How common is hypoglycaemia in older people with diabetes who have falls, dizziness or other symptoms suggestive of hypoglycaemia? A continuous glucose monitoring study

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1 Administrative information

This document describes the **single-centre, non-randomised study investigating the use of continuous glucose monitoring (CGM) in older people with diabetes presenting to hospital with falls and/or other symptoms suggestive of undetected hypoglycaemic episodes,** sponsored by the University of East Anglia (UEA).

It provides information about procedures for entering participants into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, the medical device, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct.

1.1 Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the UK Data Protection Act, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF).

1.2 Sponsor

UEA is the trial sponsor and has delegated responsibility for the overall management of the study to the Chief Investigator. Queries relating to sponsorship of this trial should be addressed to the Chief Investigator, or via the trial team.

1.3 Structured Trial Summary

Source of Monetary or Material Support	Norfolk Diabetes Trust
Sponsor	University of East Anglia
Contact for Scientific Queries	Dr Katharina Mattishent Norwich Medical School University of East Anglia Bob Champion Research and Education Building Norwich NR4 7TJ. e-mail: k.mattishent@uea.ac.uk
Public Title	How common is hypoglycaemia in older people with diabetes who fall?
Scientific Title	How common is hypoglycaemia in older people with diabetes who have falls, dizziness or other symptoms suggestive of hypoglycaemia? A continuous glucose monitoring study
Countries of Recruitment	England
Health Condition(s) or Problem(s) Studied	Older people with diabetes
Intervention	Use of continuous glucose monitoring (CGM)
Key Inclusion and Exclusion Criteria	**Inclusion Criteria:** Patients 75 years and older, Type 1 or Type 2 diabetes mellitus on insulin and/or sulfonylureas, presenting to hospital with a fall and/or symptoms suggestive of unrecognised hypoglycaemia (such as dizziness, feeling muddled). **Exclusion criteria**: treatment with metformin only, lack of capacity, not willing to participate, terminal illness (less than one-year life expectancy). Evidence of bruising, bleeding, cellulitis and/or skin tears on the upper arms or abdomen.
Study Type	Single-centre, non-randomised study
Date of First Enrolment	TBC
Target Sample Size	30
Objectives	**To investigate the pick-up of hypoglycaemic (and hyperglycaemic) episodes with the use of CGM in older people with diabetes presenting to hospital with falls and/or other symptoms suggestive of undetected hypoglycaemic episodes**
Outcomes	**Primary outcomes**: • Proportion of participants with captured hypoglycaemia; within that group, the time spent in the hypoglycaemic range. **Secondary outcomes:** • Overall Time in Range; emergency department re-attendances and/or hospital re-admissions for falls, fractures, heart attacks, ischaemic strokes and death within 30 days.

	Adverse events: • Pain and/or skin reactions at site of sensor insertion

1.4 Roles and responsibilities

Protocol contributors

Name	Affiliation	Role
Professor Yoon Loke, Professor of Medicine and Pharmacology	Norwich Medical School, UEA	Initiated and developed the trial question and study development. Lead the writing of the protocol and funding application.
Dr Katharina Mattishent, Clinical Lecturer in Older People's Medicine	Norwich Medical School, UEA	Initiated and developed the trial question and study development. Contributed significantly to the drafting of the protocol and funding application.
Dr Navena Navaneetharaja, Academic Clinical Fellow in Older People's Medicine	Norwich Medical School	Contributed to the drafting of the protocol
Dr Ketan Dhataryia, Consultant in Endocrinology and Diabetes	Norfolk & Norwich University Hospital NHS Trust	Contributions on the study design with emphasis on the clinical aspects of management of diabetes.

