<HYPO-DIAD>

Frequency of nocturnal hypoglycaemia in adults with insulin-treated diabetes and adrenal failure using prednisolone or hydrocortisone: a pilot study.

9th March2023

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Protocol authorised by:

Name & Role	Date	Signature
Monika Reddy CI		

Study Management Group

Chief Investigator: Dr Monika Reddy

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Statistician: Ian Godsland

Study Management: Dr Monika Reddy

Clinical Queries

Clinical queries should be directed to Dr Monika Reddy who will direct the query to the appropriate person

Sponsor

Imperial College Healthcare NHS Trust is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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Funder

Imperial Health Charity

This protocol describes the HYPO-DIAD study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

CGM	Continuous glucose monitoring
AI	Adrenal insufficiency
T1D	Type 1 diabetes
ICRF	Imperial College Research Facility

KEYWORDS
Type 1 diabetes
Adrenal Failure
Hypoglycaemia
Continuous glucose monitoring

STUDY SUMMARY

TITLE Frequency of nocturnal hypoglycaemia in patients with insulin-treated diabetes and adrenal failure using prednisolone or hydrocortisone: a pilot study.

DESIGN A prospective observational study

AIMS (1) To measure the frequency of nocturnal hypoglycaemic episodes in people with both AI and Type 1 Diabetes, and in age, sex and steroid replacement matched controls without diabetes.

(2) To compare frequency of nocturnal hypoglycaemia in those taking prednisolone versus those taking hydrocortisone.

(3) To compare the diurnal patterns of frequency of hypoglycaemia in those taking prednisolone versus those taking hydrocortisone.

OUTCOME MEASURES Primary outcomes: Percentage time spent with glucose below 3.0mmol/L

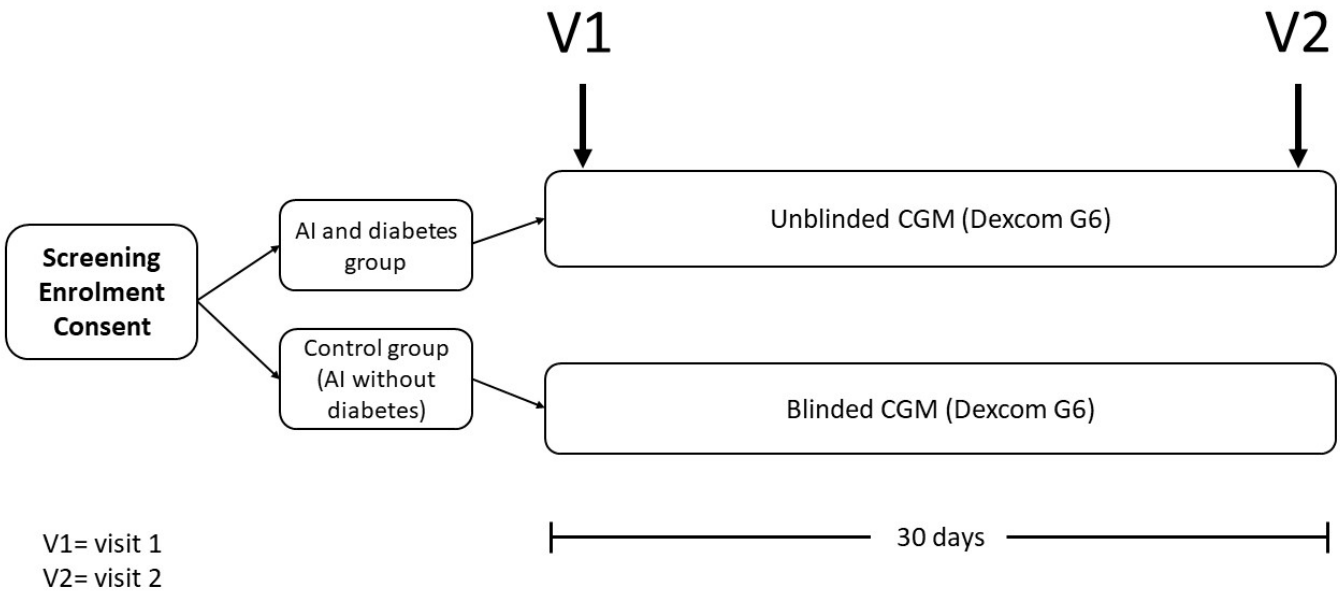
Secondary outcomes: Percentage time spent with glucose below 3.9mmol/L, between 3.9mmol/L and 10mmol/L, and above 10mmol/L. Number of episodes of hypoglycaemia and severe hypoglycaemia. Outcomes will be retrieved for the nocturnal period (midnight to 6am) and separately for the 24-hour period. Gold score, Hyperglycaemia Fear Survey-II (HFS-II) score and Hospital Anxiety and Depression (HADS) Score.

