JRMO Research Protocol for Interventional Studies

Full Title Continuous Glucose Monitoring: An evaluation of impact on improving the efficiency of diagnostic processes and enhancing patient safety in the management of reactive and spontaneous hypoglycaemia.

Short Title CGM use in diagnosis of spontaneous and reactive hypoglycaemia

Sponsor

- Barts Health NHS Trust

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List of technical departments	*None*
List of central facilities	*None*

1. Contents

2. Glossary

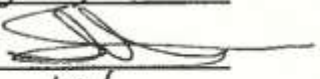
CGM – continuous glucose monitoring
CBG – capillary blood glucose

3. Signature page

Chief Investigator Agreement

The study as detailed within this research protocol will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, and the Declaration of Helsinki and any other applicable regulations. I agree to take responsibility for the statistical analysis and oversight of this study.

Chief Investigator Name: Dr S A Akker

Signature: 

Date: 17/6/19.

4. Summary and synopsis

Short title	CGM use in diagnosis of spontaneous hypoglycaemia
Methodology	*Clinical trial studying a novel intervention in clinical practice*
Research sites	*St Bartholomew's hospital*
Objectives / aims	Objectives 1) Use CGM (blinded to the patient and investigator) in advance of standard investigations (where possible) in order to record whether patient symptoms correlate with recorded hypoglycaemia. This may exclude hypoglycaemia as a cause of symptoms and allow the patient to avoid a prolonged inpatient investigation. 2) Use CGM technology (blinded to the patient and investigator) alongside standard investigations for patients with both reactive and spontaneous hypoglycaemia to see If there is additional value in using two methods in detecting hypoglycaemic episodes. 3) Use CGM (blinded to the patient and investigator) to record frequency of hypoglycaemia after medical treatment has been initiated in order to assess its effectiveness in detecting hypoglycaemic episodes of which the patient may not have been aware, potentially reducing the need for painful finger prick glucose testing. 4) Use CGM (unblinded) to titrate medication to abolish

	hypoglycaemia in order to improve outpatient management and improve patient safety. The Dexcom system has an alarm to alert patients to hypoglycaemia which will be used in the unblinded phase. Aims There will be two main arms to the study; 1) Investigation of patients suspected of having hypoglycaemia (spontaneous or reactive) alongside standard investigations 2) Management of patients with confirmed hypoglycaemia who are medically managed to see if continuous glucose monitoring can play a role in abolishing asymptomatic hypoglycaemia through optimisation of medicines.
Number of participants	30
Inclusion and exclusion criteria	<u>Inclusion Criteria</u> Able and willing to give informed consent. No vulnerable adults will be included. Either conventional gender, or non-binary. Age >18 years Any ethnicity Any socio economic group Medical condition as detailed above – arm 1 under investigation for possible/probable hypoglycaemia Arm 2 – on medical therapy for established hypoglycaemia <u>Exclusion criteria</u> Unwilling or unable to give consent Unable to speak sufficient English to give consent and understand study requirements Age<18 or >90 years Lack of capacity to consent Underlying hepatic condition Current excessive alcohol consumption (men regularly consuming >50 units/week, women >35 units/week) Diabetes Mellitus Current use of Diabetic medication or insulin Currently pregnant Any patient on haemo or peritoneal dialysis
Statistical methodology and analysis (if applicable)	
Study duration	*1 year*

5. Introduction

Suspected reactive and spontaneous hypoglycaemia can be a challenging problem to investigate. Definitive diagnosis currently relies upon the patient experiencing symptoms, reporting them accurately and then a series of complex investigations.

Current standard of care tests

Current 'gold standard' testing when reactive hypoglycaemia is suspected is with an extended oral glucose tolerance test or mixed meal test. Where spontaneous hypoglycaemia is suspected and where facilities exist, the 'gold standard' test is an admission to Hospital for a 72 hour fast with twice daily laboratory measurements of plasma glucose, insulin and c-peptide. Finger prick glucose measurements are taken throughout the day to check for asymptomatic hypoglycaemia. Additional laboratory measurements are made if the patient becomes symptomatic. The prolonged fast is terminated when a diagnostic laboratory glucose measurement of <2.2mmol/L is reached. Where a 72 hour fast is not possible, attempts are made to test insulin and glucose after three separate 15 hour fasts but this risks out of hospital hypoglycaemia and all its potential sequelae. These investigations attempt to mimic the situations which precipitate the hypoglycaemia but, in particular for reactive hypoglycaemia, often fail to do so.

Pathophysiology and significance of hypoglycaemia

Symptomatic reactive hypoglycaemia is recognized in some patients with insulin resistance before the development of type 2 diabetes and is increasingly recognized as a complication of significant weight loss following bariatric surgery. Spontaneous hypoglycaemia is most commonly caused by an insulinoma which is a very rare diagnosis outside the context of MEN1 (1-4/million patients). In patients with MEN1, insulinoma is the second most common functioning pancreatic islet cell tumour (10-30%) (1) and typically occurs before the age of 40. In MEN1, the management of an insulinoma is the most challenging as: 1) Hypoglycaemia may be under reported as long term exposure to hypoglycaemia can result in hypoglycaemic autonomic failure with blunting or loss of the body's sympathetic response (loss of hypoglycaemic awareness) and an inability to counter-regulate subsequent or more serious events (2), including the possibility of sudden death (probably through cardiac arrhythmia) (3-5). 2) The chances of successful surgical resection and cure are lower as almost all MEN1 patients have multiple pancreatic lesions, many of which are smaller than the resolution of current imaging modalities. It can be difficult or impossible to know which lesion is producing insulin and extensive surgery can lead to pancreatic insufficiency to a degree that leaves the patient with extremely difficult to manage diabetes. As such patients are therefore often given medical therapies; these however are difficult to monitor for effectiveness, especially if there is loss of hypoglycaemic awareness.

Current testing limitations

Finger-prick glucose testing is currently the only viable way of home testing. Asymptomatic nocturnal hypoglycaemia is of most concern as repeat episodes are likely to lead to cumulative long term consequences of cerebral hypoglycaemia. Finger prick testing is unpopular amongst patients – it is painful and requires disposal

of 'medical sharps'. It also only provides a 'snapshot' of the patient's glycaemic state and so will, by its very nature; only provide this 'snapshot' when the patient is awake and able to use it.

