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CLINICAL TRIAL PROTOCOL

The Bio-inspired Artificial Pancreas for the Home

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General Information

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1.0 Background

Type 1 diabetes mellitus (T1DM) is an autoimmune condition caused by destruction of the β-cells in the pancreas that produce insulin. Current regimens for treating T1DM in clinical practice are mainly based on multiple daily injections of subcutaneous insulin in dosages determined by intermittent blood glucose measurements. Continuous subcutaneous insulin infusion (CSII) via a pump provides an alternative form of insulin therapy with the advantage of delivering variable basal rates throughout the day and fewer injections. However, a significant proportion of people with T1DM on current insulin regimens do not achieve optimal blood glucose control which increases the risk of complications including kidney failure, blindness, nerve damage and heart disease. Intensive treatment can lower this risk but may lead to potentially dangerous low blood glucose levels (hypoglycaemia). The Diabetes Control and Complications Trial demonstrated that intensive management reduced complications by 50-76% (1). This was at the expense of increased hypoglycaemia, especially at HbA1c levels <58mmol/mol (7.5%). Severe or prolonged hypoglycaemia is a major concern and can result in seizures, cardiac arrhythmias and is associated with the "dead-in-bed" syndrome (2, 3). Diabetes technologies, such as insulin pumps, bolus calculators, continuous glucose monitors and closed-loop insulin delivery systems, are important in aiding self-management and optimising glycaemic control in type 1 diabetes.

A closed-loop insulin delivery system, also known as an artificial pancreas, provides the potential to improve HbA1c while avoiding hypoglycaemia. It requires continuous glucose measurement by a subcutaneous continuous glucose sensor, a control algorithm and a pump for insulin delivery. Three main control algorithms (proportional-integral-derivative,

model predictive control and MD-logic) have been employed in out-of-clinic closed-loop clinical studies to date (4). Most closed-loop systems utilise insulin alone (5-7), while some groups use a bi-hormonal (insulin and glucagon) approach (8-9).

To support mealtime insulin dosing, people with type 1 diabetes use bolus calculators to provide insulin dose recommendations. A standard bolus calculator uses a generic formula taking into account the target glucose level, current glucose level, carbohydrate content of meal (grams), insulin: carbohydrate ratio (the amount of carbohydrate (grams) covered by 1 unit of insulin), insulin sensitivity factor (the reduction in blood glucose by 1 unit of insulin) and insulin-on-board (IOB, the remaining active insulin from the previous bolus). Some bolus calculators additionally consider parameters such as exercise, but all lack the ability to automatically adapt over time to respond to individual needs. Standard bolus calculators have been incorporated into insulin pumps and some glucose meters.

The Bio-inspired Artificial Pancreas

The diabetes technology group at Imperial College have developed a bio-inspired artificial pancreas (BiAP) system which uses a control algorithm based on a mathematical model of beta-cell behaviour derived from physiological experiments, carried out by other groups, which have demonstrated how the beta cells in the pancreas produce insulin in people without diabetes. Utilising the data from these experiments it has been possible to implement the behaviour of the beta cell in software (10-12) and we have used a simulator with 200 virtual patients to demonstrate the safety and efficacy of the algorithm. The data from the simulator have previously been published (13). The simulator was developed from human data and takes into account glucose-insulin regulation, sensor errors, sensor placement, route of insulin administration and meal-time glucose absorption. It has been approved by the FDA in the United States as a step in the pathway of developing an artificial pancreas and has been validated against human data (14). The BiAP algorithm is implemented on a miniature silicon microchip within a portable handheld device, which interfaces the components of the artificial pancreas.

Clinical evaluation of the BiAP

The existing bio-inspired artificial pancreas has already been evaluated in participants with T1DM during fasting conditions, overnight and following a standard meal (breakfast) challenge and the data have shown good glycaemic control with minimal hypo- or hyperglycaemic excursions (15). Following the feasibility studies, a 24-hour randomised control clinical trial demonstrated that the BiAP system significantly reduces hypoglycaemia

compared to standard insulin pump therapy (16). We have additionally shown that the BiAP remains safe in the event that a meal is unannounced or the carbohydrate content is underestimated (16).

