Non-CTIMP Study Protocol

Can Maximising Time in Range Using Automated Insulin Delivery and a Low Carbohydrate Diet Restore the Glucagon Response to Hypoglycaemic in Type 1 Diabetes?

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Funder	**The Helmsley Charitable Trust**
Funding Reference Number	**Insert funding reference before finalisation**
Chief Investigator	**Prof. Shareen Forbes**
Sponsor number	AC19163
REC Number	**20/SS/0117**
Project registration	**Clinicaltrials.gov: NCT04614168**
Version Number and Date	**Version 8- 28/09/22**

CONTENTS

Title	Can Maximising Time-in-Range using Automated Insulin Delivery Restore Glucagon Secretion To Hypoglycaemia
Precis	A pilot study of 8 months at home, closed loop + low carbohydrate diet (LCD) vs control.
Device	Tandem t:slim X2 with Control IQ and Dexcom G6 system.
Objectives	This study aims to look at the glucagon response to hypoglycaemia in 24 participants with T1D t ascertain is maximising time in range improves glucagon response to insulin-induced hypoglycaemia.
Study Design	Randomised clinical feasibility trial with a 1:1 randomisation to Control IQ + LCD and routine care. 3-month study extension phase for routine care group where they are converted to Control IQ technology.
End Point	To assess if maximising TIR can restore glucagon secretions in T1D.
Population	Adults with c-peptide negative T1D
Sample Size	24 participants
Treatment Groups	Control- Group 1: Standard diabetes care with x3 20 day periods of blinded Dexcom G6 CGM. 3-month study extension where converted to Tandem t:slim X2 with Control IQ technology and Dexcom CGM. Quality of life questionnaires completed at the end of this period and glucose data collected from the CGM. Intervention- Group 2: Tandem t:slim X2 with Control IQ technology and Dexcom G6 CGM + LCD
Participant Duration	9 months + 3 month optional study extension for standard care group
Protocol Synopsis	After consent eligibility will be assessed. The trial will consist of 3 phases: **Phase 1**: Baseline data. All participants will complete 20 days of blinded CGM with Dexcom G6 **Phase 2**: Study Run in. Group 2 will have 2 weeks using the t:slim X2 pump with Control IQ technology and the Dexcom G6 CGM unblinded. **Phase 3**: Study. 8 months. Group 1 will continue routine care as pre-study. They will undergo two periods of blinded Dexcom G6 CGM monitoring each lasting 20 days. Group 2 will continue on their allocated devices and LCD with close monitoring by the study team to ensure TIR is maximised. Both groups will undergo a hyperinsulinaemic hypoglycaemic clamp study at 0 and 8 months. Group 1 will be invited to take part in a 3 month study extension phase where they are converted to the study devices and complete quality of life questionnaires.

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
AID	Automated insulin delivery
BMI	Body mass index
BSA	Body surface area
CGM	Continuous glucose monitor
CRF	Clinical research facility
CTIMP	Clinical trial of investigational medical product
T1D	Type 1 Diabetes
DAFNE	Dose Adjustment for Normal Eating- A course for adult's with Type 1 Diabetes to help adjusting insulin doses
iDCL	International Diabetes Closed Loop Trial
DKA	Diabetic Ketoacidosis
DPP- 4 Inhibitors	Dipeptidyl petidase 4 inhibitors
EDTA	Ethylenediaminetetraacetic Acis- a chemical used in blood collection tubes
EGP	Endogenous glucose production
ERI	Edinburgh Royal Infirmary
ERICRF	Edinburgh Royal Infirmary Clinical Research Facility
GCP	Good Clinical Practice
GLP-1	Glucagon-like peptide 1
HbA1c	Glycated Haemaglobin
ICH	International Conference on Harmonisation
ISF	Insulin sensitivity factor- how 1 unit of insulin lowers the blood glucose by
LCD	Low carbohydrate diet
NEJM	New England Journal of Medicine
QA	Quality assurance
QoL	Quality of Life
RCT	Randomised controlled trial
REC	Research Ethics Committee
SCI-Diabetes	Electronic patient record used Scotland-wide for people with diabetes
SSRI	Selective seratonin reuptake inhibitor
TIR	Time in range
USB	Universal serial bus

1 INTRODUCTION

1.1 BACKGROUND

Glucagon, the pancreatic islet alpha cell product, is a sensitive regulator of glucose homeostasis. In vivo in humans it is critical to the counter-regulatory response to hypoglycaemia (1-3). Almost all people who have had Type 1 diabetes (T1D) for 5 years develop a specific defect in alpha cell Glucagon secretion (4). This defect therefore increases the risk of severe hypoglycaemia. Glucagon secretion may also be inappropriately high in response to hyperglycaemia, meaning that the response is not just absent but is dysregulated.

It is not currently known if preserving glycaemic time in range in T1D leads to improved regulation of glucagon response to hypoglycaemia. Data from longitudinal studies shows that C-peptide (a widely used measure of pancreatic beta cell function) can be preserved in people with optimised TIR, this supports the potential argument that glucagon response to hypoglycaemia may also be preserved with this strategy.

Little is known of the aetiology of this defect, however in a mouse model of neonatal diabetes it was shown that chronic hyperglycaemia leads to a profound change in islet morphology and function without a change in islet number or density (5). Structural and electrophysiological changes in beta cells were shown and attributed to chronic hyperglycaemia. In a later study the same group showed that profound metabolic changes, including significant glycogen accumulation, contributed to the insulin secretory defect of the beta cells (6). Interestingly, in both studies, reducing glucose levels led to the restoration of normal glucose homeostasis and a reversal of the morphological changes of the beta cell.

Although no dynamic assessment of alpha cell function was made the near normalization of glucose homeostasis suggests restoration of both alpha and beta cell function.

Glucagon is a counter-regulatory hormone which helps raise blood glucose levels and it plays a significant role in rescuing people from hypoglycaemia. It is therefore important to understand if this hormonal response, if lost, can be re-established in people with Type 1 Diabetes.

This pilot study aims to look at the Glucagon response to hypoglycaemia in 24 patients with T1D to ascertain whether maximizing blood glycaemic time-in-range (TIR) improves the Glucagon response to hypoglycemia.

Continuous Glucose Monitoring systems (CGMs) have made it possible to quantify glycaemic time in range (TIR), defined as blood glucose >70 and <180 mg/dl (>3.9 and <10.0 mmol/L) (7), this has greatly expanded the understanding of glycaemic control beyond HbA1c alone. Maximising TIR is emerging as a major goal of treatment in T1D (8).

We aim to improve TIR by using an AID system, the t:slim X2 insulin pump with Control IQ technology, and the Dexcom G6 CGM in conjunction with a low carbohydrate diet. We are introducing a low carbohydrate diet as postprandial hyperglycaemia contributes significantly to overall glycaemic burden. Data from the Type 1 Diabetes Exchange indicate that < 30% of patients achieve glycaemic targets (8).

1. Automated Insulin Delivery systems, AIDs

Automated insulin delivery systems (AIDs) have been shown to improve TIR in both the paediatric and adult population (9, 10). This technology combines an insulin pump, a CGM system and an algorithm allowing automatic adjustment of insulin delivery based on a patient's blood glucose.

We propose using the Dexcom G6 CGM and the Tandem t:slim X2 insulin pump. The Tandem t:slim X2 has built in Control IQ technology, an algorithm that utilises CGM data to adjust insulin delivery (Tandem Diabetes Care, San Diego, US) (11).

The features available with this system are:

- Automated insulin correction boluses administered using CGM data.
- A dedicated hypoglycaemia safety system that attenuates smoothly, or discontinues, insulin delivery using CGM and insulin-on-board information.
- Gradually intensified control overnight. During the day the system targets a range of 112.5-160 mg/dl (6.2-8.9 mmol/l). It is more aggressive at night – the goal is to arrive at 112.5-120 mg/dl (6.2-6.7mmol/l) by the time the user wakes up.
- Control-IQ also has an "exercise mode" that changes the target to be closer to 140-160 mg/dl (7.8-8.8 mmol/l).

AIDs, using Control IQ and Dexcom G6, trial results.

Positive clinical results from studies of the Tandem t:slim X2 insulin pump with Control-IQ advanced hybrid closed-loop technology have been reported. Data demonstrated that the system achieved the primary outcome of increasing TIR without any severe hypoglycaemic events.

The iDCL study published in June 2019 (12) showed TIR for participants using Control-IQ technology for 6 months was 71% per day compared to 59% per day for participants in the control group (using sensor augmented pump therapy, i.e. open loop.). During the overnight period time in range with Control-IQ technology was 76 % compared to

59% in the control group. Time spent with glucose values above 180 mg/dL (10.0 mmol/l) was 27% in those using Control-IQ technology compared to 39% in the control group. Time spent below 70 mg/dL (3.9 mmol/l) was 1.4 % with Control-IQ technology compared to 1.9% in the control group and time spent below 54 mg/dL (3.0 mmol/l) was 0.21 % compared to 0.24 % in the control group.

Protocol 3 of the iDCL study was released in the NEJM in October 2019 (11). This showed that the TIR in the closed-loop group increased from 61±17% at baseline to 71±12% during the 6 months trial period and remained unchanged at 59±14% in the control group. The results with regard to the main secondary outcomes (percentage of time that the glucose level was >180mg/dl (10.0 mmol/l) mean glucose level, HbA1c, and percentage of time that the glucose level was <70 mg/dl (3.9 mmol/l) or <54 mg/dl (3.0 mmol/l) all favoured the closed-loop system. These results were demonstrated in people with and without prior experience with insulin pump therapy. In addition to time in range those using Control-IQ technology also saw statistically significant improvements in HbA1c and reductions in mean glucose. This is the most impressive data on AIDs to date.