Continuous glucose monitoring

CGM technology has transformed the monitoring of patients with diabetes mellitus who are insulin treated, particularly those affected by asymptomatic hypoglycaemia. The Dexcom system, which we will use for this study has performed favourably against competitors in the hypoglycaemic ranges in a head to head comparison study (6) and in a study examining the accuracy of the G6 device specifically (7). When using concomitant gold standard YSI glucose measurements as reference, for blood glucoses of <54mg/dL (3mmol/L) the G6 device was within 30% of the reference value 93.5% of the time and within 20% 85% of the time. For blood glucoses 54-69mg/dL (3-3.9mmol/L) these figures were 94.4 and 97.7% respectively (7).. Each system is composed of an implantable sensor (which can easily be placed by the patient) with a small probe that sits just under the skin and a chip which sits outside, all held in place by a dressing. Dexcom devices have enabled the instantaneous measurement of a surrogate of the capillary blood glucose simply by waving a mobile device (a proprietary device, or more recently a mobile phone or tablet) over the sensor. In addition to providing a 'stat' CBG reading, these devices can give quarter-hourly CBG readings for the entire life time of a sensor, data which can be downloaded onto a mobile device for later analysis. The Dexcom G6 device also allows the real time CBG readings to be shared 'live' with up to five people, providing additional safety and reassurance. In the context of reactive and spontaneous hypoglycaemia titration of anti-hypoglycaemia medication could be made through virtual consultations during the monitoring period.

5.1 Background

See above

5.2 Preclinical data

5.3 Clinical data

Case Vignette: A 20 year old lady with mild learning difficulties was recently found to have spontaneous hypoglycaemia and primary hyperparathyroidism on presentation to hospital. There is a family history of MEN1. Results confirmed an inappropriately high insulin and C-peptide in the presence of hypoglycaemia 8 hours into a fast; results in keeping with an insulinoma. The patient had no apparent hypoglycaemia-awareness. MRI showed three lesions in the pancreas, each in keeping with an islet cell tumour. Medical treatment was started (diazoxide) and titrated to abolish recorded hypoglycaemia while in hospital. At home however, with more physical activity, her mother reported ongoing symptoms of hypoglycaemia and a CGM device was used to monitor the situation. This recorded significant and prolonged nocturnal hypoglycaemia (Figure 1) as well as several episodes during the week when awake. With the home glucose records shared via the cloud, the medications were uptitrated and octreotide started with considerable improvement in nocturnal hypoglycemic

CGM readings (Figure 2). This allowed the patient, her mother and ourselves to be reassured that the clinical situation was now much safer.

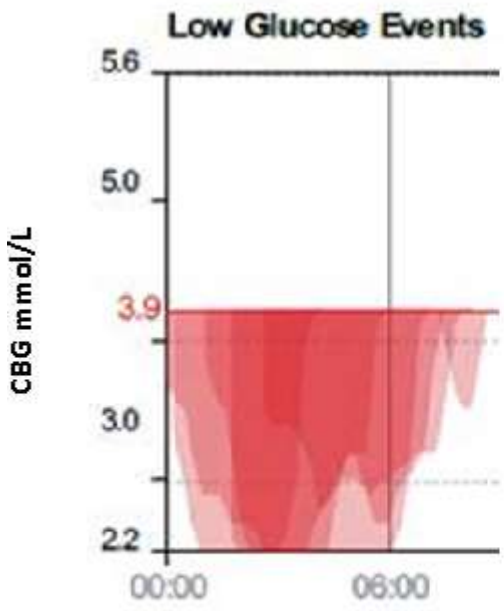


Figure 1 - Nocturnal hypoglycaemia events pre-initiation of octreotide

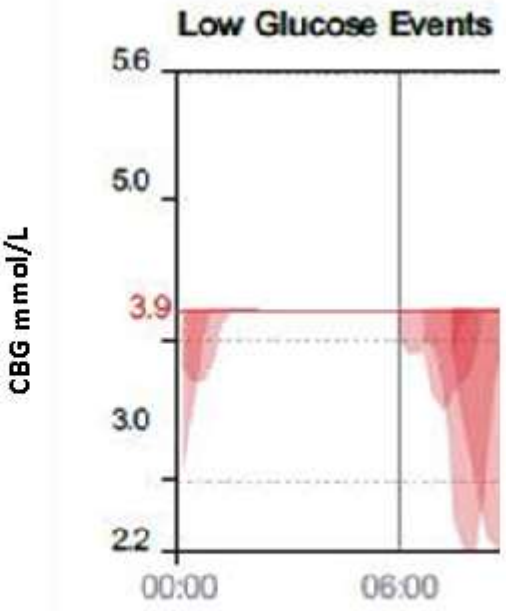


Figure 2 - Reduced nocturnal hypoglycaemia events post-initiation of octreotide

5.4 Rationale

Prompt diagnosis of hypoglycaemia is important as, untreated, it can lead to weight gain, symptomatic hypoglycaemia and increases the risk of sudden death through arrhythmia. At present, diagnosis of hypoglycaemia depends upon the reporting of symptoms and capture of hypoglycaemic range CBGs through finger prick glucose measurement. If the clinical suspicion of hypoglycaemia is strong enough, then patients will be admitted for a supervised 72 hour fast, where blood glucose is checked regularly through finger prick measurements and venous phlebotomy. Patients can lose hypoglycaemic awareness, however, and so symptoms are not always a reliable way to diagnose the problems. 72 hour fasts are labour intensive for the medical and nursing teams and may require the patient to take time off work or away from caring duties. A robustly tested CGM test may allow us to determine if blinded CGM testing can be used to obviate the need for inpatient testing. It may also provide useful diagnostic information by relating the proximity of hypoglycaemic episodes to food intake, adding to weight to diagnoses of reactive or spontaneous hypoglycaemia.
CGM has revolutionized the lives and medical management of type 1 Diabetes patients with hypoglycaemic unawareness and we hope that it can produce similarly excellent results in the field of reactive/spontaneous hypoglycaemia.

Once spontaneous hypoglycaemia has been diagnosed, treatment with medical therapy is often the first step. The goal is to try and make the patient hypoglycaemia free. This is tricky if the patient has no hypoglycaemia awareness, but can be overcome during the day with regular fingerprick glucose checks – though patients frequently complain that this is painful. At night, however, patients are asleep and

cannot check their blood glucose this way and so there is a paucity of data about their glycaemic state at night – the very time that they are fasting and hypoglycaemia is more probable. CGM can therefore tell us about their glycaemic status all day, without painful finger prick testing and also during the night whilst the patient is asleep. This information can then help doctors titrate their anti-hypoglycaemia medication with the aim of abolishing their hypoglycaemic episodes.

5.5 Risks / benefits

Risks/inconveniences

Patients will have a glucose monitoring probe inserted, this sits on the abdominal wall and protrudes just under the skin, sampling the glucose in the interstitial fluid. There is sometimes a very small amount of discomfort associated with this (84% of users state it is painless in company's literature) and sometimes a very small amount of inconvenience associated with wearing it if it catches on clothing - but it is very slim and rarely interferes with normal day-to-day activities.
CGM sensor/transmitter is fully waterproof and can be worn in showers/baths and also to the gym.
CGM system is safe to travel with. We will provide a letter explaining the system's components if study participants wish to fly in order to clear airport security.
Patient will wear a glucose monitoring sensor and data will wirelessly download to their mobile device or a proprietary glucose data receiver device. If the patient does not have a suitable mobile device then we will lend them a glucose data receiver.