Role of trial sponsor and funders

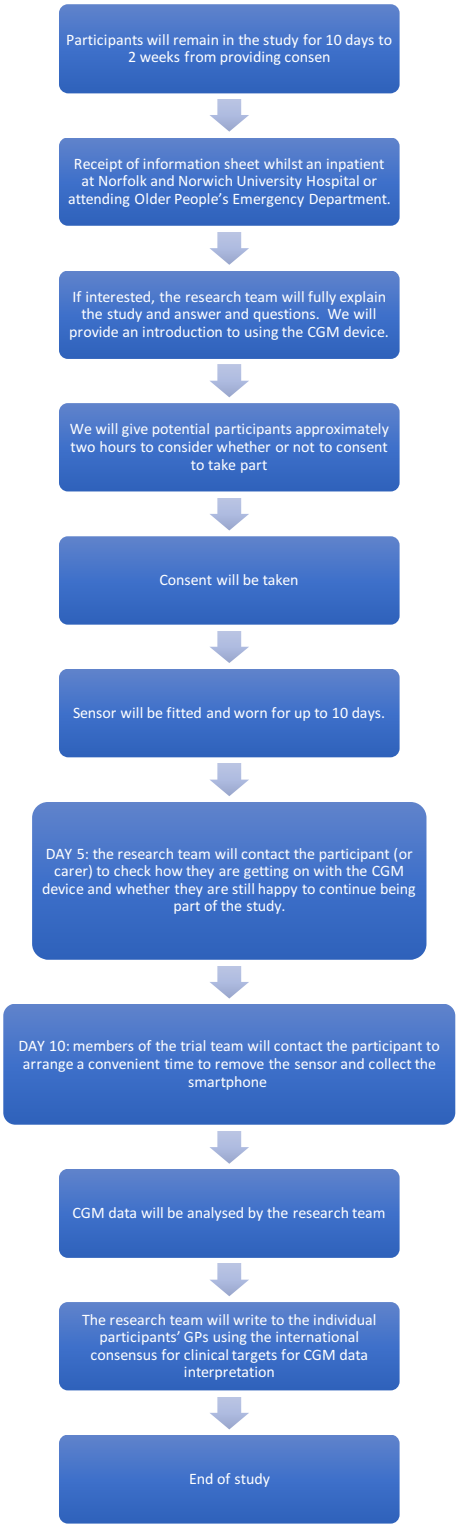
Name	Affiliation	Role
Trial sponsor	University of East Anglia	Approval of: trial design, data collection methods, conduct and monitoring with ultimate authority over these.
Funder	Norfolk Diabetes Trust (NDT)	Approval of: trial design, data collection methods, conduct, monitoring and analysis. Funding the costs for the medical device used in this study (Dexcom G6).

Trial Team

Name	Affiliation	Role and responsibilities
Dr Katharina Mattishent, Clinical Lecturer in Older People's Medicine	Norwich Medical School	*Chief investigator* with responsibility for the: conduct, data analysis, interpretation and reporting. Recruitment of participants.
Professor Yoon Loke, Professor of Medicine and Pharmacology	Norwich Medical School	*Co-Chief investigator* with overall responsibility for the: design, conduct, monitoring, analysis, interpretation and reporting of the trial. Recruitment of participants.
Dr Navena Navaneetharaja, Academic Clinical Fellow in Older People's Medicine	Norwich Medical School	*Co-investigator* - conduct and progress, responding to clinical inquiries, data analysis and interpretation and production of the final manuscript.

Dr Ketan Dhataryia, Consultant in Endocrinology and Diabetes	Norfolk & Norwich University Hospital NHS Trust	*Clinical advisor* on management of patients in the trial.
Dr Sankalpa Neupane, Consultant in Endocrinology and Diabetes	Norfolk & Norwich University Hospital NHS Trust	*Independent expert advisor* - will provide independent advice on any adverse event reports or protocol deviations. Dr Neupane has experience in running trials using CGM.

2 Flow diagram



3 Abbreviations

Acute Medical Unit	AMU
Continuous glucose monitoring	CGM
Emergency Department	ED
Glycated haemoglobin	HbA1c
Norfolk Diabetes Trust	NDT
Older People's Emergency Department	OPED
Sulfonylurea	SU

4 Introduction

4.1 Background and rationale

What is the problem being addressed?

Older people with diabetes often seek treatment in hospital for symptoms such as falls, dizziness or feeling muddled. These symptoms may potentially stem from (undiagnosed) episodes of hypoglycaemia that neither the patient nor the carers / healthcare professionals are aware of. My project aims to deliver 10 days of continuous glucose monitoring to check if recurrent hypoglycaemia may be an underlying cause that puts patients at risk of falls, dizziness and confusion.