The BiAP system has also been evaluated in standard exercise studies with insulin only artificial pancreas control, insulin and glucagon artificial pancreas control and open-loop insulin pump therapy. These have demonstrated that the controller is able to manage the challenge of prolonged aerobic exercise and that the addition of glucagon does not impact on the risk of hypoglycaemia with physical activity, immediately after physical activity or up to 16 hours after (17, 18)

The Advanced Bolus Calculator for Diabetes

The Imperial College Diabetes Technology team have developed an Advanced Bolus Calculator for Diabetes (ABC4D), a novel, adaptive decision support algorithm based on case-based reasoning (CBR) providing real-time insulin advice through a smartphone application. CBR is an artificial intelligence technique that solves newly encountered problems by applying the solutions learned from solving similar problems encountered in the past. ABC4D utilizes CBR where cases within a case-base are used to represent various meal scenarios (e.g. dinner after exercise). Each time a user requests a new insulin bolus recommendation, the current meal scenario is compared to all existing cases from the past. If a similar case is found the solution of this case is applied to calculate the insulin dose. If no similar case exists, then a new case is created. The outcome of each insulin advice is then revised by analysing the post-prandial glucose excursion provided by continuous glucose monitoring (CGM) data. The ABC4D algorithm has been validated in-silico using the FDA-accepted UVa-Padova type 1 diabetes simulator (19).

Clinical evaluation of the ABC4D

The safety and feasibility of the ABC4D has been evaluated pilot clinical study over 6 weeks in 10 adult participants with T1DM. The clinical outcomes from the pilot study showed that ABC4D is safe and maintains glycaemic control with a trend suggesting improvement in post-prandial hypoglycaemia and overall glucose outcomes (20). A separate analysis of the case parameters used in ABC4D showed that the alcohol and exercise parameters were most frequently used suggesting a clinical benefit in terms of improving post-prandial hypoglycaemia (21). The usability and acceptability of the system architecture was favourable with 8 out of 10 users trusting the advice generated and 9 out of 10 happy to use ABC4D (22). A powered randomised controlled trial over 6 months is currently underway to assess whether the ABC4D system is superior to a non-adaptive bolus calculator.

The components of the closed-loop insulin delivery system

The complete device used in this protocol comprises a commercial continuous subcutaneous glucose sensor (Dexcom G5 CGM system), the BiAP control algorithm implemented in a low-power handheld device (developed by the Imperial Diabetes Technology team), the ABC4D adaptive bolus calculator algorithm in a smartphone platform (developed by the Imperial Diabetes Technology team) and a commercial continuous subcutaneous infusion pumps (Tandem T-slim) to provide glucose control. Fig 1 gives an overview of the complete system architecture. If participants already have intraperitoneal (IP) access (DiaPort) then the insulin will be delivered via the intraperitoneal route in accordance with these participants' standard care.

Glucose sensor

The glucose sensor that will be used throughout the clinical validation studies is a CE marked and MHRA approved device commercially available (Dexcom G5 Mobile CGM system). Subcutaneous sensors sit just under the skin and sample interstitial fluid using an enzyme electrode. A small voltage is applied across the sensor and a current is fed back to the sensor instrumentation. This current is proportional to the glucose concentration in interstitial fluid and is calibrated against blood glucose a minimum of 12 hourly.

BiAP algorithm in a low-power handheld device

As outlined above

ABC4D adaptive bolus calculator algorithm in a smartphone platform

As outlined above

Insulin infusion pump

The pump is a small (6cm x 4cm) device, containing a cartridge that can be filled with insulin, which delivers a continuous infusion of insulin into the subcutaneous (fat) tissue or intraperitoneal space via a tube connected to a pump cannula. The pump device used throughout the clinical validation is the Tandem t:slim which is FDA-approved and commercially available in the United States for use with Insulin Aspart (Novorapid) and Insulin Lispro (Humalog). The insulin pump is not CE-marked and not commercially available in Europe at present and will be labelled "exclusively for clinical investigations". Participants will continue on their usual insulin, but the insulins used will be restricted to Insulin Aspart (Novorapid) and Insulin Lispro (Humalog).

Fig 1. System architecture

Glucose data from the Dexcom G5 transmitter are sent by Bluetooth LE to the BiAP handheld unit where the bio-inspired algorithm is operating and insulin microbolus data are sent on to the Tandem t:slim pump at appropriate intervals (e.g. 5 minutes). At mealtimes (any meal or snack containing 15g or more of carbohydrate), the study participants will inform the smartphone of a meal and enter a carbohydrate estimate before eating. The pump will deliver a bolus calculated either according to a fixed or adaptive algorithm. The controller and smartphone will, at all times, know insulin-on-board, ensuring safety. Data will be fed by wifi or cellular data (3G/4G) to the research team but will not be monitored in real-time.

Safety

Remote monitoring will not be routinely used but all participants will have 24-hour access to engineering and clinical support and will have a clear written plan in case of technical challenges. The facility to share data in real-time will be provided on the handset using Bluetooth to mirror data on the smartphone device with WiFi or 3G communication, to enable the support team to provide timely and appropriate advice.