CGM probe is inserted through the skin and so there is a theoretical risk of local infection if the skin is not cleaned prior to insertion as recommended.
There is a theoretical risk of the probe component breaking off under the skin.

Benefits

Discovery of hypoglycaemia earlier than would otherwise be the case.
Easier detection of asymptomatic hypoglycaemia in patients with known hypoglycaemia and therefore optimal titration of their medication.
Elimination of dangerous asymptomatic hypoglycaemia.

6. Study objectives

6.1 Primary objective

1) Use CGM (blinded to the patient and investigator) in advance of standard investigations (where possible) in order to record whether patient symptoms correlate with recorded hypoglycaemia. This may exclude hypoglycaemia as a cause of symptoms and allow the patient to avoid a prolonged inpatient investigation.
2) Use CGM technology (blinded to the patient and investigator) alongside standard investigations for patients with both reactive and spontaneous hypoglycaemia to evaluate the relative efficacy of the two methods in detecting hypoglycaemia episodes.
3) Use CGM (blinded to the patient and investigator) to record frequency of hypoglycaemia after medical treatment has been initiated in order to assess its

effectiveness in detecting hypoglycaemic episodes of which the patient may not have been aware, potentially reducing the need for painful fingerprick glucose testing.
4) Use CGM (unblinded) to titrate medication to abolish hypoglycaemia in order to improve outpatient management and improve patient safety. The Dexcom system has an alarm to alert patients to hypoglycaemia which will be used in the unblinded phase.

6.2 Secondary objective

To determine whether CGM systems accurately record hypoglycaemia and can be used in this context

6.3 Primary endpoint

Arm 1 -
Outpatient - CGM findings reflect patient's fingerprick glucose readings
- Episodes of true hypoglycaemia (as decided by finger prick glucose testing) are captured by the CGM device
- CGM detects hypoglycaemia whilst patient is asleep
Inpatient - 72 hour fast - CGM device calls hypoglycaemia when fingerprick/lab glucoses also do

Arm 2 -
Blinded phase - CGM findings reflect patient's fingerprick glucose readings - any episodes of true hypoglycaemia (as decided by fingerprick glucose testing) are captured by CGM device
unblinded phase - CGM recordings help with titration of anti hypoglycaemic medications and this reduces overall incidence of hypoglycaemic episodes or duration of time spent in hypoglycaemic range
For patients experiencing asymptomatic hypoglycaemic episodes, a reduction in asymptomatic hypoglycaemic episodes and regaining of hypoglycaemic symptoms.
For patients with symptomatic hypoglycaemia, a reduction in symptomatic episodes.

7. Study population

Clinicians in the endocrinology department at St Bartholomew's hospital will be notified of this study and encouraged to refer forward suitable patients from their clinics.

Arm 1
Patients referred to the endocrinology department at St Bartholomew's hospital for investigation of suspected hypoglycaemia by either GPs or other clinical teams in the same or external NHS trusts will be referred onwards to the study team by the doctor that sees them for their routine clinical care.
Arm 2
Patients known to the endocrinology department at St Bartholomew's hospital with hypoglycaemia that are medically managed or who are to start medical management will be referred to the study team by the doctor that sees them for their routine clinical care.
Some patients who are found to have hypoglycaemia through arm 1 of this study will be automatically offered the chance to partake in arm 2 if they are to have medical treatment.

No vulnerable groups will be included – all patient will be able to give valid consent on their own behalf
All patients will be able to understand sufficient English to give informed consent on their own behalf.

Inclusion Criteria
Able and willing to give informed consent. No vulnerable adults will be included.
Either conventional gender, or non-binary.
Age >18 years
Any ethnicity
Any socio economic group
Medical condition as detailed above – arm 1 under investigation for possible/probable hypoglycaemia
Arm 2 – on medical therapy for established hypoglycaemia

Exclusion criteria
Unwilling or unable to give consent
Unable to speak sufficient English to give consent and understand study requirements
Age<18
Lack of capacity to consent
Underlying hepatic condition
Current excessive alcohol consumption (men regularly consuming >50 units/week, women >35 units/week)
Diabetes Mellitus
Current use of Diabetic medication or insulin
Currently pregnant
Any patient on haemo or peritoneal dialysis

Length of study participation
Arm 1 - investigation of hypoglycaemia - maximum of 10 days of monitoring (5 days as an outpatient, max 5 days as an inpatient).
Arm 2 - evaluating anti hypoglycaemic drugs - maximum of 10 days of initial monitoring (investigator and patient blinded to CGM results), then up to a maximum of a further 20 days (unblinded) monitoring, likely to be far less than this though.

7.1 Inclusion criteria

Able and willing to give informed consent. No vulnerable adults will be included.
Either conventional gender, or non-binary.
Age >18 years
Any ethnicity
Any socio economic group
Medical condition as detailed above – arm 1 under investigation for possible/probable hypoglycaemia
Arm 2 – on medical therapy for established hypoglycaemia

7.2 Exclusion criteria

Unwilling or unable to give consent
Unable to speak sufficient English to give consent and understand study requirements
Age<18
Lack of capacity to consent
Underlying hepatic condition

Current excessive alcohol consumption (men regularly consuming >50 units/week, women >35 units/week)
Current use of Diabetic medication or insulin
Currently pregnant
Any patient on haemo or peritoneal dialysis

8. Study design

Arm 1
Patients will be recruited to the study via the endocrine outpatient clinic, or via referral to St Bartholomew's hospital for inpatient management of hypoglycaemia.

For those originating from the outpatient department, patients will receive a CGM kit, finger prick testing meter and glucose monitoring diary.
5 days prior to admission to hospital the patient will start the continuous glucose monitoring and will also record their finger prick glucose reading in their glucose monitoring diary at any point they experience symptoms they ascribe to hypoglycaemia.

During their admission to hospital for investigation into suspected hypoglycaemia (either patients from outpatients, or direct admissions), patients will continue/start continuous glucose monitoring, alongside standard of care twice daily venous glucose, insulin and c-peptide measurements and routine finger prick testing. As per standard of care, extra finger prick glucoses and venous glucose/insulin/c-peptide testing will be performed when the patient experiences symptoms that they associate with hypoglycaemia.