POPULATION Adults with insulin-treated diabetes and adrenal insufficiency

ELIGIBILITY Confirmed diagnoses of insulin-treated diabetes and adrenal insufficiency for at least one year

DURATION 30 days

REFERENCE DIAGRAM



1. INTRODUCTION

BACKGROUND

Adrenal insufficiency (AI) is a serious condition which, without treatment, may be life-threatening and is associated with increased mortality (1, 2). AI can be caused by primary failure of the adrenal glands (primary AI) or by pituitary disorders. Primary AI is an autoimmune condition that leads to destruction of the adrenal cortex and its ability to produce cortisol. Lack of cortisol can lead to an adrenal crisis which is an acute medical emergency requiring urgent treatment.

People with AI require lifelong steroid replacement, traditionally using hydrocortisone or more recently with prednisolone. Hydrocortisone has a short half-life and is given three times a day, which mimics the natural daily variation in production of cortisol. Prednisolone is an alternative option, and owing to its longer half-life needs only to be given once a day, offering benefits for ease of compliance.

Primary AI is often associated with other autoimmune endocrinopathies such as Type 1 diabetes, which requires treatment with insulin. Type 1 diabetes and type 2 diabetes, which may also require treatment with insulin, are both strongly associated with

cardiovascular risk factors (3) and increased mortality (4). Lifelong management with insulin requires multiple daily injections and self-management can be challenging.

Hypoglycaemia (low blood glucose) is a common and serious complication of insulin therapy and independently causes a twofold increase in risk for cardiovascular disease and mortality in insulin-treated diabetes (5). Hypoglycaemic symptoms may include irritability, dizziness or confusion. If left untreated this can lead to loss of consciousness, seizure or death. Prompt recognition and appropriate treatment is paramount and nocturnal hypoglycaemia is particularly concerning. Recurrent episodes may lead to impaired awareness of hypoglycaemia, increased frequency of episodes and subsequent risk of severe hypoglycaemia, defined as hypoglycaemia requiring the assistance of a third party for active treatment.

Hypoglycaemia also occurs in AI in the absence of insulin-treated diabetes. Cortisol has an important role in the counter-regulatory response to hypoglycaemia. Lack of cortisol in AI causes reduced hepatic glucose output and increased glucose oxidation leading to increased insulin sensitivity. Hypoglycaemia may be present in undiagnosed AI in some, and in others may be a signifier of untreated or suboptimal treatment of AI.

RATIONALE FOR CURRENT STUDY

There is a complex relationship between AI and Type 1 diabetes, which results in higher mortality in people living with both diagnoses compared to either diagnosis alone (6). Adrenal crises and hypoglycaemia are both potentially life-threatening medical emergencies which often lead to individuals requiring acute medical admission to hospital. Recent data demonstrates that more than half of severe hypoglycaemic episodes attended by paramedics result in conveyance to hospital (7). As having both conditions is rare, there are few studies on this high risk, vulnerable and relatively young group. There may be substantial potential to reduce harm and burden, and to reduce healthcare utilisation by minimising exposure to hypoglycaemia.

Previous studies conducted at ICHT reported 66% greater mortality in people with AI compared to matched controls (8). Furthermore, in people with primary AI, the mortality was three times higher in those with treated with prednisolone compared to hydrocortisone (9). These findings were reported from the first population-based dataset of adrenal failure in the UK. However, the studies were retrospective and prior to 2014, many participants took higher total daily doses of prednisolone (7.5g) than current recommended (3g or 4g). Research in optimal steroid replacement doses has since indicated that 7.5g is excessive, leading to steroid-induced complications such as hyperglycaemia, increased blood pressure and increased body weight, all of which increase cardiovascular risk factors. This is likely to have significantly contributed to the mortality excess in the past but further research in required to determine factors

affecting this group currently. This study would aim to investigate frequency of hypoglycaemia as a potential cause for this excess.