2. Low Carbohydrate Diet

Maximising TIR using an AID system as described will allow us to test the hypothesis that chronic hyperglycemia *per se* plays a causative role in the development of defective glucagon secretion in T1D. However, it remains possible that the AID system may be insufficient given that post-prandial hyperglycemia still remains difficult to fully control with these devices (13).

One additional approach that may address post-prandial hyperglycemia effectively is a Low Carbohydrate Diet (LCD), defined as <130g per day of carbohydrates or 25% carbohydrates as a proportion of calories. No randomized controlled trials (RCTs) exist in this field in T1D but small observational surveys confirm the safety and efficacy of controlling post-prandial hyperglycemia in adults with T1D using a low or very low carbohydrate diet (14).

In this study we propose a carbohydrate portion of 30-40g carbohydrate per meal. This will be initiated by experienced healthcare professionals in this field. Patients will receive education about this diet at baseline. The ERICRF routinely uses this diet for post islet transplant patients.

We will ensure patient safety in this arm of the trial by monitoring blood ketones daily and will supply the meters and test strips for this.

We will supply nutritional scales to assist with carbohydrate counting and provide support and advice on this throughout the trial.

1.2 RATIONALE FOR STUDY

It is not currently known if maximizing TIR by principally reducing the exposure of the alpha cell to hyperglycemia is sufficient to restore glucagon secretory responses to insulin-induced hypoglycaemia in people with T1D.

We will attempt to answer this question by maximizing glycaemic TIR using new-generation AIDs in combination with a LCD. In addition, participants will be intensively followed up by study investigators to achieve maximal glycaemic TIR.

This will provide proof-of-principle that restoration of the glucagon response to insulin induced hypoglycaemia is possible in T1D. If these findings are confirmed this study will drive efforts to restore the glucagon response to hypoglycaemia not only by optimising glycaemic TIR but also by other pharmacological measures. It will also drive researchers to investigate if there are compositional, structural and, or, functional changes in the islet after regulation of the glucagon response.

Most importantly however is the impact on patients and patient care. In the short and the long-term restoration of this response would significantly reduce morbidity and mortality from hypoglycaemia impacting on quality-of-life for the patient as well as having significant socio-economic implications.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

Does maximizing TIR using AIDs with a LCD restore the glucagon response to insulin-induced hypoglycaemic in people with type 1 diabetes.

2.1.2 Secondary Objectives

- Has the quality of life (QoL) improved with improved blood sugar control?
- Are there fewer hypoglycaemic episodes?
- Is there a lower burden of diabetes care?
- Has the fear of Hypoglycaemia changed as a result of using this technology?
- Has satisfaction with their diabetes treatment improved as a result of using this technology?
- Is there an improvement in HbA1c using this technology?
- Endogenous glucose production and glycerol kinetics as measured by stable isotope studies (glycerol isotope will be used when supply is available)
- Is there a similar improvement in TIR between participants using the HCL system and following a LCD and those using the HCL system and following their pre-study diet

- Is there a difference in QoL between participants using the HCL system and following a LCD and those using the HCL system and following their pre-study diet

2.2 ENDPOINTS

2.2.1 Primary Endpoint

The glucagon response to hypoglycaemia after a period of increased time in range using automated insulin delivery and a low carbohydrate diet compared with the glucagon response at baseline.

2.2.2 Secondary Endpoints

Treatment satisfaction, fear of hypoglycaemia and quality of life at baseline compared to endpoint using validated questionnaires. Changes in endogenous glucose production and glycerol kinetics as measured by stable isotope studies. The difference in time in range and QoL between participants using the HCL system and following the LCD and those using the HCL system alone will be compared.

3 STUDY DESIGN

This is a feasibility pilot study involving 24 participants with T1D. We aim to achieve improved glycaemic control using new generation Automated Insulin Delivery systems which consist of:

- Tandem t:slim X2 insulin pump
- Continuous glucose monitoring using the Dexcom G6
- Control IQ technology which uses an algorithm to adjust insulin delivery using CGM data

To reduce postprandial glucose excursions the intervention arm of this study will also follow a low carbohydrate diet (30-40g of carbohydrate per main meal portion).

Healthcare professionals who are trained in the use of these technologies will monitor patient data and implement pump setting changes as required during the study period in order to maximise TIR. Study staff will be able to obtain technical support from both Tandem and Dexcom throughout the trial period.

Participant's CGM data will be available to the study staff using Dexcom clarity which is a secure cloud based data storage system. Participant's Tandem t:2 slim X2 data will be available via the t:connect Diabetes Management Application, another secure cloud based data storage system, which participants will upload their pump data to.

Face-to-face visits will be at the Edinburgh Royal Infirmary. Each participant will be in the study for 9 months. Those in group 1 will be invited to take part in a 3-month

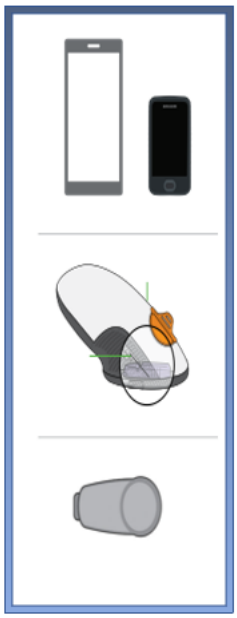
study extension phase where they will be converted to the study devices. Over this time their glucose data will be collected and at the end of the 3-months they will complete quality of life questioinnaires.

The trial is expected to last for 14 months.

Study Devices

Dexcom G6 Continuous glucose monitor (CGM)

G6 components:



Display Device
This shows glucose information on a smart device, Dexcom receiver or both.

Applicator With Built-in Sensor
Using an easy-to-use applicator with one button insertion the sensor is inserted under the skin of the abdomen or hip. This sensor receives accurate glucose information from interstitial body cells.

Transmitter
This clips into the sensor and sends glucose information from the sensor to the display device. The system is water resistant.

How it works:

The G6 sends glucose readings, via Bluetooth, to the display device every 5 minutes. The sensor is changed every 10 days. There is no calibration required so no need to check fingerstick glucose routinely.

Dexcom G6 Glucose Alarm/Alerts

The display device gives the user the power to customise an alert schedule. It alerts to;

- Low Glucose
- Urgent Low Glucose
- Urgent Low soon
- High glucose
- Rise rate
- Fall rate
- No readings

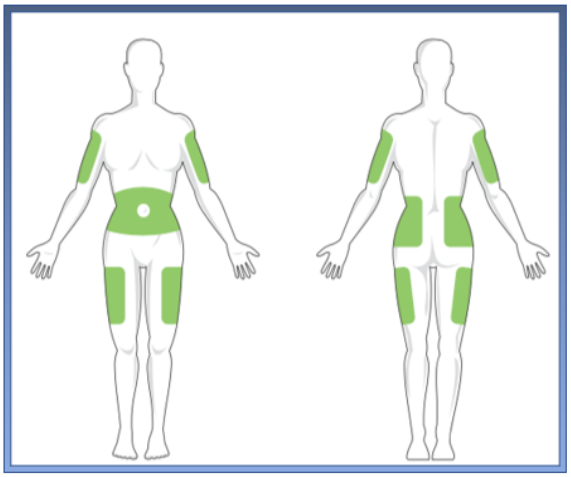
Urgent low soon alert provides a 20 minute warning of when the blood sugar is expected to be 3.1mmol/l or 56mg/dl so this can be avoided.

Tandem t:2 slim X2 Insulin Pump

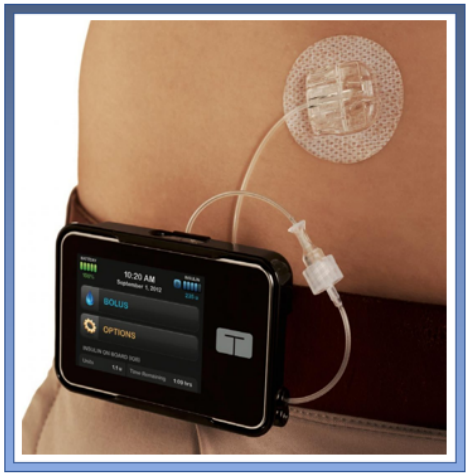
- The t:slim X2™ insulin pump is one of the smallest pumps available.
- 300 unit insulin cartridge.
- Rechargeable battery.
- Durable aluminium case.
- High-grade, shatter-resistant glass touchscreen.
- Customisable basal insulin rates.
- Integrated bolus calculator.

T:2 slim X2 infusion sets.

Tandem provide a choice of insulin infusion sets. These are inserted every 3 days using an automated, intuitive application device.



Areas of the body suitable for infusion set insertion.



T:2 slim X2 insulin pump and infusion set.

Control IQ

The t:2 slim X2 is an insulin pump that contains Control-IQ Technology. This is a third-generation closed-loop control system containing an algorithm that has been implemented in two mobile platforms (DiAs and inControl) and has been tested in 30 clinical trials by 450 adults and children with type 1 diabetes for over 280,000 hours of use to date.

This control algorithm provides the user with automated insulin correction boluses and a dedicated hypoglycaemia safety system that attenuates smoothly or discontinues insulin delivery using CGM and insulin-on-board information. It also gradually intensifies control overnight. Every five minutes Control-IQ receives CGM glucose data in order to inform insulin delivery. If glucose is in the target range, it delivers the insulin according to the user's settings. If out of range, it will give more or less insulin. The algorithm can use the CGM data to adjust insulin delivery based on the patients predicted blood glucose over the next 30 minutes.