Arm 2
Patients who have been diagnosed with spontaneous hypoglycaemia which requires medical therapy will be given a CGM kit and a finger prick glucose monitoring device and glucose monitoring diary. Patients will take the standard medical therapy and perform finger prick glucose testing when they experience symptoms that they attribute to hypoglycaemia. These values will be recorded in the glucose monitoring diary. After (up to) 10 days of blinded CGM monitoring, the diary and CGM data will be reviewed. A member of the endocrine team (consultant or registrar with consultant approval) will then make changes to the medical therapy in order to abolish any remaining episodes of hypoglycaemia. Patients will then wear the CGM device in unblinded mode for up to a further 20 days (though likely to be far less) in order to facilitate further medication titrations. Patients will be asked to confirm low CGM glucose readings during this time with a finger prick glucose measurement.

The study organisers will observe the glucose data obtained from the CGM and match it with finger prick glucose readings (from glucose monitoring diaries) and lab glucose data to check for concordance.
CGM data (in conjunction with glucose monitoring diaries) will be scrutinised and compared against drug regimens to see which doses needed to be altered, or where additional medication is required.

Patients will complete a modified Clarke and Gold hypoglycaemia questionnaire at the start of arm 2. They will complete an adapted questionnaire prior to surgery for their hypoglycaemia (if indicated) or at 6 months after the start of arm 2 – whichever comes first.

9. Study procedures

Arm 1

Patients will be recruited either through attendance at endocrinology outpatients at St Bartholomew's hospital or through inpatient transfer to St Bartholomew's hospital – both with suspected diagnoses of hypoglycaemia.
If attending the outpatients department with suspected hypoglycaemia and thought to be suitable for the study, then the patient will meet a member of the study team after their outpatient appointment or they will be offered an appointment to discuss the study at a mutually convenient time. Informed consent will be obtained during this meeting.
Once a date has been set for their admission to hospital for standard of care investigation of hypoglycaemia (usually including an oral glucose tolerance test or mixed meal test, but certainly including a 72 hour fast), an appointment will be made with the patient for 5 days prior to this date.
At this appointment, the patient will be provided with a finger prick glucose monitoring kit (and instructed in how to use it), a glucose monitoring diary to record finger prick glucose measurements and a CGM device. A CGM probe will be fitted during the consultation and checks made to ensure that it is working.

The patient will then proceed with their standard of care admission five days later. CGM monitoring will continue for the duration of their admission. The CGM device will be removed at discharge or after 5 days of admission, whichever comes first.

For patients who are transferred to St Bartholomew's directly for investigation of their hypoglycaemia, informed consent will be obtained at the earliest convenient point in their admission and the CGM device applied in preparation for the standard of care investigations. The CGM device will be removed at discharge or after 5 days of admission, whichever comes first.

Schedule of study interventions

Study intervention	Visit 1	Visit 2	Visit 3
Establishment of possible hypoglycaemia diagnosis	x		
Meet with study team to learn about study and give Informed consent	Either x	Or x	
Placement of CGM device, receive finger prick glucose meter and diary		x	
Admission to hospital for standard of care investigations Return CGM receiver device if not proceeding to arm 2			x

Arm 2

For patients with confirmed hypoglycaemia, where it is planned that they will receive medical management, we will seek informed consent for their entry into arm 2 of the study.
This might take place;

- at the conclusion of inpatient investigations for hypoglycaemia prior to initiation of anti-hypoglycaemia medication (on an inpatient or outpatient basis)
- after an endocrinology outpatient appointment for a patient with confirmed hypoglycaemia

In the first instance, patients will be fitted with a CGM device and given a finger prick glucose monitoring kit and glucose monitoring diary. Each patient will be asked to complete a modified Clarke and Gold hypoglycaemia questionnaire.
A further appointment will then be made to discuss the results of the initial CGM and to titrate the drug regimen. This appointment could be face to face or by telephone.

If periods of hypoglycaemia persist then alterations to the drug regime will be made and the patient will continue to wear the CGM device, but both they and the investigators will be unblinded to the CGMs allowing further titrations to the anti-hypoglycaemia medications to be made by telephone. Patients will be asked to take a finger prick glucose reading to confirm any low CGM readings.

At the conclusion of the patient's study participation, they will be asked to return the CGM receiver.
At 6 months, or prior to surgery to cure the hypoglycaemia (whichever comes first) the patient will attend the hospital to complete an adapted version of the modified Clarke and Gold hypoglycaemia questionnaire.

Schedule of study interventions

Study intervention	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Meet with study team to learn about study and give Informed consent	x				
Placement of CGM device, receive finger prick glucose meter and diary Complete hypoglycaemia questionnaire	Either x	Or x			
Review of CGM data and titration of medication and unblinding of CGM device		Either x	Or x		
Subsequent medication titration by telephone			Either x	Or x	
Return CGM receive device				x	
Complete adapted hypoglycaemia questionnaire					x

<u>Study Drugs/device</u>

The drugs used to treat hypoglycaemia will be those that are current standard of care and the doses/indications will not vary from standard practice.

We will use a Dexcom G6 continuous glucose monitoring device to record patient's blood glucose to aid diagnosis of hypoglycaemia prior to and during standard of care hospital investigations. The device's software will be modified by Dexcom to disable hypoglycaemia alarm functions, visible blood glucose readout (on the receiver device) and the ability to view blood glucose remotely.
For the unblinded component of arm 2 these functions will be restored

Concomitant medications

Patients will continue to take all other prescribed medications.

Criteria for discontinuation

Patients that become pregnant, or develop a critical illness during the study will be withdrawn as Dexcom devices are unreliable in these circumstances.

Procedure for data collection
Arm 1 – CGM data from each Dexcom device will be downloaded at the end of the inpatient investigations.
Finger prick Glucose monitoring diaries will be collected from patients.

Arm 2 – CGM Data from each Dexcom device will be downloaded at the end of the blinded phase and analysed. Subsequently, CGM data will be viewed remotely and downloaded.
Finger prick Glucose monitoring diaries will be collected from patients.
Hypoglycaemia questionnaires will be completed with patients

Follow-up procedures
Patients with confirmed hypoglycaemia will remain under standard endocrinology follow up irrespective of whether they choose to partake in arm 2 of the study.

Patients completing arm 2 will remain under standard endocrine follow up at St Bartholomew's hospital, unless they decide to transfer their care elsewhere.

Participant withdrawal
Participants may withdraw at any time. Any data that has been collected up to that point will be retained.

End of study definition
The end of the study (specifically - the end of collecting new CGM data) for each individual patient will be when,

- Arm 1 – The patient completes the inpatient CGM monitoring period and are found not to have hypoglycaemia, OR they complete the inpatient CGM monitoring period, are scheduled for anti hypoglycaemic treatment but do not wish to proceed to arm 2 investigations.
- Arm 2 – The patient completes the initial blinded monitoring phase and analysis shows that no further drug titration is required OR the patient goes into the subsequent unblinded monitoring phase and drug titration abolishes most/all of the hypoglycaemic episodes OR the 30 days of CGM monitoring elapses – whichever occurs first. Patients will be asked to complete a

hypoglycaemia questionnaire prior to surgery to cure hypoglycaemia, or at 6 months after the start of arm 2.