Research Question: In people with insulin-treated diabetes and adrenal failure, does hypoglycaemia occur more frequently in those treated with prednisolone or hydrocortisone?

2. STUDY OBJECTIVES

(1) To measure the frequency of nocturnal hypoglycaemic episodes in people with both AI and insulin-treated diabetes, and in age, sex and steroid replacement matched controls without diabetes.

(2) To compare frequency of nocturnal hypoglycaemia in those taking prednisone versus those taking hydrocortisone.

(3) To compare the diurnal patterns of frequency of hypoglycaemia in those taking prednisolone versus those taking hydrocortisone.

3. STUDY DESIGN

This is a prospective observational study in 16 adults with both insulin-treated diabetes and adrenal insufficiency and 16 age, sex and steroid replacement matched controls without diabetes. We will recruit and enrol 32 participants in total. Participants will spend 30 days in the study.

STUDY OUTCOME MEASURES
Primary outcomes: Percentage time spent with glucose below 3.0mmol/L

Secondary outcomes: Percentage time spent with glucose below 3.9mmol/L, between 3.9mmol/L and 10mmol/L, and above 10mmol/L. Number of episodes of hypoglycaemia and severe hypoglycaemia. Outcomes will be retrieved for the nocturnal period (midnight to 6am) and separately for the 24-hour period. Gold score, Hyperglycaemia Fear Survey-II (HFS-II) score and Hospital Anxiety and Depression (HADS) Score.

4. PARTICIPANT ENTRY

INCLUSION CRITERIA
- for test group:
Confirmed diagnoses of adrenal insufficiency and insulin-treated diabetes for more than one year.
Adults aged above 18 years

-for matched control group:
Diabetes mellitus excluded on baseline blood review
Adults aged above 18 years

EXCLUSION CRITERIA
Measured eGFR ≤ 30
Acute illness
Abnormal thyroid function
Admission to hospital
Pregnant or planning pregnancy
Breastfeeding
Enrolled in other clinical trials, except at the discretion of the chief investigator
Have active malignancy or under investigation for malignancy
Severe visual impairment
Reduced manual dexterity
Unable to participate due to other factors, as assessed by the Chief Investigators

WITHDRAWAL CRITERIA
The subject has a serious event related to study
Investigator initiated discontinuation of study due to participation or equipment concerns
Withdrawal of consent
<70% complete continuous glucose monitoring (CGM) data within 10 day run in period

Withdrawal will be immediate. Identifiable data already collected with consent will be retained and used in the study. No further data would be collected or any other research procedures carried out on or in relation to the participant.

5. ADVERSE EVENTS

5.1 Definitions

Investigational Medical Device
Medical device being assessed for safety or performance in a clinical investigation. This includes medical devices already on the market that are being evaluated for new intended uses, new populations, new materials or design changes.

Adverse Event (AE)
Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in participants, users or other persons concerned with the medical device. These may, or may not be, considered related to the investigational device, device related procedure or comparator. If the AE is considered to have a reasonable causal relationship with the device, then it is considered to be an ADE.

Adverse Device Effect (ADE) An Adverse Event (AE) related to the use of an investigational medical device. This includes any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, implantation or operation of the medical device or any malfunction. This also includes any AE that is a result of an error in use or intentional misuse of the medical device.

Device Deficiency Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device Deficiencies include malfunctions, misuse or use errors and inadequate labelling.

Serious Adverse Event (SAE) An Adverse Event that results in:

- Death.
- Life threatening illness or injury.
- Permanent impairment of a body structure or body function.
- Hospitalisation or prolongation of existing hospitalisation.
- Medical or surgical intervention to prevent life threatening illness, injury or impairment to a body structure or body function.
- Foetal distress, foetal death or congenital anomaly or birth defect.
- Is otherwise considered medically significant by the Investigator

This includes potential SAEs which were avoided as result of action or intervention. A planned hospitalisation for a pre-existing condition, or a procedure required in the protocol, without a serious deterioration in health, is not considered an SAE.