To ensure participant safety, individualised constraints based on patient specific parameters (insulin:carbohydrate ratio, insulin sensitivity factor and insulin-on-board) are applied to the insulin calculated by the controller. Hypoglycaemia prevention strategies including insulin infusion reduction and suspension are employed for forecasted glucose concentrations below predefined thresholds. An alarm system alerting for device communication errors, sensor failures, hyper- and hypoglycaemia is in place and in case of sensor or controller failure insulin infusion will revert to a safe basal rate (% of a pre-programmed optimum). Finally, remote monitoring of RT-CGM, reflecting artificial pancreas functioning, will be available to the study team using a CE marked smartphone application (Dexcom Follow App). The study team will not be monitoring the data continuously, but will be able to use this information if participants seek technical/clinical support.

Potential risks and benefits

The potential risks and burdens for research participants are as follows:

Some visits involve taking a venous blood test. These have the potential to cause discomfort. This will be minimised by experienced research personnel and appropriate use of equipment.

Throughout the study, participants will have a subcutaneous insulin infusion pump cannula inserted and these need to be replaced every 3 days. All participants will use subcutaneous insulin infusion pumps for routine care. Participants will also have the glucose sensor inserted and these need to be changed every 7 days. Both pump cannula and glucose sensor insertion can be associated with some discomfort but the insertion devices are spring-loaded with introducers, making the process rapid and often painless. Any discomfort will be minimised by adhering to manufacturer's instructions.

During the closed-loop study periods there is a risk from the new technology. The controller may suggest an excess or relatively deficiency of insulin infusion. Participants will be advised to check their capillary blood glucose as per routine care and in addition they will have access to real-time CGM. glucose values are frequently monitored to prevent adverse events related to elevated or low glucose values. To date the BiAP system and the ABC4D system have been evaluated in clinical studies in participants with T1DM without incidents of severe hypo- or hyperglycaemic excursions.

It is well-known that insulin requirements change during pregnancy and hence participants who are female and of childbearing age will have a urine pregnancy test done at screening and prior to each intervention. Participants will be excluded from the study if they are pregnant or planning pregnancy within the study time frame, to minimise any potential risk.

It is acknowledged that the clinical schedule is demanding of subject's time and includes overnight visits. This inconvenience is necessary to adequately and safely ensure participants receive the appropriate training on how to use the device and we will minimise the burden as much as possible by providing entertainment (TV, radio, reading material, internet access) in a comfortable environment with privacy. We will also ensure to make every effort to schedule visits around participants' lifestyles.

Research participants will benefit from being in the study by having increased access to diabetes professionals and more frequent visits to hospital with an emphasis on improved glycaemic control. They will also have the opportunity to use continuous glucose monitoring and review the results with a consultant diabetologist experienced with monitoring. The benefits to people with T1DM include the potential to carry forward technology to improve the risks of high glucose concentration leading to complications and distressing low glucose values.

Route of administration, dosage, dosage regimen, and treatment period

Insulin will be administered subcutaneously or intraperitoneally (in those who already have IP access with a DiaPort). This is the standard route of administration for insulin in T1DM. Alternative routes of administration include intravenous or inhaled. Intravenous insulin is used clinically in people with diabetes who are acutely unwell or those unable to eat and drink, inhaled insulin is no longer commercially available in the UK. The insulin dosage will be expressed as units infused subcutaneously as microboluses and will be calculated by the control algorithm of the closed-loop at 5-minute intervals. The treatment periods are defined by time spent in closed-loop insulin delivery.

2.0 Clinical study

The trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

Trial Objectives and Purpose

The main objectives of the research study is to evaluate the safety, efficacy and cost-effectiveness of a bio-inspired artificial pancreas (BiAP) with, and without, the addition of an adaptive bolus calculator (ABC4D) compared to gold-standard sensor-augmented pump therapy.

Hypothesis

1. A bio-inspired artificial pancreas (BiAP) device has a positive impact on glucose control, as measured by time in target after 6 weeks of use, when compared with sensor-augmented pump with low-glucose suspend (LGS).
2. A bio-inspired artificial pancreas (BiAP) device with an adaptive bolus controller (ABC4D) has an additional positive impact on post-prandial glucose control.