10. Assessment and management of risk

11. Safety Information

Adapted From Dexcom's website https://www.dexcom.com/safety-information

Our annotations are in bold, italics and underlined

Dexcom G6 Continuous Glucose Monitoring System

Indications for Use

The Dexcom G6 Continuous Glucose Monitoring System (Dexcom G6 System) is a real time, continuous glucose monitoring device indicated for the management of diabetes in persons age 2 years and older.

The Dexcom G6 System is intended to replace fingerstick blood glucose testing for diabetes treatment decisions. Interpretation of the Dexcom G6 System results should be based on the glucose trends and several sequential readings over time. The Dexcom G6 System also aids in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments.

The Dexcom G6 System is also intended to autonomously communicate with digitally connected devices, including automated insulin dosing (AID) systems. The Dexcom G6 System can be used alone or in conjunction with these digitally connected medical devices for the purpose of managing diabetes.

Contraindication

No MRI/CT/Diathermy – MR Unsafe
Don't wear your CGM (sensor, transmitter, receiver, or smart device) for magnetic resonance imaging (MRI), computed tomography (CT) scan, or high-frequency electrical heat (diathermy) treatment.

The G6 hasn't been tested in those situations. The magnetic fields and heat could damage the components of the G6, which may cause it to display inaccurate G6 sensor glucose readings (G6 readings) or may prevent alerts. Without G6 readings or alarm/alert notifications, you might miss a severe low or high glucose event.

Warnings

Don't Ignore Low/High Symptoms
Don't ignore how you feel. If your glucose alerts and readings don't match what you're

feeling, use your blood glucose meter to make diabetes treatment decisions or, if needed, seek immediate medical attention.When in doubt, get your meter out.

NB – we will be blinding patients to their continuous glucose monitoring (except in the latter half of arm 2) and will ask patients to check their finger-prick glucose if they experience hypoglycaemic symptoms.

Don't Use If…
Do not use the G6 if you are pregnant, on dialysis, or critically ill.

NB – pregnant patients or those on renal dialysis will be screened out of our study

Precaution
Avoid Sunscreen and Insect Repellent
Some skin care products, such as sunscreens and insect repellents, can make the plastic used in your G6 crack. Before using your G6, make sure there are no cracks in your receiver, transmitter, and transmitter holder. If you find a crack, please contact Technical Support. Do not allow these skin care products to contact your G6. After using skin care products, wash your hands before touching your G6. If any skin care products get on your G6, immediately wipe with a clean cloth.

Start Up Safety Statements

Warnings
Use Meter During Startup
When you start a new sensor, you won't get any readings or alarm/alerts until you enter your sensor code or two calibrations. Use your meter to make treatment decisions during the 2-hour sensor warmup period.

NB – Patient will be blinded to CGM data (except for latter part of arm 2). Data from the first 2 hours of CGM will be discarded.

Precautions

Use Correct Sensor Code
When you start a new sensor, you must enter a code into your display device to use the G6 without fingerstick calibrations. Each sensor has its own code printed on the back of the adhesive patch. Do not use a code from a different sensor or make up a code. If you do not enter the correct code, your sensor will not work as well and could be inaccurate. If you lost the sensor code, you may calibrate the G6 using fingersticks.

Calibration Safety Statements

Calibration is not required if users enter a sensor code. If users do not enter a sensor code, the following warnings and precautions apply.

Warnings
Don't Wait – Calibrate!
If you have not used the calibration code, you must manually calibrate your G6 using

values obtained from a blood glucose meter and fingersticks daily. You must calibrate immediately when the G6 notifies you. If you haven't calibrated when notified, your G6 may not be accurate, so use your glucose meter to make treatment decisions until you calibrate your G6.

Use Fingersticks
Use fingertips to calibrate from your BG meter. Blood from other places may be less accurate and not as timely.

Precautions
Be Accurate, Be Quick.
Enter the exact BG value displayed on your meter within five minutes of using your meter. Don't enter the G6 reading as a calibration.

System/Hardware/Software Safety Statements

Warnings
Wire Breaks Off
Don't ignore broken or detached sensor wires. A sensor wire could remain under your skin. If this happens, please contact our 24/7 Technical Support.
If a sensor wire breaks off under your skin and you can't see it, don't try to remove it. Contact your HCP. Also seek professional medical help if you have symptoms of infection or inflammation – redness, swelling, or pain – at the insertion site.

Where to Insert: Belly or Buttocks?
All patients can use their bellies (abdomen). Patients 2 to 17 years old can also choose their upper buttocks. Look for a place on your belly or upper buttocks where you have some padding.
The sensor is not tested or approved for other sites. Talk to your HCP about the best site for you.

Where to Store
You can store your sensors at room temperature or in your refrigerator – as long as it's between 36° F and 86° F. Don't store sensors in the freezer.
Follow G6 instructions. If you don't, you could have a severe low or high glucose event.

Precautions
Don't Use if Expired
Don't use expired sensors, because they may give incorrect results. Check the package label for the expiration date. It's in YYYY-MM-DD (Year-Month-Day) format.

Check Package
Don't use sensor if its sterile package has been damaged or opened, because it might cause an infection.

Clean and Dry Skin
Clean and dry your hands and your insertion site before inserting your sensor.
Wash your hands with soap and water, not gel cleaners, and then dry them before opening the sensor package. If your hands are dirty when you insert the sensor, you may get germs on the insertion site and get an infection.
Clean your insertion site with alcohol wipes to prevent infections. Don't insert the sensor until your skin is dry. If your insertion site is not clean and completely dry, you run the risk of infection or the transmitter holder not sticking well.
Make sure you don't have insect repellent, sunscreen, perfume, or lotion on your skin.

Where to Insert: Things to Check
Keep the safety guard on until you put the G6 applicator against your skin. If you remove the safety guard first, you may hurt yourself by accidentally pushing the button that inserts the sensor before you mean to.
Change your insertion site with each sensor. Using the same site too often might not allow the skin to heal, causing scarring or skin irritation.
Sensor placement is important. Choose a site:
• At least 3 inches from insulin pump infusion set or injection site
• Away from waistband, scarring, tattoos, irritation, and bones
• Unlikely to be bumped, pushed, or laid on while sleeping

Transmitter Safety Statements

Warnings
Inspect
Don't use a damaged or cracked transmitter. A damaged transmitter could cause injuries from electrical shocks and may make the G6 not work correctly.
Use as Directed
The transmitter is small and may pose a choking hazard. Don't put it in your mouth or let children hold it without adult supervision.