NOTE Device deficiencies that might have led to a serious adverse event where a suitable action had not been taken or an intervention had not been made or if circumstances had been less fortunate are handled under the serious adverse event reporting system.

Such adverse events should be reported as soon as possible. When reporting these events please include the total number of patients treated in the UK at the time of reporting.

Medical judgement should be exercised in deciding whether an adverse event is serious in other situations. Important adverse events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Severity: The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious”, which is based on patient/event outcome or action criteria.

Suspected Serious Device Effect (SADE) An Adverse Device Effect (ADE) that results in:

- Death.
- Life threatening illness or injury
- Hospitalisation, or prolongation of existing hospitalisation.
- Persistent or significant disability or incapacity.
- Foetal distress, foetal death or congenital anomaly or birth defect.
- Is otherwise considered medically significant by the Investigator

Any hospitalisation planned prior to enrolment is not a SADE.

Unanticipated Serious Adverse Device Effect (USADE) Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Responsibilities There are a number of responsibilities when managing adverse events. Below is a list of responsibilities for both the Investigator and the Sponsor (the Research Governance and Integrity Team (RGIT) will act on behalf of the Sponsor).

The CI has overall responsibility for the conduct of the study. The Principal Investigator (PI) has responsibility for the research at a local site where the study involves specified procedures requiring site-specific assessment. There should be one PI for each research site. In the case of this single-site study, the CI and the PI are the same person.

Investigator’s Responsibilities

1. CI to report all SAEs within agreed timelines to Sponsor
2. CI to report SAEs within agreed timelines to Sponsor, REC and relevant NHS Trust Research and Development Office (R&D)
3. Provide the Sponsor with details of all AEs identified in the protocol as critical to the evaluation of safety within the agreed timeframes specified in the protocol.
4. Review SAE reports from Investigators and perform an evaluation with respect to seriousness, causality and expectedness.
5. Supply the Sponsor, REC and relevant NHS Trust R&D with any supplementary information they request.

Sponsor's Responsibilities

1. In collaboration with the Device Manufacturer, perform ongoing safety evaluation of the trial device and report any findings that may affect the health of subjects to the Device Manufacturer.
2. Promptly notify all Investigators and REC(s) of any findings that may affect the health of subjects.
3. Keep detailed written reports of all AEs reported by PIs and performing an evaluation with respect to seriousness, causality and expectedness.
4. Report all relevant safety information and SAEs to the relevant REC within the relevant timelines
5. Submit the annual report to Sponsor and REC.

Note that for Imperial AHSC sponsored studies the above sponsor responsibilities are delegated to the CI.

PROCEDURES

Study Planning The device's User Guide written by the device manufacturer lists known side effects and adverse reactions contained within the manufacturer's product information. Rare/very rare events may or may not be included depending on individual study requirements.

During the Trial Each AE will be evaluated for seriousness, causality, and expectedness. The responsibility for this evaluation and reporting to the sponsor rests with the CI.

Causality Adverse reactions will be assessed for causality. The definitions below will be used.

Relationship	Description
Unrelated	There is no evidence of any causal relationship to the medical device
Unlikely	The relationship with the use of the investigational medical device seems not relevant and/or the event can be reasonably explained by another cause.
Possible	The relationship with the use of the device is weak but cannot be ruled out completely
Probable	The relationship with the investigational medical device seems relevant and/or the event cannot be reasonably be explained by another cause.
Causal Relationship	The serious event is associated with the investigational medical device beyond reasonable doubt.

Assessment of Expectedness
Expected: The reaction is consistent with the effects of the device listed in the manufacturer's User Guide
Unexpected: the reaction is not consistent with the effects of the device listed in the manufacturer's User Guide .

Reporting
Once the CI has evaluated the AE in terms of seriousness, causality and expectedness, the following guidelines will be followed.

AEs/ADEs AEs that will be reported and are not considered serious will be included in the patient notes and on the relevant case report forms (CRFs). The completed form will be filed along with the other CRFs for the study.