In the closed-loop group of the recently published iDCL trial the median percentage of time Control IQ was in closed-loop mode was 90%, this was consistent throughout the 6 months (11).

Control IQ has FDA approval in the USA. December 2019. It launched in the UK in July 2020 after receiving a CE mark.

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

Enrolment will proceed with the goal of having 24 participants enter the trial. The participants will be people with type 1 diabetes recruited from the NHS Lothian diabetes pump waiting list and type 1 diabetes clinic. Recruitment will be staggered with each participant entering the trial for a 9 month period. The trial is expected to last 14 months.

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4.2 INCLUSION CRITERIA

- Participants with Type 1 diabetes with C-peptide levels less than 200pmol/L.
- Age 21-65.
- Type 1 diabetes for 5 years or more.
- HbA1c greater than or equal to 53 mol/mol.
- Normal renal function.
- Normal thyroid function.
- Willingness to monitor blood ketones daily.
- Use of freestyle libre device is permitted at study entry and may be continued in participants in group 1

4.3 EXCLUSION CRITERIA

- Current use of a non-approved closed loop / AID system or those on a predictive low glucose suspend insulin pump.
- Proliferative retinopathy
- Regular use of real time CGM in the preceding 3 months.
- History of Diabetic ketoacidosis in the preceding 6 months.
- Severe hypoglycaemic episode requiring external assistance in the preceding 6 months.
- Inability to safely use technology used in this study (e.g. impaired vision, memory or dexterity that prevents safe operation of CGM or insulin pump.)
- Inability to support the technology requirements for the study (e.g. unable to upload study device at home)
- History of Haemophilia, Cystic Fibrosis, pancreatic disease or complete pancreatectomy, ischaemic heart disease, cardiac arrhythmia, epilepsy or hypoglycaemia induced seizure
- History of severe reaction or allergy to adhesive necessary to this study.
- Unable to adhere to study timetable.
- Unable to give informed consent.
- Pregnancy or planning pregnancy. We will perform a pregnancy test on all eligible participants at baseline.
- Concurrent use of any non-insulin glucose-lowering agent (including GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas. These may lower insulin requirements and predispose to diabetic ketoacidosis.
- Concurrent use of medication that may affect blood glucose such as SSRIs
- A condition, which in the opinion of the investigator, would put the patient or study at risk

4.4 CO-ENROLMENT

Study staff will discuss with participants on a case-by-case basis if they are planning on enrolling in another study. The participant and study staff must consider the burden on the participant of being enrolled in more than one study. Any other study that a participant enrolled in would need to have no impact on their glycaemic control as this would potentially make the results from this study invalid.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Study staff, who are part of the diabetes care team in NHS Lothian, will identify potential participants from the type 1 diabetes clinic and the insulin pump waiting list.

Electronic health records, Trakcare and SCI Diabetes, of potential participants will be screened for any exclusion criteria. If no exclusion criteria are identified study staff will write to the potential participant inviting them to contact the research team if they would like to know more about the study. Potential participants will be able to contact study staff by post or email to arrange a telephone call to discuss the study. If after discussion with study staff on the phone potential participants would like to know more about the study they will be sent the participant information leaflet and the consent form by post to review.

5.2 CONSENTING PARTICIPANTS

Before completing any procedures or collecting any data that are not part of usual care written informed consent will be obtained. This will be obtained at the screening visit.

The study protocol will be discussed with the potential participant by study staff over the phone. They will be sent the Patient Information Leaflet and Informed Consent Form to read and will be encouraged to discuss the study with family members, study staff and their personal doctors before deciding whether to participate in the study. Participants will be given a minimum of 5 days and a maximum of 14 days to consider taking part in the study. The participant will be given contact details for study staff should they wish to ask further questions during this 14 day period. If study staff are not contacted by the potential participant within this 14 day period they will follow-up with a telephone call.

5.2.1 Withdrawal of Study Participants

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form, if possible. The participant will have the option of withdrawal from:

(i) all aspects of the trial but continued use of data collected up to that point . To safeguard rights, the minimum personally-identifiable information possible will be collected.
(ii) Participants can also ask for all data previously collected about them to be removed and not used in analysis
(iii) Participants do not have to give a reason for withdrawal from the trial

6 STUDY ASSESSMENTS

6.1 STUDY ASSESSMENTS

Study Visit 1: Eligibility Assessment

After informed consent has been signed the potential participant will be evaluated for study eligibility. This will be done through the elicitation of a medical history, performance of a physical examination by study staff and local laboratory testing if needed to screen for exclusionary medical conditions.

The following data will be collected:

- Inclusion and exclusion criteria assessment.
- Demographics (date of birth, sex)
- Contact information (retained at the site and not entered into study database)
- Medical history
- Concomitant medications
- Pregnancy test if applicable
- HbA1c blood test
- Urine sample for albumin:creatinine ratio
- Physical examination to include: Weight, height, BMI, vital signs including measurement of blood pressure and heart rate
- Retinal screening will be arranged if this has not occurred in the previous 6 months
- Modified Clark and Gold score

At the end of this visit participants will be given the following questionnaires:

1. EQ5D
2. Fear of Hypoglycaemic Scale
3. Hypoglycaemic Confidence
4. Diabetes Technology Attitudes
5. Diabetes Specific Emotional Distress (DDS-1)
6. Diabetes Treatment Satisfaction Questionnaire

They can either complete these at the time of the visit of complete at home and return to study staff at the following visit. A stamped addressed envelope will be provided to return the forms.

Randomisation

We will perform stratified random sampling according to age, gender and BMI. We will then provide envelopes to randomly assign final members from the various strata,

these envelopes will be kept in a secure, locked unit within in the clinical research facility. This technique ensures that observations from all relevant strata are included in the sample. by stratified sampling to match for: age, gender and BMI. They will be assigned to one of two groups:

• Group 1: Controls: standard diabetes care with blinded CGM (Dexcom G6) on three occasions lasting 20 days. All will be invited to a 3-month study extension phase where they will be converted to the study devices.

• Group 2: New-generation AIDs (t:slim X2 insulin pump with Control-IQ technology) with CGM (Dexcom G6) and a low carbohydrate diet (30-40g of carbohydrate per main meal portion). They will also have a 20-day period of blinded CGM (Dexcom G6) at baseline

Amendment: 28/09/22: Recruitment and retention to group 1 has been challenging with potential participants not wanting to engage with the study if allocated to group 1. This has led to unbalanced study groups. Currently there are 11 participants in group 2 and only 3 participants in group 1 (with a further 2 participants previously recruited but choosing to leave the study early). In order to balance groups from now on participants will be approached to take part in the study and informed up-front that they will be allocated to group 1.

Dexcom G6 clinical supplies, technical and software assistance will all be provided by Dexcom (see letter of support: Dr T Walker, Senior US Medical Director, Dexcom).

Participants will be asked to choose an envelope at random at the end of the screening visit which will allocate them to a group. At this time arrangements for subsequent visits will be made. We will send those randomised to group 2 training materials for the insulin pump and CGM. Participants will be allocated to a group within 1 week of the screening visit. This will change in version 8 of the protocol (28/09/22), from this point participants will only be recruited to the control group (group 1) and not randomised.

Visit 2- Baseline Data

All participants will attend for a second visit at ERICRF or ERI outpatient department. Participants will be fitted with a Dexcom G6 CGM. They will use this, blinded, for twenty days to gain experience in its insertion and for the research team to gain baseline data on glycaemic control. They will be required to insert two CGM devices to cover this 20 day period with support from study staff as required. If during this time the CGM device falls off or is faulty a replacement CGM device will be provided to the participant if less than 14 days of data has been collected. As participant's will not be able to view their CGM data during this time they will have to continue to monitor their own blood glucose as they would do normally.

All participants will be asked to complete a 7-day food diary during this period of blinded CGM. They will be asked to include 5 week days and 2 weekend days in the diary. This diary can take the form of a paper diary provided by study staff or participants can use a mobile phone application if they prefer. They will be asked to document food consumed and their insulin doses. They can return this to study staff

by post or at the next visit. A stamped addressed envelope will be provided if returning the diary by post.

Study Visit 3 (Group 2 only)

Participants randomised to Group 2 will attend the ERI to meet study staff, be fitted with their insulin pump and CGM device. This will take place after the 20-day period of blinded CGM monitoring. They will return the completed food diary at this visit. Participants in this group will be given training in the use of the pump that is in-line with was is received by NHS patients commencing on insulin pump therapy. This will require the participant to complete online training modules prior to attending this visit. They will also undergo a virtual or face-to-face pump start session with study staff and a training representative from the pump distributer. At this training session their knowledge of the pump will be checked against a standard checklist and we will ensure that the training modules have been completed. They will also be provided with written materials on the use of the pump and the algorithm which are produced by the pump manufacturer. Ongoing support on the use of the pump will be provided by study staff throughout the study period as is required by the participant, this can be via telephone contact for face-to-face if required. The pump manufacturer also has an online presence, including training and troubleshooting videos that can be freely accessed by participants (Tandem YouTube cannel: https://www.youtube.com/channel/UCBpeIuXQrQC-SGGooyxOhKA and Dexcom online training resources: https://www.dexcom.com/en-GB/training-resources).