Precautions
Reuse – Don't Throw Away
When ending a session, don't throw away the transmitter. The transmitter is reusable until the G6 notifies you that the transmitter battery is about to expire.
Don't Share
Never share your transmitter. The G6 is a prescription-only medical device and is meant for your use only. The transmitter is tied to the G6 readings. If used by more than one person, the G6 readings, reports, alarm/alerts, etc., may be wrong.

System Safety Statements

Precautions
Treatment Decisions
Use your G6 reading and trend arrow to make treatment decisions.

Use Correct Transmitter, Receiver, and Sensor
G6 components are not compatible with any previous Dexcom products. Do not mix transmitters, receivers, and sensors from different generations.

Going Through Security Check Point

When wearing your G6, ask for hand-wanding or full-body pat-down and visual inspection instead of going through the Advanced Imaging Technology (AIT) body scanner (also called a millimeter wave scanner) or putting any part of the G6 in the baggage x-ray machine.
You can wear the G6 for the walk-through metal detector. If you do, use your meter for treatment decisions until you leave the security area.
Because we haven't tested every x-ray and scanner, we don't know if they damage the G6.
Not sure what kind of machine it is? Be safe – either ask the TSA officer, request hand-wanding, or request full-body pat-down.

Interfering Substance Risks

In previous generations of Dexcom CGM systems (G4/G5), acetaminophen could affect your sensor readings, making them look higher than they really were. However, with the G6, you can take a standard or maximum acetaminophen dose of 1 gram (1,000mg) every 6 hours and still use the G6 readings to make treatment decisions. Taking higher than the maximum dose of acetaminophen (e.g. > 1 gram every 6 hours in adults) may affect the G6 readings and make them look higher than they really are.

Receiver and Smart Device Safety Statements

Precautions
Keep Transmitter Close to Display Device
Keep your transmitter and display device within 20 feet with no obstacles (like walls or metal) between them. Otherwise, they might not be able to communicate. If water is between your transmitter and the display device – for example, if you're showering or swimming – keep them closer to each other. The range is reduced because Bluetooth® doesn't work as well through water.

Get Alarm/Alerts on Display Device You Use
To get your alarm/alerts, set them on the display device you use. Your receiver won't get the alarm/alerts you set on your app. Likewise, your app won't get the alarm/alerts you set on your receiver.

NB – patients will not receive alarms/alerts except for those in the unblinded phase of arm 2.

Is It On?
If the receiver or smart device is turned off (shut down), it will not show G6 readings or alarm/alerts. Make sure your display device is turned on.

Smart Device Safety Statements

Warnings

Check Settings

NB – patients will not receive glucose alarms/alerts except for those in the unblinded phase of arm 2.

When using your smart device, you should confirm that your volume is turned up, your phone is not muted, and you do not have headphones plugged in. If your volume is not turned up, the device is muted, or headphones are plugged in, you will not hear the sound of any notifications, including important alarms. When you have headphones connected to your Android®, alarm/alerts will sound through the headphones and the speaker. On your Apple, they will sound only in the headphones.

Some notifications are silent during the first visual and vibrate notification and then make a sound on the second notification. If you don't clear the alert, it repeats at half volume after 5 minutes and at full volume after 10 minutes.

Your alarm and important alerts sound and display information even when your volume is low or muted. Specifically, if your smart device is on mute, only these notifications make a sound:
Glucose Alarm/Alerts:
• Urgent Low
• Urgent Low Soon
• Low Glucose
• High Glucose
• Rise Rate
• Fall Rate
• No Readings Alert
System Alerts:
• Calibration Required (after 2-hour sensor warmup, only appears when a sensor code is not active)
• Calibration Error (only appears when a user enters a calibration; calibration is not required)
• Sensor Expired
• Replace Sensor
• Transmitter (not working)
• No Storage Error
• App Stopped
There's one exception: On Apple® devices, Signal Loss doesn't sound when your volume is low or muted.
Bluetooth: Your transmitter talks to your app with Bluetooth. Make sure your smart device Bluetooth is on. If not, you will not get alarm/alerts or CGM information.
Notifications:
• Make sure your smart device settings allow Dexcom app notifications to show on your Lock screen. This will allow you to see notifications without unlocking your phone.
• Apple: During G6 setup, enable Dexcom app notifications or you won't get alarm/alerts. Battery: The app must always be running in the background and may

drain your smart device battery. Keep the battery charged.
Compatibility: Before upgrading your smart device or its operating system, check dexcom.com/compatibility. Automatic updates of the app or your device operating system can change settings or shut down the app. Always update manually and verify correct device settings afterward.
Time: Let the date and time on your smart device automatically update when you travel across time zones or switch between standard and daylight saving times. Don't manually change your smart device time, because it can make the time on the trend screen wrong and the app may stop displaying data.

Precautions
Check Peripheral Devices
Do you use headphones with your smart device? What about Bluetooth speakers or a smart watch? When using peripherals, keep in mind you may get your alarm/ alerts on only one device or peripheral, not all. After connecting any peripheral devices, make sure that your smart device settings allow you to continue receiving alarms or alerts.

Receiver Safety Statements

Warnings
Don't Use if Damaged
Don't use a receiver that is damaged or cracked. A damaged receiver could cause injuries from electrical shocks and may make the G6 not work correctly.
Use Cable as Directed
Use USB cable only as directed, and store safely. Misuse of the USB cable can be a strangulation risk.
Follow G6 instructions. If you don't, you could have a severe low or high glucose event.

Precautions
Test Speaker and Vibrations
You have to hear or feel alarm/alerts to react to them, so test your receiver speaker and vibrations regularly.
To make sure the speaker and vibrations work, plug in the receiver to charge. The Speaker Test screen appears for a few seconds. Follow the directions on the screen to test the speaker and vibrations. If you hear and feel them, great! But if it doesn't beep and vibrate – perhaps it got wet or was dropped – contact Technical Support and use your app until the receiver is fixed.
Keep Clean and Dry
Don't submerge your receiver in water and don't get dirt or water in the USB port. That could damage it.

Dexcom Share Safety Statements

Important User Information

Dexcom Share (Share) lets you send your sensor information from your app to your Followers' smart devices! Read the indications, warnings, and precautions below to find out how you can safely use this app feature.

Share and Managing Your Diabetes Safety Statements

Indications
Keep Followers Informed
Use Share to send your sensor information from your smart device to your Followers' smart devices.
Use as Secondary Notice
The information on your smart device is sent directly from your G6 transmitter. After it is on your device, Share sends it to your Followers. So your Followers' information is always older than yours. Use your current information to manage your diabetes, not your Followers' possibly outdated information.
Your Followers can use the information they get to reach out to you and support you in managing your diabetes. The information they get is not meant to be used for treatment decisions, analysis, or teaching. Followers can't change your information.