We regularly attend to patients these symptoms in the emergency department (ED)/Older People's Emergency Department (OPED) and the Acute Medical Unit (AMU). We usually order a battery of tests to find the underlying cause(s) but we currently do not have a good way of testing for recurrent hypoglycaemia in this vulnerable group. The actual reason for the falls and dizzy spells may remain unexplained, and patients are sent home without an exact diagnosis.

In truth, most older patients are likely to have multiple contributing factors to their falls. We try to identify and remedy all underlying factors that put the patient at risk of falls. We carry out a medication review (optimise sedative medication or anti-hypertensives) and check lying/standing blood pressures for postural hypotension. Physiotherapists give falls advice and occupational therapists check whether any adjustments are needed in the home (eg stairlift, grab-rails, pendant alarms).

In terms of monitoring, we request 24-hour heart monitoring if we suspect a possible problem with the heart. **However, we have previously been unable to perform 24-hour glucose monitoring in older people with diabetes to check if low blood sugars are an important contributing factor to their falls and dizzy spells.**

Here, a **significant issue** is that commonly used blood tests (finger-prick monitoring and HbA1C) cannot reliably capture hypoglycaemia over a 24-hour period. Use of continuous glucose monitoring (CGM) in research studies has unearthed far more hypoglycaemic episodes than previously thought. A 5-day CGM study of 108 patients in Europe reported

that 49% had one or more hypoglycaemic episodes, and 75% of the patients were unaware that they had suffered from hypoglycaemia (1).
A systematic review of CGM in older people found that hypoglycaemic episodes were detected in a sizeable proportion of participants, most of which were asymptomatic, with some patients spending nearly 2 hours per day in the hypoglycaemic range (2).

In a feasibility trial of CGM in 12 older people with memory problems, nine participants were insulin users, of which six (66%) were found to be affected by hypoglycaemic events (some prolonged). The average duration of hypoglycaemic events ranged from 106 minutes to 437 minutes (3). **After reviewing the CGM data with a Consultant Diabetologist, we wrote to four participants' GPs advising a change in their respective medication regimens**.

Hypoglycaemia can have devastating consequences on the lives of older people with diabetes. My research has demonstrated that hypoglycaemic episodes are associated with serious complications including heart attacks, stroke, falls, fractures, dementia and death (4, 5). Randomised trial data of intensive versus standard diabetes therapy found that rigorous lowering of glucose led to significantly more hypoglycaemia, cardiovascular events and death.
A large US study of 201705 adults with diabetes found several important factors for emergency admissions due to hypoglycaemia (6):

- age >75 years
- diabetes medications - insulin and/or sulfonylureas (SUs)
- lower annual household income
- number of comorbidities
- HbA1c at either low or high end of range.

<u>Traditional monitoring of diabetes cannot reliably detect hypoglycaemia</u>

Intermittent finger-prick testing is the traditional method of monitoring blood glucose. It requires patients to recognize impending hypoglycaemia and initiate self-testing. This can be problematic in older people because they may have:

1. Age-related physiological changes that mask symptoms of hypoglycaemia;
2. Memory problems or decline in cognition;

3. Become confused/ drowsy with hypoglycaemia and cannot test;

4. Nocturnal hypoglycaemia when asleep;

5. Age-related physical changes making it difficult to conduct testing (poor vision, arthritis).

The other commonly used blood test (**HbA1c**) only represents the average blood sugar value over the past two to three months as a single snapshot. It is used as a long-term marker of diabetes control e,g, NICE recommends HbA1C level of 53 mmol/mol (7.0%) for type 2 diabetes (7). What the HbA1c cannot provide is a detailed picture of individual daily glucose patterns and glucose variability. For example, three people with diabetes could all have a HbA1C level of 53 mmol/mol (7.0%) but vastly different glucose variability. This is illustrated in Table 1 and Figure 1, where a patient with 'rollercoaster' high and lows could have the same HbA1C as a very stable patient (8) (9). Similarly, finger-prick testing has poor temporal resolution and hypothetical four times daily testing could miss important hypo- and hyperglycaemic episodes (Figure 2).