Trial Design

A 3-way crossover randomized controlled trial (Fig 3). Description of the three arms:

1. Sensor augmented pump (open-loop)
2. BiAP with a fixed bolus calculator
3. BiAP with the Advanced Bolus Calculator for Diabetes (ABC4D)

The primary outcome from the studies will be % time spent with a glucose concentration in the target range (3.9-10.0mmol/l). This outcome incorporates safety as it ensures participants do not have low or high glucose excursions and is the principal measure of efficacy for closed-loop insulin delivery systems in the scientific literature. Other measured outcomes will be % time spent in euglycaemia (3.9-7.8mmol/l), % time spent in hypoglycaemia (<3.9mmol/l), % time spent in hyperglycaemia (>10mmol/l), mean venous blood and sensor glucose, glycaemic variability as measured by standard metrics (SD, CONGA, LI, JINDEX, GRADE, MODD, MAGE, ADDR, MVALUE, MAG), glycaemic risk as measured by low blood glucose index (LBGI) and high blood glucose index (HBGI), closed-loop error grid analysis, glucose area under the curve. All measures have been previously published and validated. Quality of life, treatment satisfaction and device acceptability outcomes will be measured using mixed methods (questionnaires and semi-structured interviews).

Methodology Randomised controlled cross-over open label study

Timescale It is anticipated that the study will take 1 year, each subject will be in the study for up 6 months, with a total of 6 visits in that timeframe.

Population

n = 20

Inclusion criteria

- Adults over 18 years of age
- Type 1 diabetes confirmed on the basis of clinical features and a random c-peptide <200 pmol/L
- Type 1 diabetes for greater than 1 year
- Continuous subcutaneous insulin infusion for greater than 6 months
- Structured education done (either 1:1 or group education)
- HbA1c <10% (86mmol/mol)
- A negative pregnancy test in female participants of childbearing age

Exclusion criteria

- More than one episode of severe hypoglycaemia (defined as hypoglycaemia requiring 3rd party assistance) in the preceding year
- Impaired awareness of hypoglycaemia (Gold score >4)
- Pregnant or planning pregnancy
- Breastfeeding
- Enrolled in other clinical trials
- Have active malignancy or under investigation for malignancy
- Severe visual impairment
- Reduced manual dexterity
- Ischaemic heart disease
- Anti-anginal medications (e.g. GTN)
- Regular use of paracetamol
- Unable to participate due to other factors, as assessed by the CI

Subject withdrawal criteria

Participants will be withdrawn from the study in the case of:

1. Loss of capacity to give informed consent
2. Cessation of CSII as usual care for type 1 diabetes

3. Recurrent (>1 episode) severe hypoglycaemia (defined as needing 3rd party assistance)
4. Terminal illness

Withdrawal will be immediate and participants will be followed up in the appropriate outpatient diabetes clinic within 4 weeks of withdrawal.

Recruiting will be undertaken in the insulin pump clinics at Imperial College Healthcare NHS Trust, from registered research databases and from interested participants who contact us. Participant information sheets will be given to potential participants and, after a minimum of 48 hours and following any questions, informed consent will be taken.

Usual care will be maintained for diabetes throughout the study. No concomitant medical therapies are contra-indicated, except for GLP-1 analogues and high dose steroids.

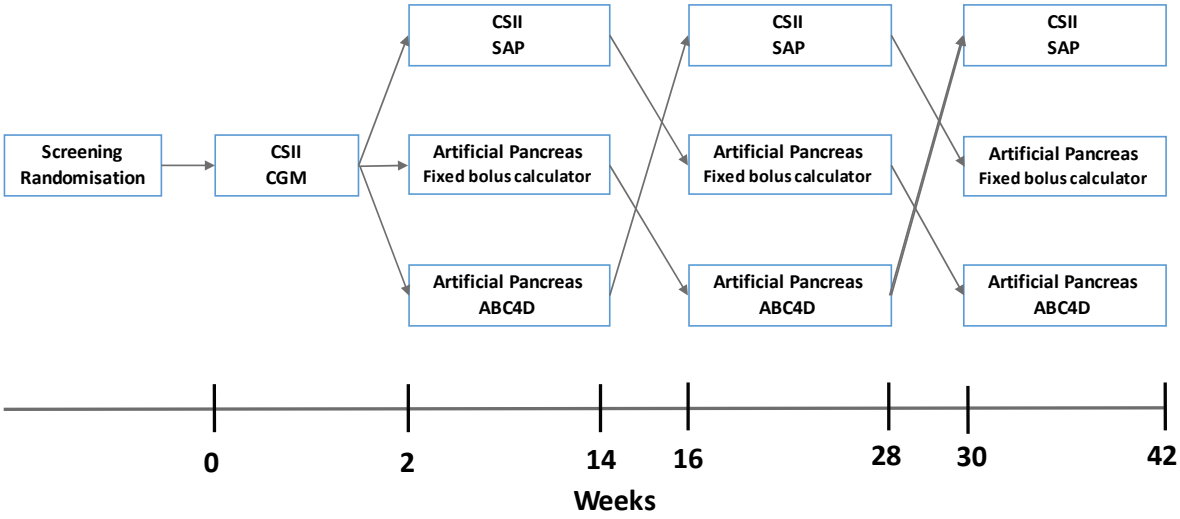

Fig.3 Study design.