NB sharing will be disabled during the study, except during the unblinded phase of arm 2

Risk mitigation strategies discussed above.
Trial subjects will be counselled on the above side effects and how to manage them.
The endocrine team at St Bartholomew's hospital is contactable 24 hours/day – either through the ward team in 5B ward (0900-1700) or through an on-call endocrine registrar (1700-0900) for all endocrine patient and GP enquiries.

We will include side effect occurrences as part of our monthly study management meetings and will introduce additional methods if it becomes clear that these are required.

12. Statistical considerations

This is a non-randomised study with a small (30 patients) population, no statistician involvement will be required.

12.1 Sample size

30 patients

This is intended to be a pilot study to test the feasibility of using CGM for this purpose. It may in future complement (or in some instances replace) inpatient investigation of hypoglycaemia.
The inpatient investigation of hypoglycaemia is relatively uncommon, even within tertiary centres. Spontaneous hypoglycaemia requiring medical treatment is similarly uncommon, even in tertiary centres.

12.2 Method of analysis

P<0.05 will be considered statistically significant

Arm 1
Positive and negative predictive value of CGM diagnosis of hypoglycaemia as an outpatient or an inpatient vs 72 hour fast (considered the 'gold standard')

Arm 2
In each patient, comparison of number of episodes of hypoglycaemia by finger prick glucose vs CGM vs symptoms during CGM blinded phase.
Severity of hypoglycaemia excursions

Amount of time spent in the hypoglycaemic range after medication titration – as measured by area under the curve on a time vs glucose graph generated by CGM machine. Comparisons of mean hypoglycaemic frequency and time within hypoglycaemic range within patients (blinded vs unblinded phase) using paired T test.

Change in hypoglycaemia questionnaire score before/after CGMs monitoring and medication titration
Regain of symptomatic hypoglycaemia in patients with asymptomatic hypoglycaemia, reduction of symptomatic hypoglycaemia in other patients.

13. Ethics

- Informed consent

Patients will be offered the chance to partake in the study should their treating consultant feel that they meet the inclusion criteria. Declining an invitation to take part in the study or leaving at any time means that the patient will default back to standard of care investigations. Their care will not be prejudiced or compromised in any way through either taking part or not taking part in the study.

- Recruitment

Only patients under investigation/treatment for hypoglycaemia at St Bartholomew's hospital will be considered for entry to the study. Patient being treated/investigated elsewhere who wish to be considered for the study would need to have their care transferred to St Bartholomew's by their GP/current endocrinologist.

- Inclusion / exclusion criteria

Inclusion/exclusion criteria is intended to screen out patients who have conditions that may affect their blood glucose (Diabetes Mellitus, underlying hepatic pathology) or in whom CGM is not recommend (pregnancy, critical illness) or in whom hypoglycaemia may be cause be extrinsic factors such as Diabetes medication.

- Study design

Aside from the wearing of a CGM device and completion of modified Clarke and Gold hypoglycaemia questionnaire (arm 2), all treatment is 'standard of care'.
In arm 1 (and, initially, arm 2) Patients and investigators are blinded to the CGM readouts. Patients are provided (as is usual) with finger prick glucose meters that they can use to check their blood sugar should they develop symptoms that they attribute to hypoglycaemia. The patients are therefore not disadvantaged by the 'blinding' process.

- Risks, burdens, and benefits

Patients will be counselled about (the few) risks associated with use of the Dexcom device, the main risks are those of infection from insertion of the probe under the skin and the risk of retained parts upon removal of the probe – and how to minimise these risks. The device is worn and as such may restrict the wearer's choice of clothing and place some minor limitations on physical activity – mainly laying on top of the probe or engaging in close contact activities which might disrupt the probe's positioning.

- Confidentiality

All patients recruited for the study will already be under the medical care of the endocrine team at St Bartholomew's hospital, the study team is made up of staff from this department and they will therefore already have legitimate access to medical records and pathology results.

Any published data arising from this study will be anonymised.
Any data shared with Dexcom will be pseudonymised – each participant will receive a study number which will not be related to any of their identifiable details (name/DOB/address/NHS or hospital number).

- Conflicts of interest.

Dexcom will provide the study team with free receivers, transmitters, consumables and training in their equipment's use. They have not had any influence on the study design, but have reviewed our design internally prior to granting approval for provision of the above equipment.
Dexcom will be allowed to share the data that we obtain, which will be pseudonymised. They will also be allowed to view the manuscript of any work (containing anonymised data) prior to submission to a peer reviewed journal, so that they can make suggestions but will not be the determining factor in the decision to submit work arising from this study for publication. This decision will reside with the study team and be based on scientific merit of the findings.

No other members of the study team have any relevant conflicts of interest.

13.1 Annual Safety Reporting

The CI will send an Annual Progress Report to the REC and the sponsor using the HRA template on the anniversary of the REC favourable opinion.

14. Public Involvement

No public involvement is planned

15. Data handling and record keeping

15.1 Data management

All electronic data will be stored on password protected NHS computers at an NHS site. Data back-ups will be made on NHS encrypted USB sticks, which will be stored alongside any paper based records (glucose diaries) in a locked cabinet within a locked room inside a hospital ward, accessed only by NHS staff.

CGM data will be obtained through downloading from the patient's CGM device onto a password protected NHS computer.

15.2 Source data

Glucose data will be obtained from;

- CGM devices during the study
- Fingerprick glucose devices and patient glucose diaries
- Lab measured venous glucose (and other blood tests) – from computerised hospital pathology system
- Formal diagnosis after inpatient investigation of diagnosis and supporting lab results – patient's electronic notes and pathology results from computerised record.

Medication record;

- Computerised patient record
- Paper drug chart

15.3 Confidentiality

Information related to participants will be kept confidential and managed in accordance with the Data Protection Act 2019, the General Data Protection Regulation (GDPR), NHS Caldecott Principles, the UK Policy Framework for Health and Social Care Research, and the conditions of NHS Research Ethics Committee favourable opinion.

Potential participants will be identified by their treating endocrine consultants (or deputy) in clinic or on the wards. The patient's permission to forward them to the study will then be sought. Once this permission is obtained then their details (hospital/NHSnumber) will be forwarded internally either by verbally or by secure NHS email.

Prior to publication, all data will be anonymised and is likely to be discussed as a whole rather than individually. In the event that an individual patient's results are discussed then they will be referred to in an anonymous way e.g. 'patient 1', with the numbering bearing no relation to their name, hospital/NHS number or date of birth.