Whilst on an insulin pump the participant will change their own insertion site every three days. This is routine in insulin pump use and is a marked reduction in injections when compared with insulin pens and needles, which is often done five to six times daily. They will also receive advice from the study team with respect to the low carbohydrate diet plans and management of insulin doses for their carbohydrate portions. This advice will be informed by the food diary completed by the participant. Participants in this group will be given blood ketone testing sticks and asked to do these tests daily. If blood ketones are greater than 1.5 mmol/L they will be asked to contact the health care professionals involved in the study or the out of hours care team. Participants will be given a paper record for them to record their ketone readings. This will change from protocol version 8 (28/09/22), from this point routine ketone monitoring will no longer be required. Participants will only be asked to monitor ketones as per standard diabetes management guidelines.

Study Run- in and Visit 4 (by telephone)

Participants in Group 2 will enter a maximum 2-week study run in period to adjust to their new equipment. Over this time the participants will be unblinded to their CGM data. The length of the run-in period will be determined on an individual basis after discussion between the participant and the investigators and will be based on the participant's previous experience with and confidence in using the technology.

Data will be monitored by the study staff and participants will be able to contact study staff by telephone or email to discuss any issues. At the end of this run-in period participants will meet with study staff either virtually or in person if they prefer this to assess:

1. Compliance with the use of the study devices

2. Any skin reaction in areas where a CGM sensor or pump set site was worn
3. Proficiency with the CGM and insulin pump technology by reviewing the individual items listed on the pump training checklist
4. Eligibility to continue to in the trial, which requires:
    a. CGM readings being obtained on at least 11 of the previous 14 days- if completing the full 14-day run in period
    b. Successful use of the pump every day

Additional visits and phone contacts for further training are at investigator discretion.

The pump settings (insulin: carbohydrate ratios, basal rates and insulin sensitivity) will be reviewed and optimised as appropriate based on the participant's blood glucose readings over the run-in period.

Study Visit 5: Hypoglycaemic Clamp Study 1

All Participants will attend the ERICRF, group 2 after the 2-week run-in period, for the first hypoglycaemic clamp study. This technique is safe and is considered, world-wide, as the gold standard approach in the assessment of hypoglycaemia (15-17). The clamp study will last for 5-6 hours. Blood glucose data for the preceding 24 hours will be reviewed prior to the study and if there have been any hypoglycaemic episodes the clamp study will be postponed.

During the clamp study the participant's blood glucose will be lowered in three steps to 2.5mmol/l.

In the 48 hours preceding the study participants will be asked to avoid moderate/high intensity exercise and any medication that may affect blood glucose such as: salicylates and quinolone antibiotics.

In the 24 hours preceding the study participants will be asked to do the following:

• Avoid alcohol and caffeine

• Consume a moderate carbohydrate (40-60g) evening meal the night before

• Fast for at least 8 hours before presenting to the clinical research facility at 07:00 (participant can continue to consume water as required)

• Avoid hypoglycaemia- the study will be postponed if the blood glucose is <3mmol/l for >20 minutes

• If on basal/bolus or open loop pump system to reduce their basal insulin the night before by 20%

• If on a closed loop system to place the pump on exercise settings the morning of testing

The clamp study will be rescheduled if the participant has donated blood in the preceding 12 weeks if male and the preceding 16 weeks if female.

When participants arrive in the ERICRF they will have anthropological measurements taken to calculate their infusion rates accurately. They will also have a pregnancy test if applicable.

Two peripheral intravenous cannulas will be inserted. This first of these will be in the nondominant hand which will then be placed in a heated box at 55°C to aterialise venous blood. This will be used for blood sampling during the study. The second cannula will be inserted an antecubital fossa vein for the infusions. At the time of cannula insertion baseline bloods will be obtained for: glucose, glycerol, D2 Glucose, D5 Glycerol, Free Fatty Acids, lipid profile, insulin, glucagon, cortisol, adrenaline and noradrenaline. Note that bloods for D2-Glucose and D5-Glycerol will only be taken when the investigators have received supply of the isotopes. There is currently a delay in this supply and the investigators anticipate receiving the isotopes in January 2022. Clamp studies carried out before receipt of the isotopes will not have these samples taken.

Stable Isotope Studies

Endogenous glucose production (EGP) and glycerol kinetics will be further assessed by infusion of the stable isotopes D2 Glucose and D5 Glycerol. This is a safe method for assessing EGP in humans (18, 19). The isotopes will be supplied by Tayside Pharmaceuticals (Patrick Blair Place, Dundee DD1 9SY). There are supply issues with the D5-glycerol but is important that study visits are allowed to continue so that participants can progress through the 8 months of the study. Not using the D5-glycerol will not impact on the primary outcome of the study. The D5-glycerol supply issues will continue for the remainder of the study due to there being less raw material available from the supplier. This means that supply of the D5-glycerol will be intermittent and unpredictable for the remainder of the study. Visits that take place when D5-glycerol is available will be completed as described below. Visits taking place when D5-glycerol is not available will continue without using the D5-glycerol. The D5-glycerol is infused alongside the D2-glucose from the same infusion bag. So that the process for making this infusion remains unchanged the D5-glycerol will be replaced with 0.9% Sodium Chloride, which will not impact on the participant or the study results. Participants impacted by this change will be asked to sign another consent form.

This will involve:

1. A priming dose:
    a. D2 Glucose: 26.4 micoromol/kg
    b. D5 Glycerol: 2 micromol/kg (if available)
2. A continuous infusion:
    a. D2 Glucose: 0.5micromol/kg/minute for the remainder of the clamp study
    b. D5 Glycerol: 0.1micromol/kg/minute for the remainder of the clamp study (if available)

The continuous infusion of each isotope will run for 90 minutes before the clamp study is commenced. During this time blood samples will be drawn for Glucose, Glycerol, D2 Glucose and D5 Glycerol (if being infused) on three occasions.

If the participant's blood glucose is >7mmol/l at the start of the study they will begin a priming infusion of Novorapid insulin 0.3U/ml at 50ml/hour until the blood glucose is <7mmol/l but >5mmol/l. Once blood glucose is <7mmol/l a basal inuslin infusion will run at 6mU/m2/min until the start of the clamp study to maintain blood glucose in the euglycaemic range.

Insulin infusion rates will be calculated using the participants body surface area, which avoids overdosing insulin in overweight participants. The body surface area will be calculated using the formula:

BSA (m2) = √((height (cm) x weight (kg))/ 3600 (20)

After the isotopes have been infused for 90 minutes the insulin infusion will be increased to 60mU/m2/min. At the same time a variable rate 20% Dextrose infusion will also be commenced. The rate of this will be adjusted as required to obtain the desired blood glucose nadir.

We will have three blood glucose plateaus during the clamp study each lasting for 40 minutes: 5mmol/l, 3mmol/l and 2.5mmol/l. Throughout the clamp study blood glucose will be monitored every 5 minutes using near-patient testing and the participant will remain blinded to their blood glucose level. During each plateau blood will be drawn on 3 occasions at 10-minute intervals for: insulin, cortisol, adrenaline, noradrenaline, glucagon, glucose, glycerol, free fatty acids and the stable isotopes.

During the clamp the following additional tests will be carried out:

• Physiological measurements: Blood pressure and heart rate every 10 minutes.

• Symptoms scoring: Participants will rate symptoms at set intervals during hypoglycaemia. Symptoms will be scored on a validated questionnaire, The Edinburgh Hypoglycaemia Scale, scoring from 1 (not at all) to 7 (very severe) on a visual analogue scale. At any point participants may stop the test if symptoms are intolerable.