CSII – Continuous Subcutaneous Insulin Infusion, SAP – Sensor Augmented Pump, CGM – Continuous Glucose Monitoring, BiAP – Bio-inspired Artificial Pancreas, ABC4D – Advanced Bolus Calculator for Diabetes

Visit 1: Screening

- Routine clinical examination
- ECG
- Venous blood taken for glucose, c-peptide, HbA1c, lipids, creatinine

- Urine pregnancy test in female participants of childbearing age
- Random urine sample for albumin: creatinine ratio (UACR) ratio and c-peptide creatinine ratio (UCPCR)
- Gold score
- Continuous glucose monitoring (Dexcom) will be connected according to manufacturer's instructions. Participants will be shown how to insert the sensor themselves and written instructions on how to calibrate the CGM every 12 hours and sensor change every 7 days as per manufacturer's instructions will be provided. Participants will be asked to wear the CGM for 2 weeks in total.
- Participants will be provided with the study pump and receive training on how to use it.
- Mixed methods psychological assessment: Diabetes quality of life (DQOL), Diabetes Treatment Satisfaction Questionnaire (DTSQ) and PAID Questionnaire to be completed. Semi-structured interviews by the investigators will be carried out.

Visit 2: CGM review

- 14 days following visit 1
- Remove CGM, upload data and review results with the participant.
- Make adjustments to insulin: carbohydrate ratio(ICR), insulin sensitivity factor (ISF), insulin basal infusion rates if necessary.

Randomisation:

The order of the three intervention arms will be completely randomised using sealed envelope (www.sealedenvelope.com).

Irrespective of which intervention the participants are allocated to for the first 6 weeks they will spend the first 24 hours at the clinical research facility for education and training on how to use the BiAP system as a whole (as outlined under visit 3).

Visit 3: 24 hours in clinic and start of 1st 6-week intervention period

- Attend the CRF at 16:00 until next day at 18:00.
- Participant will be connected to the BiAP system at 17:00.
- Finger prick blood sampling will be done eight times (before after each meal, bet-time, one random during night) and analyzed immediately for glucose concentration using a standard glucometer.

- Standardized meals will be provided at 19:00 (dinner), 07:00 (breakfast) and 12:00 (lunch).
- The research team will ensure that the participants are comfortable with the BiAP system, particularly in the following situations:
  - How to switch the system from open-loop to closed-loop and vice versa.
  - When to calibrate the CGM system.
  - When to seek help.
  - Should the participant want a snack overnight they can record the carbs on the smartphone. For snacks of 15g or below participants will be advised not to bolus, but in cases of larger snacks they can calculate the bolus using the meal announcement button on BiAP/smartphone. Participants will be shown how to do this.
- They will be free to go home at 18:00 with the BiAP device to continue the remaining 6 weeks.
- Participants will be trained to use the sensor, controller and insulin pump.
- They will have a structured education refresher.
- All training will be delivered by the study team and will be supported with written information. Participants will be expected to be able to self-manage the sensor, controller and pump prior to leaving the clinical research facility and competencies will be clearly recorded. Videos to support sensor insertion, and pump cannula and reservoir operations will be provided to all participants via email or on a USB stick and can be uploaded to participants' smartphones for off-line use. Contact details for clinical and technical support will be provided.
- The study team will phone the participants on day 1, day 3, day 7 and at 3 weeks.

Visit 4: End of first 6-week intervention period

- Attend the clinical research facility.
- Review any issues with the technology used.
- Download data from the study pump (the pump stores data for 90 days).
- Provide consumables (sensors, transmitter, insulin infusion sets) for the next 6-week intervention period.
- Gold score
- Mixed methods psychological assessment: Diabetes quality of life (DQOL), Diabetes Treatment Satisfaction Questionnaire (DTSQ) and PAID Questionnaire to be completed. Semi-structured interviews by the investigators will be carried out.
- Acceptability questionnaire to be completed.
- Repeat urine pregnancy test in female participants of childbearing age

- Participants will be instructed to revert back to their usual care for 2 weeks (wash-out period) before commencing the next intervention for 6 weeks.

