monitoring Board

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 Coordinator, and Study Data Manager will be responsible for the day to day management of the trial. The Principal Clinical Investigators may also participate.

17.3. Study Monitoring

The Study Coordinator will ensure that the study is conducted in accordance with ICH 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 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 Coordinator

The Study Coordinator 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 (64th WMA General Assembly, Fortaleza, Brazil, October 2013).

19.1. Independent Research Ethics Committees

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 will be submitted. Written approval will be obtained from the REC prior to the commencement of the study. Any additional requirements imposed by the REC 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 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 will be obtained from participants according to REC 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. Timetable

Inclusion of the first subject in the study is planned to take place in Q2 2019. The expected completion of the last subject is Q4 2020 and the planned completion of the Clinical Study Report is Q1 2021.

21. Amendments to the Protocol

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

22. Deviations from Protocol

Deviations from the protocol should not occur without prior approval of the REC 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 and Sponsor as soon as possible/ in a timely manner, following nationally agreed guidelines.

23. Reports and Publications

Data will be published 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 of time period as permitted by relevant institutions. Other source documents and the Investigator's Site File must be retained for at least 15 years in line with the General Data Protection Regulation (GDPR) (EU) 2016/679. The Principal Investigator will archive the documentation pertaining to the study in an archive after completion or discontinuation of the study.

25. Indemnity Statements

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, but no-one has acted negligently.

The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the clinical trial.

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