SAEs/SADEs If the AE is assessed as serious, the CI must be informed immediately and within 24 hours. The CI will record the event with assessment of seriousness, (along with causality, expectedness and severity) on a trial SAE form. The CI will ensure that follow-up information is provided when available. Where supporting documents are sent with this form, these will be pseudonymised. Where the information available is incomplete at that time, as much information as can be ascertained will be sent to ensure timely reporting, with additional information provided as soon as it is known. Additional information received for an event (follow-up or corrections to the original event data) will to be detailed on a new SAE form. The CI must ensure that SAEs are reported to RGIT within 24 hours via email to RGIT@imperial.ac.uk.

USADEs Reports of USADEs shoulde be submitted to the REC within 15 days of the CI becoming aware of the event.

Follow-up of adverse events All adverse events will be followed-up until resolution or death of the participant.

6. ASSESSMENT AND FOLLOW-UP

6.1 Recruitment

Recruitment will be undertaken in endocrinology and diabetes clinics at Imperial College Healthcare NHS Trust. Participant information sheets will be given to potential subjects and, following any questions, informed consent will be taken. We will identify potential participants from medical records and post/email them a copy of the Patient Information Sheet (PIS) prior to approaching them in clinic.

Participants will be given as much time as they require (and at least 24 hours) to decide whether or not to take part – this can vary on a per participant basis.

6.2 Enrolment and study conduct

6.2.1 Visit 1: Baseline Screening

(Day 0, to last approximately 2 hours)

Participants will attend an initial screening visit at the NIHR Imperial College Research Facility (ICRF). Following informed consent, the research team will collect full medical and medication history and conduct routine anthropometry (height and weight). The research team will also carry out a physical examination including a general chest examination and abdominal examination (auscultation of lungs, heart and abdomen and palpation of the chest wall and abdomen). Participants will be asked to provide a urine sample (urine albumin:creatinine ratio) and a venous blood sample will be taken (full blood count, HbA1c, urea, creatinine and electrolytes, thyroid function, c-peptide and glucose). We will measure baseline steroid replacement with serum prednisolone levels or hydrocortisone day curves (see appendix 2). Blood samples will be sent to the accredited Imperial College Healthcare NHS Trust laboratory for analysis. Urine pregnancy tests will be done in females of childbearing age. Urine and blood samples will not be stored. Participants will complete the Gold questionnaire to assess for hypoglycaemia awareness, the Hyperglycaemic Fear Survey-II and Hospital Anxiety and Depression Survey. All questionnaires used are validated.

Participants will be provided with a continuous glucose monitoring (CGM) device. The system continuously measures glucose levels in interstitial fluid through a small sensor which is inserted under the skin. For the control group, the device will be blinded to the participant. In participants who have insulin-treated diabetes, the data can be read on a display device (receiver) or a compatible smart app. Each participant will have a sensor fitted in clinic. They will be given education for use of the device according to the manufacturer's guidelines. They will have access to the Dexcom G6 User Guide, which is available online. Participants will be shown how to insert the sensors themselves and provided with adequate sensors and transmitters for the duration of the trial. If the participants' sensor fails or falls out the research team will provide a new sensor. Participants will be instructed to test their glucose as per standard care, and to manage as their usual care if symptoms of hypo- or hyperglycaemia occur. Refresher education regarding general diabetes management and management of hypoglycaemia specifically will be offered.

Participants will be supported to change their glucose sensor every 10 days at home. Those with unblinded devices will be given education and support to manage the alerts

and alarms provided by the system. At this visit the glucose threshold low alert will be set to 4.4 mmol/L and the high threshold alert will be set to 12mmol/L. These can be personalised by participants throughout the study to manage alert burden. Participants will have access to a helpline for any queries or concerns regarding their device.

6.2 Visit 2: Final Study Visit

(Day 30, to last approximately 1 hour)

Participants will attend the ICRF 30 days after their baseline screening for data collection. Participants will be invited to review and discuss the data collected with a clinician. This review may be conducted over the telephone as per the participant's preference.

All study equipment will be returned, and participants will return to standard care.