Visit 5: End of 2nd 6-week intervention period

- Attend the clinical research facility.
- Review any issues with the technology used.
- Download data from the study pump.
- Provide consumables (sensors, transmitter, insulin infusion sets) for the next 6-week intervention period.
- Gold score
- Mixed methods psychological assessment: Diabetes quality of life (DQOL), Diabetes Treatment Satisfaction Questionnaire (DTSQ) and PAID Questionnaire to be completed. Semi-structured interviews by the investigators will be carried out.
- Acceptability questionnaire to be completed.
- Repeat urine pregnancy test in female participants of childbearing age
- Participants will be instructed to revert back to their usual care for 2 weeks (wash-out period) before commencing the next intervention for 6 weeks.

Visit 6: End of 3rd 6-week intervention period and end of study

- Attend the clinical research facility.
- Review any issues with the technology used.
- Gold score
- Mixed methods psychological assessment: Diabetes quality of life (DQOL), Diabetes Treatment Satisfaction Questionnaire (DTSQ) and PAID Questionnaire to be completed. Semi-structured interviews by the investigators will be carried out.
- Acceptability questionnaire to be completed.
- Participants will be asked to return all components of the study device and will be instructed to revert back to their usual care.

Table: Overview of activities at each visit for participants

Activity / Visit no	**1**	**2**	**3**	**4**	**5**	**6**	**Additional information**
Insertion of CGM sensor	x						Participants will change the sensor every week at home throughout the study
CGM review with participant		x					
Randomisation + Initialise the			x	x	x		

intervention/control							
Update CBR algorithm with new cases							This will be done automatically in the BiAP+ABC4D intervention
Clinical examination	x						
Weight measurement	x						
Venous blood test	x						
Urine test	x			x	x		
Pregnancy test (if applicable)	x						
ECG	x						
Questionnaire/s	x			x	x	x	
Follow-up clinical visits		x	x	x	x	x	
Overnight stay in clinical research facility			x				
Semi-structured interview	x			x	x	x	

3.0 Statistics

From our previous published data[1,6] we anticipate that the BiAP/ABC4D intervention will increase the percentage of time for which plasma glucose concentrations were in the target range by a mean of 6% (SD 9.9) compared with the BiAP/fixed bolus artificial pancreas system, and by an estimated mean of more than 6% (9.9) compared with the control group. We intend to do three pairwise comparisons between the interventions, and therefore have conducted a power analysis using the typical sample size formula for the paired t test. We estimate, using mean 12% (9.9), that 20 participants would provide 90% power at the 5% significance level (corrected for multiple comparisons) to detect differences between the three interventions.

Missing, unused, and spurious data will be assessed on an individual basis and may be ignored, withdrawn or the visit may be removed from the analysis with appropriate justification adjudicated by the Principal Investigator.

Efficacy

Primary outcome will be:

- % time in target range defined as 3.9-10mmol/l

Secondary outcomes will be:

- % time spent in euglycaemia (3.9-7.8mmol/l)
- % time spent in hypoglycaemia (<3.9mmol/l)
- % time spent in hypoglycaemia (<2.8mmol/l)

- % time spent in hyperglycaemia (>10mmol/l)
- % time spent in severe hyperglycaemia (<15mmol/l)
- Mean sensor glucose
- Glycaemic variability
- Glycaemic risk as measured by LBGI and HBGI
- Closed loop error grid analysis
- Glucose area under the curve
- Insulin requirement in units/kg/hr
- Hypoglycaemia awareness (Gold scores)
- Quality of life by mixed quantitative and qualitative methodologies
- Cost-effectiveness
- Device usability and acceptability
- % time in closed loop control
- Severe hypoglycaemia
- Diabetic ketoacidosis
- Sensor MAD%

These are validated, published metrics, which will be assessed at the end of each visit from CGM data. There will be an interim analysis of the data after each visit to ensure efficacy and safety.

4.0 Data

During the course of the study visits some data will be stored on laptop computers, not connected to the Internet, for later statistical analysis. These data will be coded and non-identifiable. Any identifiable participant data collected at screening will be stored in a locked filing cabinet in a secure room in Imperial College Healthcare NHS Trust. Only the clinical research team will have access to the filing cabinet.

Electronic data will be stored by subject number only on NHS and Imperial College desktop computers which are in the same locked room. Laptop computers may be used during the visits for portability and convenience. At the end of each visit the anonymised data will be transferred immediately to the secure NHS and Imperial College computers and will be deleted from the laptop.

All data will be stored in an anonymised form by using study numbers for identification of participants. The NHS code of confidentiality will be followed and all activity will meet the requirements of the data protection act.