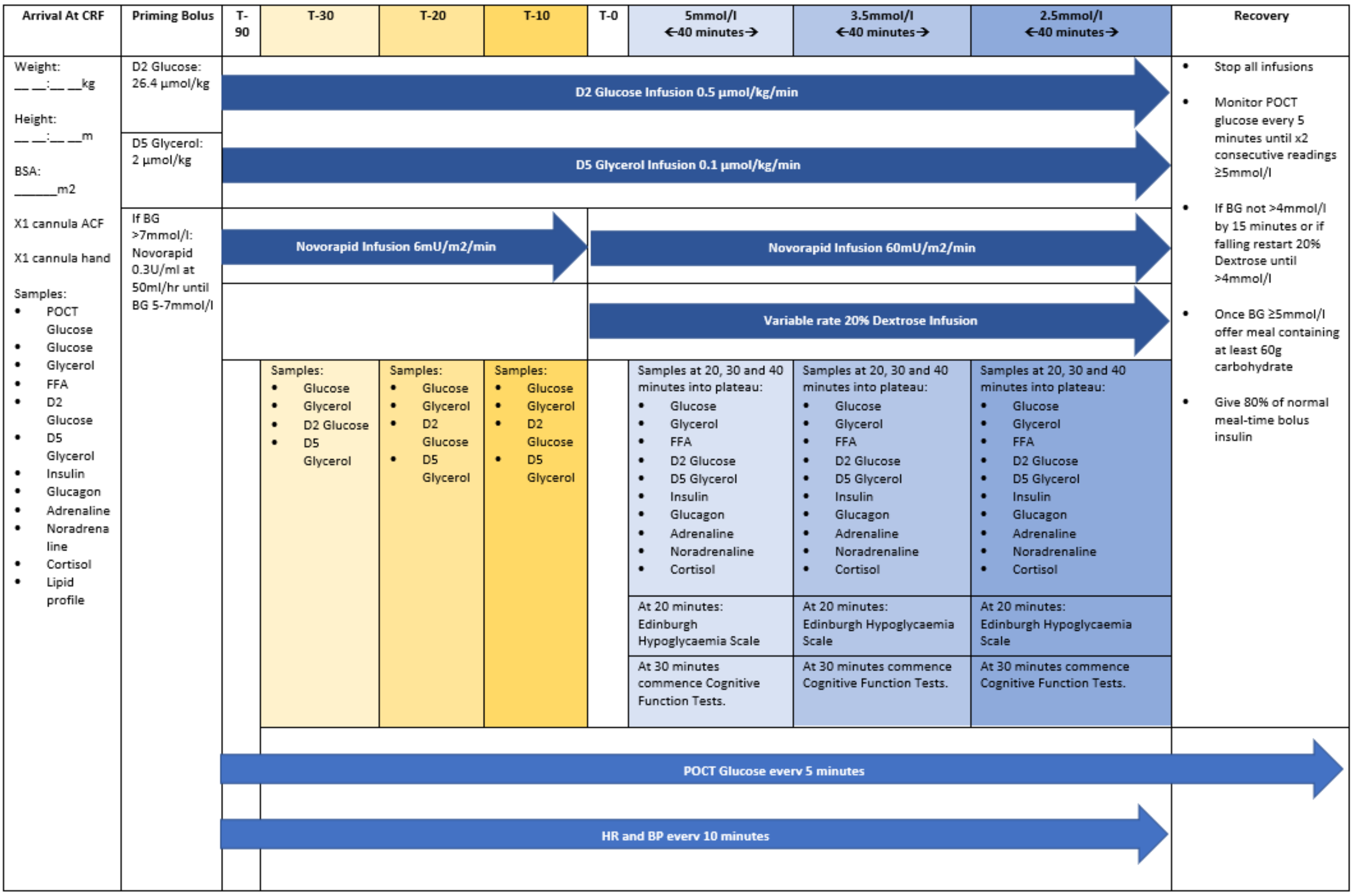
• Cognitive Function Tests: Psychometric tests known to be sensitive to hypoglycaemia will be applied at set time intervals during hypoglycaemia: Trail Making Test, Digit Span Test, Digit Symbol Substitution Test and Four Choice Reaction Time Test.

At the end of the study the participants will be examined and assessed to ensure they have fully recovered from the clamp. They will be given lunch consisting of at least 60g of carbohydrate and post clamp advice. They may leave the CRF when blood glucose is stable above 5mmol/l.

In total we will take not more than 300ml of blood during the clamp study. The blood samples will be stored in a secure and monitored environment and will be disposed of according to the Human Tissue Authority's code of practice after a period of 5 years. The samples will be centrifuged before being frozen at -80 degrees Celsius. Serum samples will be allowed to clot at room temperature before centrifugation.

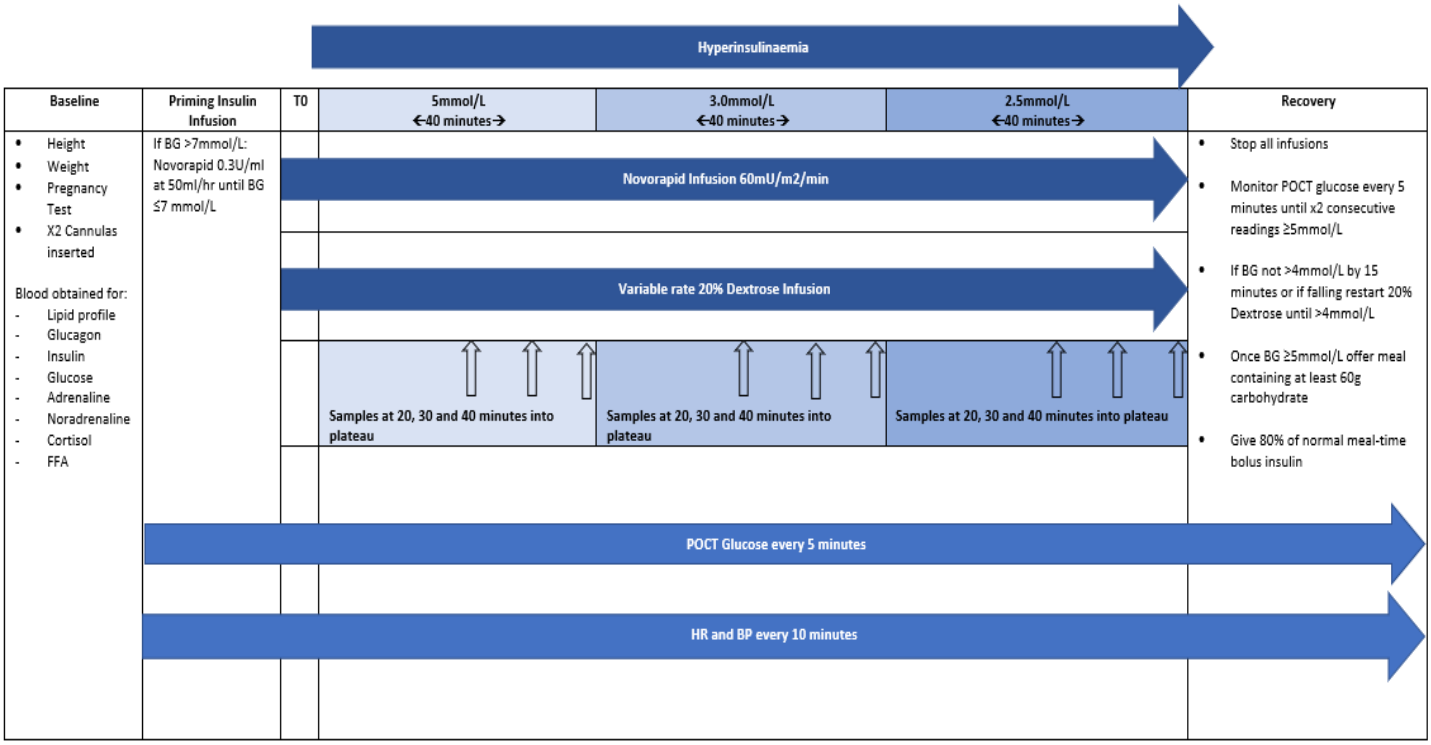
At the beginning and end of the clamp study a sample will be taken from the infusates to confirm the isotope concentration in these. These samples will be frozen until analysis.

Figure 1: Hypoglycaemic Clamp Study with stable isotopes



Note in visits where the D5-glycerol is not available on the D2-glucose will be infused.

Figure 2: Hypoglycaemic Clamp Study without stable isotopes



Monitoring Period

Group 1

Group 1 will continue on their standard diabetes care. At 4 months they will perform a 20 day period of blinded CGM monitoring. This will require them to insert the CGM device on two occasions during this 20 day period. During this 20 day period this group will continue on their standard diabetes care, including monitoring their own blood glucose, as they will not be able to view the data from the CGM device. Participants in this group will perform a further 20 day period of blinded CGM monitoring prior to the second hypoglycaemic clamp study. This means that participants in this group will have to insert the CGM device on 6 occasions during the study period. In each of these periods of blinded CGM monitoring the aim will be to collect at least 14 days of data. Study staff will collect the CGM devices at the end of each 20 day blinded period so that the data can be downloaded for analysis. CGM devices for these two blinded periods will be delivered to the participants' home. The device for the 4 month period will then be collected from the participant by study staff. The device used prior to the second clamp study can be given to study staff at the clamp study visit. During each of these blinded CGM periods participants will be asked to complete a 7-day food diary, to include 5 week days and 2 weekend days. This can be in the form of a paper diary provided by study staff or a mobile phone application. This can be returned to study staff at the next visit or by post, a stamped addressed envelope will be provided. After the second clamp study participants will be invited to take part in a 3-month study extension phase. During this time they will be converted to the study devices. They will be asked to upload their study pump once a week and will have ad hoc contact with the investigators over this time to adjust pump settings as required. At the end of the 3 months they will be sent quality of life questionnaires to complete along with a stamped addressed envelope to return these to the investigators.

Group 2

Participants in group 2 will be continually monitored throughout the study period to ensure time in range is optimised throughout the 8 months. They will be asked to upload their insulin pump data at least once weekly to the online platform Tandem t:connect. This is done using a USB device provided with the insulin pump and the participants own computer or laptop with internet access. Participants will be given training in the use of the platform and account logins as part of their pump training. The data from the participant's CGM device will also be reviewed by study staff. This data automatically uploads to the Dexcom Clarity cloud platform without the need for the participant to physically attach the device to their computer. Study staff will review blood glucose data on Dexcom clarity daily to ensure time in range is being maximised.

Study staff will review the uploaded pump data at least once weekly using administrative log-in details and will contact participants by telephone if the data suggests:

1. Adjustments are required to insulin pump settings (carbohydrate ratios, insulin sensitivity factor, basal rates) as they are experiencing time out of the target glycaemic range
2. The participant is not changing the insulin pump set every 3 days
3. The participant requires further education about the low carbohydrate diet or carbohydrate counting

4. The participant is experiencing multiple alarms or error codes

Participants will have contact information for study staff and will be able to contact staff via email or telephone on an ad hoc basis throughout the study.

Study Visit 6

A scheduled mid-point telephone consultation at 3-4 months will be arranged for all participants. This can be a face-to-face appointment if requested by the participant. All participants will also have a HbA1c measured at 4 months. This will be done using a home testing kit provided by Exeter Clinical Laboratory International if participants decide to have a telephone visit Samples are collected via a fingerstick blood test, in the same manner as checking a blood glucose, and then posted to the reference lab in Exeter for sample analysis. If the participant decided to have a face-to-face visit a laboratory HbA1c will be taken in place of the home testing kit.