Table 1

Example of 3 people with the same HbA1c, but different glucose variability

	Person A	**Person B**	**Person C**
Above target range (>10mmol/L)	40%	25%	0%
In target range (3.9-10mmol/L)	40%	70%	100%
Below target range (<3.9mmol/L)	20%	5%	0%
HbA1C	**53mmol/mol (7.0%)**	**53mmol/mol (7.0%)**	**53mmol/mol (7.0%)**

adapted from https://www.mysugr.com/en-us/blog/5-things-know-about-time-range/

Figure 1

Example of 3 people with the same HbA1c, but different glucose variability

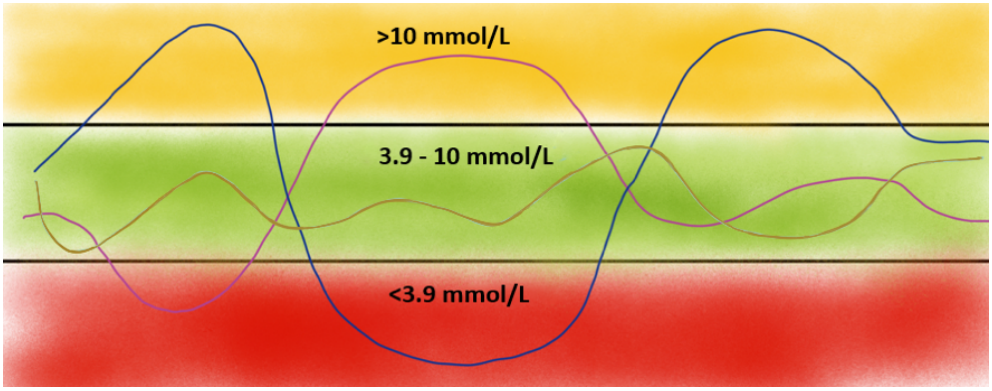
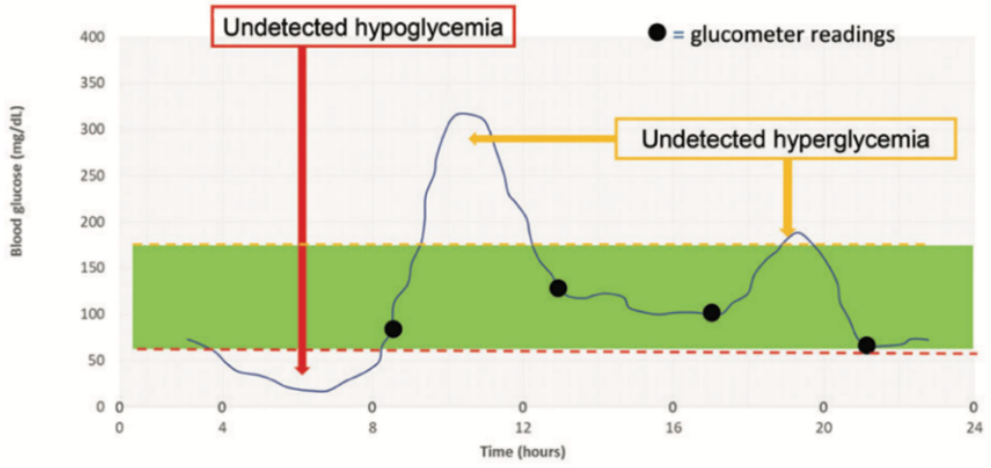


Figure 2

Example of glucose levels readings picked up by finger-prick testing ("glucometer readings") versus CGM



Continuous glucose monitoring (**CGM**) is a newer way to capture glucose levels, where the patient inserts a sensor just under the skin (either back of an arm or stomach). The sensor measures interstitial glucose levels continuously (day and night) throughout its lifetime, which is usually around 10-14 days.

Patients can access glucose recordings by swiping a reader over the sensor or through Bluetooth smartphones. There are alarms if glucose levels go too high or low, as well as graphs displaying trends of rising or falling glucose levels. The 24-hr glucose pattern is summarized, as are longer-term trends. Users can consent to share data with carers, relatives or healthcare teams, with real-time updates about an individual's glucose levels.