Only members of the clinical research team and those responsible for direct care will have access to participants' data during the study. The data generated by the study will be analysed by the research team including the engineering team from Imperial College. The analysis will be on anonymised data and will take place in Imperial College Healthcare NHS Trust and in Imperial College academic buildings, both in the Faculty of Medicine and in the Faculty of Engineering. Fully anonymised data may be shared with future collaborators to support further development.

Electronic data transmission and storage

Data security and privacy will be a priority whilst dealing with data obtained throughout the study. During the clinical study anonymised clinical data (real-time continuous glucose data and insulin doses recommended by the BiAP and ABC4D algorithms) will be automatically transmitted between components of the BiAP system and stored locally on the BiAP device. In addition, RT-CGM data will be available to the study team using a CE marked smartphone application (Dexcom Follow App) to allow remote supervision of the artificial pancreas functioning. All data will be stored and protected against non-authorised access; transmission of data will be secured; only authorised users will have access to stored data. Authorised users will include the clinical and engineering study team members and individual participants will have access to their own data.

Direct Access to Source Data/Documents

The investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

5.0 Safety

During intercurrent illness, study visits will be postponed as insulin requirements will be altered.

Adverse Event Reporting

Adverse events will be reported to the Health Research Authority (HRA), the sponsor and the Chief Investigator (CI) immediately. Participants will be followed-up after one week following an adverse event and thereafter in the diabetes clinic or any other clinically indicated follow up. A reporting log form will be kept in the TMF.

A “serious adverse event” is one of which:

a) led to death,

b) led to serious deterioration in the health of the subject, that earlier resulted in ;

1) a life-threating illness or injury, or

2) a permanent impairment of a body structure or a body function, or

3) in-patient or prolonged hospitalization, or

4) medical or surgical intervention to prevent life-threating illness or injury or permanent impairment to a body structure or body function,

c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

Summary Reports

In addition to the reporting of individual serious adverse events as detailed above, a summary report of all serious adverse events on a 6 monthly basis will be notified to HRA, sponsor and CI. A table will be reported including the number of serious adverse events, number of participants affected by those events and percentage of the total number or enrolled participants affected by those events.

6.0 Regulatory Issues

Ethics Approval

The Chief Investigator, Professor Nick Oliver, has obtained approval from the National Research Ethics Service Committee London-Stanmore. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

Consent

Consent to enter the study will be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Delegated research health care professional will obtain signed participant consent. The right of the participant to refuse to participate without giving reasons will be respected. After the participant has entered the study the health care professional remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the

participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

Sponsor

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

Funding

The Wellcome Trust is funding this study.

Audits

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

Study Management

The day-to-day management of the study will be co-ordinated by Professor Nick Oliver and the rest multidisciplinary research team. The chief investigator or other senior researchers will chair weekly research meetings and monthly data reviews. Annual reports to the funder and sponsor will be written and submitted. A data monitoring committee, including statistical expertise, a lay member with diabetes and a consultant diabetologist not involved with the study, will be established to provide overview of the clinical study. The data monitoring committee will meet regularly to review and evaluate the study data for participant safety, study conduct and progress.

Publication Policy

The study will be registered on the clinicaltrials.gov system and results will be disseminated by peer reviewed scientific journals, internal report, conference presentation and publication on websites. No identifiable personal data will be published. All anthropometry and personal clinical data will be expressed as mean/ median and spread of the population in the study. All participants will be informed of the results by letter at the conclusion of the study and details of any publications that arise from the study will be disseminated to participants.

References

1. Nathan D, Cleary P, Backlund J, Genuth S, Lachin J, Orchard T et al. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes," N Engl J Med, vol. 353, no. 25, pp. 2643-53, 2005
2. Buckingham B, Wilson DM, Lecher T, Hanas R, Kaiserman K, Cameron F. Duration of nocturnal hypoglycemia before seizures. Diabetes Care 2008; 31: 2110-2112
3. Sovik O, Thordarson H. Dead-in-bed syndrome in young diabetic patients. Diabetes Care 1999; 22(Suppl 2): B40-42
4. Thabit, H. & Hovorka, R. Coming of age: the artificial pancreas for type 1 diabetes. Diabetologia (2016) 59: 1795. doi:10.1007/s00125-016-4022-4
5. Nimri R, Muller I, Atlas E et al (2014) MD-Logic overnight control for 6 weeks of home use in patients with type 1 diabetes: randomized crossover trial. Diabetes Care 37:3025–3032
6. Phillip M, Battelino T, Atlas E et al (2013) Nocturnal glucose control with an artificial pancreas at a diabetes camp. N Engl J Med 368:824–833
7. Thabit H, Tauschmann M, Allen JM et al (2015) Home use of an artificial beta cell in type 1 diabetes. N Engl J Med 373:2129–2140
8. Russell SJ, El-Khatib FH, Sinha M et al. Outpatient glycemic control with a bionic pancreas in type 1 diabetes. N Engl J Med 2014; 371: 313-25
9. Haidar A, Legault L, Messier V, Maria Mitre T, Leroux C, Rabasa-Lhoret R. Comparison of dual-hormone artificial pancreas, single-hormone artificial pancreas,