Participants in group 2 will be asked to attend for repeat retinopathy screening at 3-4 months.

Study Visit 7: Hypoglycaemic Clamp Study

All participants will undergo a second hypoglycaemic clamp study, as previously described, at 8 months. Participants will be given the following questionnaires to complete.

1. EQ5D
2. Fear of Hypoglycaemic Scale
3. Hypoglycaemic Confidence
4. Diabetes Technology Attitudes
5. Diabetes Specific Emotional Distress (DDS-1)
6. Diabetes Treatment Satisfaction Questionnaire
7. Gold Score

Participants will return their study devices. They will be given the opportunity to discuss the study with study staff and provide any feedback.

Study Visit 8 (Group 1 only)

Participants in group 1 who have agreed to take part in the 3-month study extension phase will attend for training on using the Dexcom CGM along with the Tandem t:slim X2 insulin pump. This session will take a variable amount of time depending on if the participant was on an insulin pump prior to the study.

After this visit participants will have ad hoc telephone contact with investigators to review insulin pump setting or provide advice regarding the devices. They will be asked to upload their pump once weekly to the t:connect platform. They will be sent the following questionnaires to complete at home after 3 months (+/- 2 weeks) which they will return to the investigators in a stamped addressed envelope:

1. EQ5D
2. Fear of Hypoglycaemic Scale

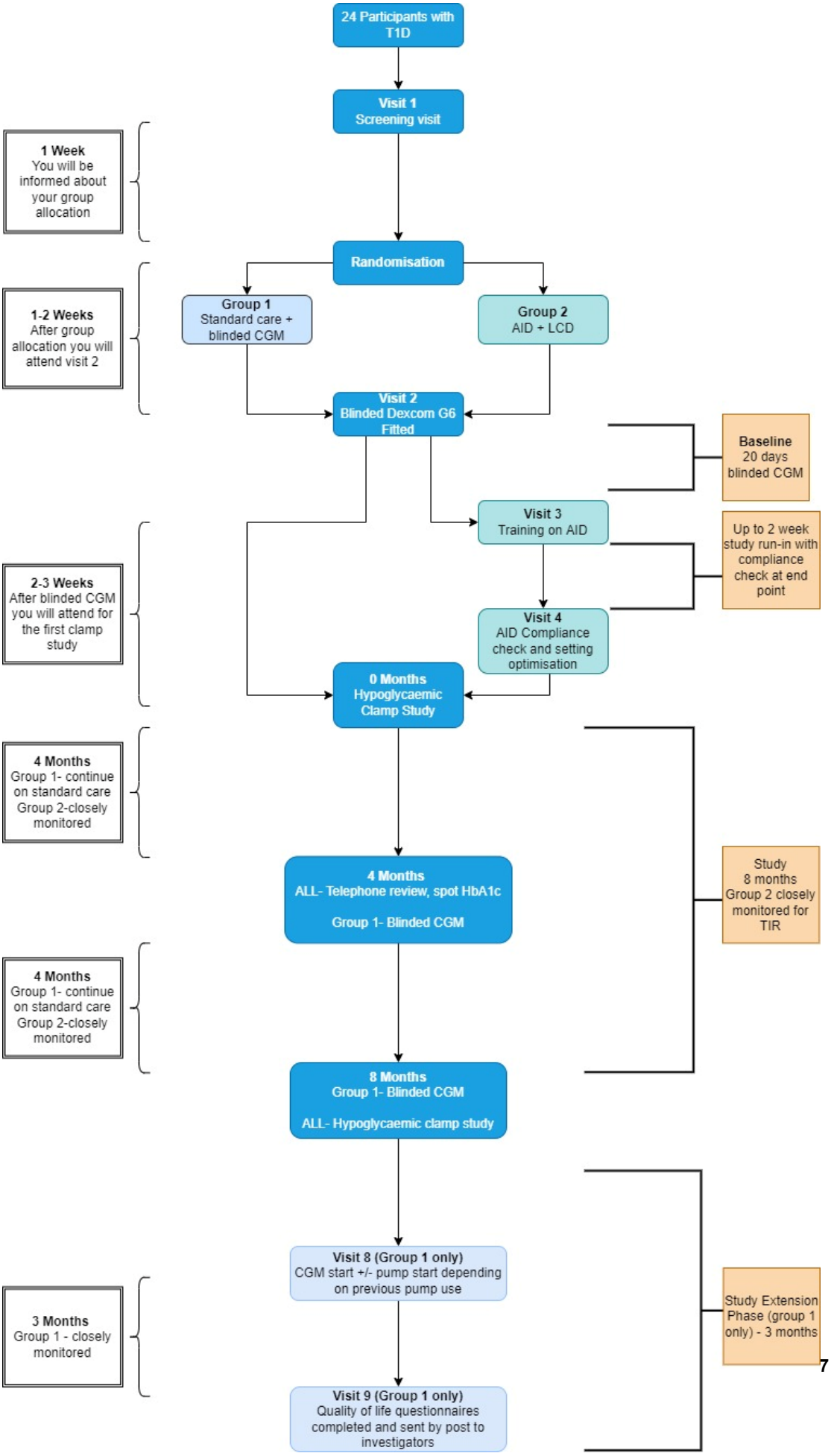
3. Hypoglycaemic Confidence
4. Diabetes Technology Attitudes
5. Diabetes Specific Emotional Distress (DDS-1)
6. Diabetes Treatment Satisfaction Questionnaire
7. Gold Score

All participants will undergo repeat retinopathy screening at the end of the trial period.

Table 1: Study Procedures

	Study Preparation				Study				3 Month Extension Phase	
Assessment	**Visit 1- Screening**	**Visit 2- Baseline**	**Visit 3 (Group 2 only)**	**Up To 2-week Study run-in**	**Visit 4 (Group 2 only**	**Visit 5 (Study start)**	**Visit 6 (4 months)**	**Visit 7 (8 months)**	**Visit 8 (Group 1 only)**	**Visit 9 (Group 1 only)**
Eligibility Assessment	X									
Written informed consent	X									
Demographic data, contact details	X									
Weight	X					X		X		
Height	X					X		X		
BMI	X									
Pregnancy Test	X					X		X		
Food diary, 7 days		X					X (Group 1)	X (Group 1)		
Vital signs: heart rate, blood pressure	X					X		X		
Questionnaires		X				X		X		X (returned by post)
Medical History	X									
Urine sample: Albumin:creatinine ratio	X									
Retinal Screening	X						X (Group 2)	X		
Spot HbA1c	X						X	X		
HbA1c	X							X		
Hypoglycaemic Clamp Study						X		X		
ALL- Blinded CGM for 20 days		X								
ALL- telephone review							X			
All- return study devices								X		
GROUP 1- Blinded CGM for 20 days							X	X		
Fitting of t:slim X2			X						X (if not previously on pump, otherwise CGM fitting only)	
Group 2- pump check-list					X					
GROUP 2- Use of pump and CGM device in unblinded mode	■	■	■	→	→	→	→	→		
Group 2- Low carbohydrate diet	■	■	■	■	→	→	→	→		
Group 1- Use of pump and CGM device in unblinded mode	■	■	■	■	■	■	■	■	→	→
Review- telephone or face-to-face as required	→	→	→	→	→	→	→	→	→	→

Figure 3: Study Flowchart


24 Participants with T1D
Visit 1
Screening visit
1 Week
You will be informed about your group allocation
Randomisation
1-2 Weeks
After group allocation you will attend visit 2
Group 1
Standard care + blinded CGM
Group 2
AID + LCD
Visit 2
Blinded Dexcom G6 Fitted
Baseline
20 days blinded CGM
Visit 3
Training on AID
Up to 2 week study run-in with compliance check at end point
2-3 Weeks
After blinded CGM you will attend for the first clamp study
Visit 4
AID Compliance check and setting optimisation
0 Months
Hypoglycaemic Clamp Study
4 Months
Group 1- continue on standard care
Group 2-closely monitored
4 Months
ALL- Telephone review, spot HbA1c
Group 1- Blinded CGM
Study
8 months
Group 2 closely monitored for TIR
4 Months
Group 1- continue on standard care
Group 2-closely monitored
8 Months
Group 1- Blinded CGM
ALL- Hypoglycaemic clamp study
Visit 8 (Group 1 only)
CGM start +/- pump start depending on previous pump use
3 Months
Group 1 - closely monitored
Study Extension Phase (group 1 only) - 3 months
Visit 9 (Group 1 only)
Quality of life questionnaires completed and sent by post to investigators

6.2 STORAGE AND ANALYSIS OF SAMPLES

The blood tests set out in the table below will be required during the study. The volumes represent the volume required during the whole trial.