These data are absolutely vital for fine-tuning and avoiding harm from over-treatment with medication.

Clinical targets for CGM have been produced by international experts (10). For older people the recommendation is that they should spend less than 15 minutes in the hypoglycaemic range (below 3.9 mmol/L) and more than twelve hours between 3.9-10 mmol/L (time in range).

Funding for CGM in health service

At present, the availability of CGM for older people with diabetes has not been a priority. In England, the National Health Service has prioritized CGM for patients with type 1 diabetes. There is no explicit mention of CGM in older people with type 2 diabetes on medications (insulin, SUs) which carry a high risk of hypoglycaemia, and who may need carer support (for example due to underlying dementia) with diabetes management.

Why is this research important in terms of improving the health and/or wellbeing of the public and/or to patients/service users, carers and health and care services?

Patients and carers

We know that hypoglycaemia in people with diabetes is associated with serious adverse events (cardiovascular events, falls, fractures, death)(5) and that hypoglycaemic episodes are underreported (11).

We might be doing patients a disservice, if we fail to recognize that their symptoms are actually also due to hypoglycaemia, rather than other causes such as infection, stroke, postural hypotension etc. Equally, we may discharge an older person with a diagnosis of "unexplained fall", where we could have completely missed episodes of hypoglycaemia that contributed to the fall.

Equally, the use of CGM can provide reassurance to a patient and/or carers if the data shows that large proportions of the day are spent between 3.9-10 mmol/L (time in range).

From a feasibility study of older patients with diabetes and dementia, we know that caregivers felt safer when they were able to use CGM, and it was easier to measure glucose levels.

"…when [glucose level] was low and then when I then gave him something, it had then gone up so I knew it was working, so I was happy, more than happy with it. Yes, I felt happy and I felt safer."

"…with the whole package of the […] dementia he's not always understanding and doesn't want it done and will pull his hand away and you know sometimes it's just all too much" (caregiver reporting difficulty of finger-prick test) .

Healthcare utilization

Existing evidence has demonstrated the high economic burden and healthcare utilization resulting from hypoglycaemia (12) (13, 14). Hypoglycaemia has been identified as one of the top three preventable adverse drug events by the US Department of Health and Human Services (15). In the US, serious hypoglycaemic episodes resulted in nearly 300,000 emergency department (ED) visits in adults (15). Insulin is the second most common medication associated with ED visits or hospitalization (16). Similar research in Asia found a 10-fold increase in hospital admissions due to hypoglycaemic episodes in older people (17) (18). This upsurge has been attributed to increased intensity of medical treatment, as well as greater co-morbidities and frailty.

There is also a large burden on ambulance services. The East Anglia emergency service hypoglycaemia programme recorded 62 referrals per week, with almost one-third of patients found unconscious (19). In the East Midlands, the annual estimated costs of ambulance call-outs for hypoglycaemia is approximately £235,000 (20).

Review of existing evidence

Serious Consequences of hypoglycaemia in older people with diabetes

The immediate effect of hypoglycaemia can be confusion, visual disturbance, alteration in mood and lack of concentration. It also disrupts day-to-day activities, including exercise and driving.

I conducted a large Clinical Practice Research Datalink cohort study examining the association of hypoglycaemia with serious adverse events in older people with dementia and diabetes. Patients with hypoglycaemia had substantially higher risks of death,

cardiovascular events, falls, fractures and emergency department attendances, than those who have not had a hypoglycaemic event (21).

In addition, a systematic review and meta-analysis of 44 studies involving 2,507,434 participants aged 55 and older (22) confirmed significant associations between hypoglycaemia and the following serious adverse events:

- Doubling in risk of death.
- 50% increased risk of dementia.
- 81% and 77% increased risk of macro- and microvascular complications respectively.
- 78% and 68% increased risk in falls and fractures respectively.

Studies assessing mortality also confirmed a time-response relationship with the highest risk of complications within 90 days after hypoglycaemia.