6.3 End of Study

End of study will be defined as Last Subject Last Visit (LSLV)

6.3.1 Incidental findings

Incidental findings identified from laboratory investigations during the study will be reviewed by the investigators and will then be communicated by the study team to the participant and to the participant's GP.

Incidental findings identified from laboratory investigations during the study will be reviewed by the investigators and will then be communicated by the study team to the participant and to the participant's GP with a clear management plan.

Examples of potential incidental findings include:
1. A new diagnosis of pre-diabetes or diabetes in the control group
2. Hypothyroidism (underachieve thyroid) or hyperthyroidism (overactive thyroid)
3. Anaemia

7. STATISTICS AND DATA ANALYSIS

This is a pilot study and therefore we are not proposing a fully-powered study (4). The data gathered from the proposed work will serve as robust pilot data to support a larger randomised study.

The primary outcome is the percent time spent with glucose below 3.0mmol/L. This is in accordance with international consensus for hypoglycaemia. Glucose data will be extracted from the 30 days of unblinded/blinded CGM and used for analysis.

A two-tailed unpaired t-test will be performed to compare the primary and secondary glucose outcomes between groups. A p-value of <0.05 will be considered statistically significant.

All study data including personal and pseudoanonymised data and all appropriate documentation will be stored for a minimum of 5 years after the completion of the study, including the follow-up period.

8. REGULATORY ISSUES

ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the xxx Research Ethics Committee (REC) and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician 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

Pseudonymised data is data that can be linked back to a person (e.g. coded data). It is considered both personal and identifiable data. Anonymised data is data that has no code and cannot be linked back to a person (e.g. aggregated data for publication, data without a code that cannot be linked back to a person)

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

Data will be pseudonymised
Dexcom is a separate data controller and is able to access pseudoanonymised CGM data from Dexcom device users. They have a separate privacy notice and subject rights which can be accessed online here: https://www.dexcom.com/en-GB/linked/documentservice/PrivacyPolicy.

INDEMNITY
Imperial College Healthcare NHS Trust holds standard NHS Hospital Indemnity and insurance cover with NHS Resolution for NHS Trusts in England, which apply to this study

SPONSOR
Imperial College Healthcare NHS Trust 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 Imperial Health Charity are funding this study.

AUDITS
The study may be subject to audit by Imperial College Healthcare NHS Trust under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Dr Shaila Khan.

10. 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. Details of any publications that arise from the study will be disseminated to participants on request.

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Appendix 1. Summary of activities at and between visits

	VISIT 1 Day 0	Day 10	Day 20	VISIT 2 Day 30
Medical history	x			
Medication history	x			
Physical examination	x			
Pregnancy test (urine)	x			
Full Blood Count	x			
Renal Function	x			
HbA1c	x			
TFT	x			
C peptide	x			
Glucose	x			
Cortisol day curve/ Prednisolone level	x			
Gold score	x			
QoL questionnaires	x			
CGM education	x			
CGM insertion **(supervised by research team)**	x			
CGM insertion (independently by participant		x	x	
CGM download	x			x
Data review				x

Appendix 2. Protocols for baseline steroid measurement

Prednisolone Level

Preparation

- Stop all oestrogen therapy 6 weeks prior to test.
- No need to fast.
- Take normal morning prednisolone and patient should note down actual time taken.

Method

A sample is taken 8h following the administration of prednisolone. If the dose was taken at 7am at home, the final sample should be taken at 3pm.

Hydrocortisone Day Curve

Preparation

- Stop all oestrogen therapy 6 weeks prior to test.
- No need to fast.
- Take normal morning hydrocortisone and patient should note down actual time taken.
- Equipment required: 18-20g cannula. Red or yellow top Vacutainers. Syringes.

Method

Take blood at the following times:

1. Blood sample on arrival, noting time of sample and time and dose of hydrocortisone.
2. Pre lunchtime (2nd) dose
3. 1 hour post lunchtime (2nd) dose
4. pre evening (3rd) dose
5. post evening (3rd) dose or at 6pm.

Source: Endocrinology Handbook. Imperial Centre for Endocrinology. Imperial College Healthcare NHS Trust. Latest edition February 2018. Bible2018.pdf (imperialendo.co.uk)