All patients involved in the study will be under the care of the endocrine team at St Bartholomew's hospital. The study is being conducted by the same department and so as treating physicians, the study team already have legitimate access to patient

records. Patient records are held securely on (password and username protected) NHS computers and require a passcard and separate password to gain access.

15.4 Record Retention and Archiving

At the end of the study, all electronically held data relating to the study will be printed and added to any paper documentation (glucose diaries etc) and stored in Barts Health NHS trust's secure repository for 20 years, as per the UK policy framework for health and social care research.
Destruction after this period will be in the standard, approved way.

16. Laboratories

16.1 Central and local laboratories

Patient samples for glucose and other blood parameters will not be collected separately for this study – patients will continue to have routine 'standard of care' blood tests associated with standard work-up of suspected hypoglycaemia. These will be processed in the normal way in the laboratories at St Bartholomew's and the Royal London Hospitals

16.2 Laboratory procedures

Current standard of care lab tests will be performed on inpatients having 24 hours fasts. These samples will undergo testing in an NHS lab as usual. No extra blood samples will be drawn.

16.3 Sample storage and transfer

N/A

17. Interventions and tools

17.1 Devices

- Name - Dexcom G6 Mobile continuous glucose monitoring system
- Manufacturer - Dexcom
- Indication – continuous glucose monitoring, usually in Diabetes Mellitus
- CE mark status – has a CE mark under Medical Device Directive MDD 93/42/EEC as amended by 2007/47/EC
- Source of device - Dexcom

For arm 1 and the blinded portion of arm 2, the device will be worn/used in the standard way and used to monitor for hypoglycaemia. The device will be programmed so that the alarm functions which usually signal hypoglycaemia are inactivated and the screen which displays the current glucose reading will not show this information.
During the unblinded portion of arm 2, the device will be worn in the standard way with hypoglycaemia alarms active and the glucose display showing the current glucose.

- Name – Contour next ONE blood glucose monitoring system
- Manufacturer – Ascensia Diabetes care
- Indication – finger prick glucose monitoring, usually in Diabetes Mellitus
- CE mark status – has a CE mark Source of device – either through NHS trust or directly from Ascensia

Finger prick glucose testing is standard in inpatient investigation of hypoglycaemia and also in home monitoring of blood sugar in patients being treated for proven hypoglycaemia. We will additionally use prior to patient's admission for investigation of hypoglycaemia (arm 1) as a correlate for CGM data. Patients will be asked to perform a finger prick glucose measurement whenever they experience the symptoms that they attribute to hypoglycaemia

17.2 Techniques and interventions

Interventions – patients will be shown how to apply the CGM device upon enrolling in study and the start of the monitoring phase, or will have the CGM device applied for them by a medical/nursing professional
Patients will also be shown how to use the finger prick glucose testing device as part of standard care.

17.3 Tools

Each patient will receive a glucose monitoring diary where they can record the finger prick glucose level, time, date and symptoms.

17.4 Medicinal product

None

17.5 Other biological or chemical products

None

18. Safety reporting

- Adverse Events (AEs) and Adverse Reactions (ARs) will be recorded
- Serious Adverse Events (SAEs) and Serious Adverse Reactions (SARs) will be reported to the CI as medical assessor for the sponsor and coordinating team.
- All unexpected SARs (SUSARs) will be reported to the JRMO and REC.

18.1 Adverse Events (AEs)

An AE is any untoward medical occurrence in a participant to whom an intervention has been administered, including occurrences which are not necessarily caused by

or related to that intervention. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with study activities.

18.2 Adverse Reaction (ARs)

An AR is any untoward and unintended response in a participant to an intervention. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to the intervention qualify as adverse reactions. The expression 'reasonable causal relationship' means in general that there is evidence or an argument to suggest a causal relationship.

18.3 Notification and reporting of Adverse Events and Reactions

If the AE is not defined as serious, the AE will be recorded in the study documents and the participant followed up by the research team. The AE will be documented in the participants' source documents, the Case Report Form (CRF), and, where appropriate, medical records.

18.4 Serious Adverse Events (SAEs) or reactions

A serious adverse event (SAE) is defined as an untoward occurrence that:

- Results in death,
- Is life-threatening,
- Requires hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity,
- Consists of a congenital anomaly or birth defect, or
- Is otherwise considered medically significant by the investigator.

SARs will be reported to the REC where in the opinion of the Chief Investigator the event was serious and:

- Related (it may have resulted from administration of any of the research interventions), and
- Unexpected (the type of event is not listed in the protocol or other Reference Safety Information as an expected occurrence).

18.5 Notification and reporting of Serious Adverse Events

Serious Adverse Events (SAEs) that are considered to be 'related' and 'unexpected' will be reported to the sponsor within 24 hours of learning of the event, and to the REC within 15 days in line with the required timeframe.

The treatment code for the participant will be broken when reporting an 'unexpected and related' SAE. The unblinding of individual participants by the PI / CI in the course of a clinical study will only be performed if necessary for the safety of the study participant.

18.6 Urgent Safety Measures

The CI will take urgent safety measures if necessary to ensure the safety and protection of the clinical study participant from immediate hazards to their health and safety. The measures will be taken immediately. The approval of the REC prior to implementing urgent safety measures is not required. However the CI will inform the sponsor and Research Ethics Committee (via telephone) of this event immediately.

The CI will inform the REC in writing within 3 days, in the form of a substantial amendment. The sponsor (Joint Research Management Office (JRMO)) will be sent a copy of the correspondence with regards to this matter.

18.7 Annual Safety Reporting

The CI will send the Annual Progress Report to the REC using the HRA template (the anniversary date is the date on the REC "favourable opinion" letter) and to the sponsor.

18.8 Overview of the Safety Reporting responsibilities

The CI is the medical assessor on behalf on the sponsor and will review all events reported. The CI will ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements.

19. Monitoring and auditing

The sponsor or delegate retains the right to audit any study, study site, or central facility. Any part of the study may be audited by the funders, where applicable.

20. Trial committees

The chief investigator will convene a monthly trial committee meeting, consisting of at least the chief investigator and one other investigator from the single site study

21. Finance and funding

Dexcom will be providing free sensors, receivers and transmitters for this study.

22. Indemnity

NHS indemnity scheme will apply. It provides cover for the design, management, and conduct of the study.

23. Dissemination of research findings

We intend to publish the results of this work in a peer reviewed journal. Should publishing constraints allow and a suitable occasion arise we will put forward an abstract of this work to the British endocrine society for consideration for an oral presentation at their annual conference, similarly we will seek opportunities to disseminate our work internally within Barts Health NHS Trust and QMUL. Research findings are likely to form the basis of any departmental review on the investigation, diagnosis and management of hypoglycaemia.

All study participants will be offered the chance to receive a lay summary of any published work.

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