and conventional insulin pump therapy for glycaemic control in patients with type 1 diabetes: an open-label randomised controlled crossover trial. Lancet Diabetes Endocrinol 2014 (Early online publication) doi:10.1016/S2213-8587(14)70226-8

10. Georgiou P, Toumazou C. A silicon pancreatic beta cell for diabetes. Biomedical Circuits and Systems, IEEE Transactions on, vol. 1, no. 1, pp. 39-49, 2007.
11. Ho M, Georgiou P, Singhal S, Oliver NS, Toumazou C. A bio-inspired closed loop insulin delivery based on the silicon pancreatic beta-cell. Circuits and Systems, 2008. ISCAS 2008. IEEE International Symposium on, pp. 1052-1055, 2008
12. Oliver NS, Georgiou P, Johnston D, Toumazou C. A Benchtop Closed Loop System Controlled by a Bio-Inspired Silicon Implementation of the Pancreatic Beta Cell. *J Diab Sci Tech* 2009 2009;3:1419–1424
13. Herrero P, Georgiou P, Oliver N, Toumazou C. A bio-inspired glucose controller based on pancreatic β-cell physiology . Diabetes Sci Technol 2012; 6: 606-615
14. Kovatchev B, Breton M, Dalla Man C, Cobelli C. In Silico Preclinical Trials: A Proof of Concept in Closed-Loop Control of Type 1 Diabetes. J Diabetes Sci Technol 2009;3(1):44-55
15. Reddy M, Herrero P, El Sharkawy M et al Feasibility Study of a Bio–inspired Artificial Pancreas in Adults with Type 1 Diabetes. Diabetes Tech and Therapeutics 2014; 16(9) – in press.
16. Reddy M, Herrero P, El Sharkawy M, Pesl P, Jugnee N, Pavitt D, Godsland I, Alberti KGMM, Toumazou C, Johnston D, Georgiou P, Oliver N. Metabolic Control with the Bio–inspired Artificial Pancreas in Adults with Type 1 Diabetes: a 24-hour Randomised Controlled Crossover Study. *Journal of Diabetes, Science and Technology* 2016;10:408-413
17. Seechurn S, Reddy M, Jugnee N, El Sharkawy M, Pesl P, Herrero P, Godsland I, Toumazou C, Georgiou P, Oliver N. Does the addition of glucagon to a closed loop system impact on post exercise glycaemia? *Diabetes Technology and Therapeutics* 2016;18(S1):A148
18. Seechurn S, Reddy M, Jugnee N, El Sharkawy M, Pesl P, Herrero P, Godsland I, Toumazou C, Georgiou P, Oliver N. Does the addition of glucagon to the closed loop insulin pump add any benefit? *Diabetes Technology and Therapeutics* 2016;18(S1):A149
19. Herrero P, Pesl P, Reddy M, Oliver N, Georgiou P, Toumazou C. Advanced Insulin Bolus Advisor based on Run-To-Run Control and Case-Based Reasoning. IEEE journal of biomedical and health informatics. 2014.
20. Reddy M, Pesl P, Xenou M, Toumazou C, Johnston D, Georgiou P, Herrero P, Oliver N. Clinical safety and feasibility of the Advanced Bolus Calculator for Type 1

Diabetes (ABC4D) based on Casebased Reasoning: a 6-week non-randomised single-arm pilot study. *Diabetes Technology and Therapeutics 2016*

21. Pesl P, Herrero P, Reddy M, Oliver N, Johnston D, Georgiou P, Toumazou C. Case-Based Reasoning for Insulin Bolus Advice: Evaluation of Case Parameters in a Six-Week Pilot Study. *Journal of Diabetes, Science and Technology 2016*
22. Pesl P, Herrero P, Reddy M, Xenou M, Oliver N, Johnston D, et al. An Advanced Bolus Calculator for Type 1 Diabetes: System Architecture and Usability Results. IEEE journal of biomedical and health informatics. 2015.

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