Test	Container	Volume Required (ml)	Number of Tests	Total Volume
Screening Visit				
HbA1c	EDTA	1ml	1	
HbA1c spot	Testing kit	0.5ml	1	
FBC	EDTA	2ml	1	
Urea and Electrolytes	LithHep	5ml	1	
Thyroid Function	LithHep	5ml	1	
Pregnancy Test (urine)	n/a	n/a	1	n/a
Total Volume				**13.5ml**
Clamp Study 1				
Glucagon	EDTA	3ml	10	30ml
Cortisol	Serum	3ml	10	30ml
Adrenaline	LithHep	3ml	10	30ml
Noradrenaline	LithHep	3ml	10	30ml
Insulin	LithHep	3ml	10	30ml
Glucose	Fluoride	1ml	48	48ml
Glucose (near-patient test)	n/a	0.5ml	48	24ml
Glycerol	Plasma	2ml	13	26ml
Free Fatty Acids	Fluoride	2ml	10	20ml
D2 Glucose	Plasma	1ml	13	13ml
D5 Glycerol (only in study visits when supply available)	Plasma	1ml	13	13ml
Lipid profile	Serum	4ml	1	4ml
Pregnancy Test (urine)	n/a	n/a	1	n/a
Total Volume				**298ml**
4 Month Test				
HbA1c Spot (telephone visit)	Testing kit	0.5ml	1	0.5ml
HbA1c (face-to-face visit)	EDTA	1ml	1	1ml
Clamp Study 2				
Glucagon	EDTA	3ml	10	30ml
Cortisol	Serum	3ml	10	30ml
Adrenaline	LithHep	3ml	10	30ml
Noradrenaline	LithHep	3ml	10	30ml
Insulin	LithHep	3ml	10	30ml
Glucose	Fluoride	1ml	48	48ml
Glucose (near-patient test)	n/a	0.5ml	48	24ml
Glycerol	Plasma	2ml	13	26ml
Free Fatty Acids	Fluoride	2ml	10	20ml
D2 Glucose	Plasma	1ml	13	13ml
D5 Glycerol	Plasma	1ml	13	13ml
Lipid profile	Serum	4ml	1	4ml

Pregnancy Test (urine)	n/a	n/a	1	n/a
HbA1c Spot	Testing kit	0.5ml	1	0.5ml
HbA1c	EDTA	1ml	1	1ml
Total Volume				**299.5ml**
Volume for all tests (maximum):				**611ml**

The measurement of blood glucose during the clamp study is critical for the safety of the participants and integral to the study itself. Without this we would not know if a participant was at the desired blood glucose level. Measurement of glucagon during the clamp study is key to determining the primary outcome of the trial- the glucagon response to hypoglycaemia. Other hormones that are involved in the body's response to hypoglycaemia will also be measured during the clamp study (adrenaline, noradrenaline and cortisol). While these are not directly related to the primary outcome of the trial they are linked as the intervention may show an improvement in these responses. An improvement in these responses is also linked to improvement in awareness of hypoglycaemia, which is a secondary outcome measure for the trial for those with IAH. This trial is looking at time in range as a measure of blood glucose control in type 1 diabetes. This is an emerging tool for measuring control in diabetes that has only been made possible in recent years through new technologies such as CGM. Traditionally HbA1c is used as a measure of blood glucose control. That is why participants will have this measured at baseline, midpoint and endpoint. The HbA1c blood spot samples will not be analysed locally. They will be sent to a reference lab in Exeter for analysis (Exeter Clinical Laboratory International, Royal Devon and Exeter NHS Trust, Exeter).

The blood taken during the screening visit and the lipid profile taken during the clamp studies are part of the standard monitoring of people with type 1 diabetes.

During the trial period participant blood samples will be stored in the ERICRF. The blood samples will be stored in a secure and monitored environment and will be disposed of according to the Human Tissue Authority's code of practice after a period of 5 years.

7 DATA COLLECTION

During the trial data will be collected by study staff. The following data will be collected at these time points:

1. Selection of potential participants prior to consent:
    a. Review of electronic health care records, Trakcare and SCI Diabetes, for exclusion criteria
    b. This data will be reviewed by study staff who are part of the participant's healthcare team
2. Eligibility Assessment (after obtaining written informed consent):
    a. Inclusion and exclusion criteria assessment.
    b. Demographics (date of birth, sex, race and ethnicity)

c. Contact information (retained at the site and not entered into study database)
d. Medical history
e. Concomitant medications
f. Pregnancy test if applicable
g. HbA1c blood test
h. Bloods test for : Renal function and thyroid function
i. Urine sample for albumin:creatinine ratio
j. Physical examination to include: Weight, height, BMI, vital signs including measurement of blood pressure and heart rate
k. Modified gold score
l. Retinal screening will be arranged if this has not occurred in the previous 6 months

3. Baseline:
    a. CGM Data:
        i. All participants will have blinded CGM data collected over a 20 day period (aiming to capture at least 14 days of data)
        ii. This data will be collected automatically by the device after being fitted by the participant before being uploaded to a secure cloud-based platform
    b. All participants will complete the study questionnaires:
        i. Quality of life: EQ5D, Diabetes Specific Emotional Distress (DDS-1)
        ii. Treatment satisfaction: Diabetes treatment satisfaction questionnaire
        iii. Technology: Diabetes technology attitudes
        iv. Fear of hypoglycaemia: Hypoglycaemia confidence, Fear of Hypoglycaemic Scale
    c. All participants- first hypoglycaemic clamp study
4. Trial period
    a. Participants in group 2 will have data collected from their insulin pump and CGM device
    b. Insulin pump data will be uploaded by the participant at least once per week to the secure platform Tandem t:connect
    c. CGM data will be automatically uploaded to the secure cloud-based platform Dexcom Clarity

5. Midpoint
    a. Participants in group 1 will undergo a further 20 day period of blinded CGM data collection
    b. All participants will have blood taken for HbA1c
6. Endpoint:
    a. Participants in group 1 will undergo a further 20 day period of blinded CGM data collection
    b. All participants will complete the study questionnaires:

i. Quality of life
ii. Treatment satisfaction
iii. Technology
iv. Fear of hypoglycaemia

c. All participants- second hypoglycaemic clamp study

7. Study extension phase (3 months)
   a. Participants in group 1 who agree to the extension phase will have data collected from their pump and CGM device
   b. Insulin pump data will be uploaded once weekly to the to the secure Tandem t:connect
   c. CGM data will be automatically uploaded to the secure cloud-based platform Dexcom Clarity
   d. The following questionnaires will be completed:
      i. EQ5D
      ii. Fear of Hypoglycaemic Scale
      iii. Hypoglycaemic Confidence
      iv. Diabetes Technology Attitudes
      v. Diabetes Specific Emotional Distress (DDS-1)
      vi. Diabetes Treatment Satisfaction Questionnaire
      vii. Gold Score

Participants will be given different options for completing the questionnaires related to the trial. They can be completed while at a visit with study staff, can be taken home and returned to staff by post or handed to study staff at the next visit.

7.1 Source Data Documentation

Source documents for the study:

- Electronic health records- Trakcare and SCI Diabetes
- Participant case report forms
- Study questionnaires
- Dexcom G6 glucose data on Dexcom Clarity
- Tandem pump and control IQ data on t:connect
- Food diary
- Ketone recording sheet

7.2 Case Report Forms

Participant data will be collected on paper case report forms. The case report form will be identified using the participant's unique study identifier and not identifiable information such as name or CHI. The case report form will be stored in locked and secure rooms in the ERICR /ERI outpatient department. Any electronic information collected will be stored on an NHS computer with password-controlled access. All patient identifiers will be removed and allocated a study ID number. This will be stored on a secure NHS server for 6 years.

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8 DATA MANAGEMENT

8.1 Personal Data

The following personal data will be collected as part of the research:

- Name
- Address
- Date of birth
- Contact telephone number(s)
- Email address
- CHI number

Personal data will be stored by the research team in the Edinburgh Royal Infirmary under lock and key. Data will only be accessible by study staff. The code break will be kept on a password protected NHS computer.

Personal data will be stored for 12-24 months.

8.2 Data Information Flow

Data collected by study staff will be held on secure password protected NHS computers in the Edinburgh Royal Infirmary and in a locked cupboard in the Edinburgh Royal Infirmary. Only study staff will have access to this data. Anonymised reports on the study will be sent during the trial period to the Helmsley Charitable Trust, Tandem and Dexcom. The headquarters of these companies are based in the United States.

8.3 Transfer of Data

Data collected or generated by the study (including personal data) will not be transferred to any external individuals or organisations outside of the Sponsoring organisation(s).

Reports containing anonymised data will be sent during the trial period to the Helmsley Charitable Trust, Tandem and Dexcom.

8.4 Data Controller

A data controller is an organisation that determines the purposes for which, and the manner in which, any personal data are processed.

The University of Edinburgh and NHS Lothian are joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws (e.g. the site).

8.5 Data Breaches

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

9 STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

Sample size is based on previous work by Cranston et al 'Restoration of hypoglycaemic awareness in patients with long-duration insulin dependent diabetes' which was published in the Lancet in 1994. They used a similar sample size in this study.

9.2 PROPOSED ANALYSES

In primary analyses, the glucagon response to insulin induced hypoglycaemia at 0 and 8 months will be compared to the individual's baseline glucagon responses within each group. In further exploratory analyses, the participants in the highest tertile of glycaemic TIR as a group over the 8 months will be compared to those in the lowest tertile over the 8 months as a

group. The rate of appearance (Ra) of the stable isotopes will be used as a marker of endogenous glucose production. Analysis of tracee:tracer ratio will be made by mass spectrometry. The TIR of participants completing the study 3-month extensions will be compared to that of group 2 during the study.

We predict minimizing exposure of alpha cells to hyperglycemia with AID +/- VLCD should significantly enhance glucagon.

10 ADVERSE EVENTS

10.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant, which does not necessarily have a causal relationship with the study intervention.

An **adverse reaction** (AR) is any untoward and unintended response that has occurred due to the intervention

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that:

- results in death of the clinical trial participant;
- is life threatening*;
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

*Life-threatening in the definition of an SAE or SAR refers to an event where the participant 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.

^Any hospitalisation that was planned prior to enrolment will not meet SAE criteria. Any hospitalisation that is planned post enrolment will meet the SAE criteria.

Adverse Device Effect (ADE) is an adverse event related to the use of a medical device. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. An ADE includes any event that is a result of a use error or intentional misuse. Use error refers to an act or omission of an act that results in a different device response than intended by the manufacturer or expected by the user. An unexpected physiological response of the subject does not in itself constitute a use error.

Serious Adverse Device Effect (SADE) is an adverse event effect that has resulted in any of the consequences characteristics of a SAE (as defined above). This includes device deficiencies that might have led to a SAE if:

- Suitable action had not been taken
- Intervention had not been made
- If circumstances had been less fortunate

Anticipated Serious Adverse Device Effect (ASADE) is a serious adverse device effect..

Unanticipated Serious Adverse Device Effect (USADE) is a serious adverse device effect which by its nature, incidence, severity or outcome is not expected in terms of what is known about the device.

We will reference the manufacturer manuals for each device to identify anticipated and unanticipated adverse device effects. The manual for the Dexcom G6 can be found here: https://s3-us-west-2.amazonaws.com/dexcompdf/G6-CGM-Users-Guide.pdf and the manual for the tandem t:slim X2 with Control IQ can be found here: https://www.tandemdiabetes.com/docs/default-source/product-documents/t-slim-x2-insulin-pump/k%c3%a4ytt%c3%b6opas-(t-slim-x2--pumppu-control-iq-teknologialla)cf14759775426a79a519ff1100a9fd393f6fb39775426a79a519ff1200a9fd39.pdf?sfvrsn=18a507d7_66.

Device Deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labelling.

10.2 IDENTIFYING AEs AND SAEs

Participants will be asked about the occurrence of AEs/SAEs at every visit during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.

AEs and SAEs may also be identified via information from support departments e.g. laboratories.

10.3 RECORDING AEs, SAEs and SADEs

When an AE/SAE occurs, it is the responsibility of the Investigator, or another suitably qualified physician in the research team who is delegated to record and report AEs/SAEs, to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The investigator will record all relevant information in the CRF/AE logs.

Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

10.3.1 Pre-existing Medical Conditions

Pre-existing medical conditions (i.e. existed prior to informed consent) should be recorded as medical history and only recorded as adverse events if medically judged to have worsened during the study.

10.3.2 Worsening of the Underlying Condition during the Trial

Medical occurrences or symptoms of deterioration that are expected due to the participant's underlying condition should be recorded in the patient's medical notes and only be recorded as AEs on the AE log if medically judged to have unexpectedly worsened during the study. Events that are consistent with the expected progression of the underlying disease should not be recorded as AEs.

10.4 ASSESSMENT OF AEs AND SAEs

Each AE must be assessed for seriousness, causality, severity and expectedness by the Principal Investigator or another suitably qualified physician in the research team who has been delegated this role.
Where there are two assessments of causality (e.g. between PI and Chief Investigator (CI)), the causality assessment by the Investigator cannot be downgraded. In the case of a difference of opinion, both assessments are recorded and the 'worst case' assessment is used for reporting purposes.

10.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 10.1.

10.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the study intervention or medical device according to the definitions below.

- Unrelated: where an event is not considered to be related to the study intervention or device.
- Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study intervention or device.

10.4.3 Assessment of Expectedness

10.4.3.1 IMP

If the AE is judged to be related to the study intervention, the PI will make an assessment of expectedness.

The event may be classed as either:

Expected: the type of event is expected in line with the study intervention

Unexpected: the type of event was not listed in the protocol or related documents/literature as an expected occurrence.

10.4.3.2 Medical Device

If the AE is judged to be related to the device, the investigator will make an assessment of expected based on knowledge of the reaction and any relevant product information. The event will be classed as either:

Expected: the reaction is consistent with the effects of the device that are known.

Unexpected: the reaction is not consistent with the effects that are known

The above will be assessed in relation to the manufacturer user guides for each device.

10.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE and record this on the CRF/AE log or SAE form according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

Note: the term 'severe', used to describe the intensity, should not be confused with 'serious' which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

10.5 REPORTING OF SAEs and SADEs TO THE SPONSOR

Once the Investigator becomes aware that an SAE/SADE has occurred in a study participant, the information will be reported to the ACCORD Research Governance within 24 hours. If the Investigator does not have all information regarding an SAE, SADE they should not wait for this additional information before notifying ACCORD. The SAE report form (and SADE report form where appropriate) can be updated when the additional information is received. Reports will be complete as far as possible and will be signed and dated by the Investigator.

The SAE form (and SADE report form where appropriate) will be transmitted via email to safety@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

Once an SAE or SADE report is received by ACCORD it will be entered onto the ACCORD PhV database by the Research Governance Coordinator or designee.

All safety reports transmitted to ACCORD (including any follow-up information and correspondence) will be kept by the Investigator in the Trial Master File (TMF).

10.6 REPORTING OF DEVICE DEFICIENCIES

Device deficiencies will be documented on the ACCORD Medical Device Deficiency Form and will be reported to the sponsor in accordance with section 10.5 above.
On receipt of device deficiency reports, the Research Governance Coordinator, or designee, will assess the report to ensure the correct assessment has been made. In the case of the event meeting SAE, SADE or USADE criteria, the Research Governance Coordinator, or designee will ensure that all the correct reporting procedures have been followed.
The Research Governance Coordinator, or designee, will complete and return the Cover Sheet and Return Receipt or send an email to confirm receipt of the Device deficiency report within 1 working day. If this email/fax is not received within 1 working day of sending the report to ACCORD, the Investigator must telephone ACCORD on +44 (0)131 242 3330 to check that the report has been received by ACCORD
The Investigator is responsible for reporting device deficiencies to the relevant NHS Medical Physics department.
Device deficiency reports emailed or faxed to ACCORD and any follow-up information and correspondence will be kept by the Investigator in the TMF.

10.7 MEDICAL DEVICE QUARANTINE

If the event is defined as serious i.e. a SAE or device deficiency that could have led to SADE or USADE the Investigator must quarantine the device as soon as possible e.g. segregating the device from other equipment and labelling as not for use with contact details attached.
Until the Sponsor has been given the opportunity to carry out an investigation, all items (together with relevant packaging materials) should be quarantined. They should not be repaired, or discarded or returned to the manufacturer without agreement from the sponsor.
Investigators should contact the manufacturer to obtain information relating to the procedure for returning the device, where considered appropriate.
The device should be cleaned and decontaminated where appropriate, securely packaged, and clearly labelled, including the manufacturer reference number if needed.

11 OVERSIGHT ARRANGEMENTS

11.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

11.2 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency.

Risk assessment, if required, will determine if audit by the ACCORD QA group is required. Should audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

12 GOOD CLINICAL PRACTICE

12.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

12.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

12.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by representatives of the sponsor(s).The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes (if applicable).

12.2.2 Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

12.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

12.2.4 Investigator Documentation

The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs.

12.2.5 GCP Training

For non-CTIMP (i.e. non-drug) studies all researchers are encouraged to undertake GCP training in order to understand the principles of GCP. However, this is not a mandatory requirement unless deemed so by the sponsor. GCP training status for all investigators should be indicated in their respective CVs.

12.2.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study.. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

12.2.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data and be of a form where individuals are not identified and re-identification is not likely to take place.

Dexcom clarity uses standard internet access to a specific set of IP addresses. No interface with clinic medical records is required for a clinic to operate. Data traffic is secured using TLS 1.2. Data is encrypted at rest using AES-256 encryption. Data is redundantly backed up across wide geographic separation. Published results will not contain any personal data that could allow identification of individual participants.

The Tandem t:connect application utilizes a stand-alone relational database that is setup specifically for each Clinical Trial. The original pump data that is extracted from the device is validated with a Checksum value before uploading, uploaded via a secure web service (SSL) and stored in a database table in its original XML form for archival purposes; this essentially serves as a Read-Only data store. The pump XML data is then read, transformed and stored into respective database tables which maintain integrity through the use of indexes and

relational key constraints. The database's integrated Security Roles and Users control access to the data, allowing only the Application, secure Web Services and authorized support personnel to access the data. Data access is logged using a combination of integrated database logs and custom code.

13 STUDY CONDUCT RESPONSIBILITIES

13.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

13.2 MANAGEMENT OF PROTOCOL NON COMPLIANCE

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

13.3 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

13.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

13.5 END OF STUDY

The end of study is defined as the last participant's last visit.

The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R+D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot

A summary report of the study will be provided to the REC within 1 year of the end of the study.

13.6 CONTINUATION OF TREATMENT FOLLOWING THE END OF STUDY

Participants recruited to the study will be on the NHS Lothian insulin pump waiting list. At the end of the study participants will have to return their study devices, Tandem t:slim X2 insulin pump and Dexcom G6 CGM, to the study team. They will continue with their pump process as per the NHS Lothian pump waiting list. The pump used in this trial is one of the pumps offered by NHS Lothian and so participants may choose to continue with this pump. Dexcom CGM is not currently available through NHS Lothian. If participants wish to continue with this they would have to self-fund the CGM device, they would need to do this in order to use the Control IQ algorithm. At the end of the study participants following the low carbohydrate diet may choose to revert back to their pre-study diet.

13.7 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

14 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

14.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. Anonymised data will be shared with the Helmsley Charitable Trust, Tandem and Dexcom. The company

headquarters for these organisations are based in the United States. The study team intend to also disseminate anonymised data through presentation at conferences, publication in peer reviewed journals and the completion of a thesis.

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