Clinical impact of CGM guided management

The Dexcom G6 CGM device was tested in an RCT of 99 patients within a US integrated healthcare setting. Almost half the patients were >65 years of age. **Patients receiving CGM had significant reductions in emergency department visits and HbA1C compared to patients using finger-prick testing**. The authors recommend that replication in a larger RCT is needed (23).

4.2 Explanation for choice of device

This study will use Dexcom G6 (Dexcom, Inc., San Diego, CA) CGM (https://www.dexcom.com/en-GB).

Sensors last for 10 days and can be worn either on the back of an arm or the abdomen. Interstitial glucose concentrations are measured every five minutes throughout the lifetime of a sensor. The device does not require calibration with finger-stick readings. In addition, there is no requirement to manually scan the sensor with a transmitter in order to obtain a reading. In a previous feasibility study using a device which required scanning of the sensor to obtain readings, people with memory problems forgot to do so. This meant that amount of data captured varied considerably between participants (range 3-92%; mean 55%) throughout the study period. By using Dexcom G6, the trial team will overcome this as the glucose data is automatically sent to a Bluetooth equipped smartphone. This phone will be equipped with a data SIM to capture and transmit CGM findings to the research team.

4.3 Objectives

This study will examine the use of a single 10-day period of CGM to detect hypoglycaemia in older people who present to hospital with falls and/or symptoms that could be attributed to hypoglycaemia.

Being able to capture hypoglycaemia and time in range will enable a more informed medication review and subsequent adjustment of treatment to achieve safer control of diabetes (as advised by Consultant Diabetologist on research team). This may then potentially lead to reduced ED visits, falls and reduce possible risk factors behind cognitive deterioration.

4.4 Trial Design

Single-centre, non-randomised study (no change in participants' diabetes management during the study period).

5 Methods

5.1 Study setting

Eligible participants will be identified and invited to participate whilst they either attend OPED or are admitted under AMU having presented with a fall or other symptoms suggestive of unrecognised hypoglycaemia.

Participant Information Sheets will be handed out and interested patients will be consented by the research team.

5.2 Participants

5.2.1 Inclusion criteria

75 years and older with diabetes on glucose-medications which carry a high risk of hypoglycaemia (sulfonylureas and/or insulin) presenting to hospital with a fall and/or symptoms suggestive of unrecognised hypoglycaemia (such as dizziness, feeling muddled).

5.2.2 Exclusion criteria

Treatment with metformin only, lack of capacity, not willing to participate, terminal illness (less than one-year life expectancy). Evidence of bruising, bleeding, cellulitis and/or skin tears on the upper arms or abdomen.

5.3 Data Collection

All participants will be issued with the Dexcom G6 device. The trial team will buy the readers or smartphones and sensors and provide the participants with all the necessary equipment. Participants will be shown how to wear the Dexcom G6 device, which they will be asked to wear for up to 10 days (=the lifespan of one sensor).

There will be **no change** in the standard care of the participants' diabetes management, during the study period.

There will be no blinding of the glucose readings. If participants and/or carers have any concerns about prolonged or recurrent glucose trends that indicate the patient is running significantly out of their individual target range, they can either contact their usual clinical team (e.g. GP or diabetes team) that provides their care, or alternatively alert the trial team (via a helpline) who will then assess the readings and make appropriate referrals. The trial team includes a Consultant in Diabetes, who will be able to evaluate glucose patterns and make recommendations for any further care through usual channels. No adjustment to the diabetes medication should be made by the participants/carers, unless advised by a medical practitioner.

The trial team will look at the data retrospectively (after the participant has worn the device for up to 10 days). If, on retrospective review of the glucose data, there are clinically significant patterns of a participant spending a lot of time in the hypo/hyperglycaemic ranges, trial team will make recommendations to the participant's healthcare team with regard to adjustments to the individual's medication regime.

5.4 Discontinuation

Participation in this study is completely voluntary and participants can choose to discontinue at any stage. If so, they (or their nominated consultee) will be informed they: do

not need to give a reason (although they will be voluntarily asked to supply one) and that their medical and legal rights are not affected.

5.5 Concomitant Care

Whilst wearing the CGM device, participants will be advised to continue with the standard care for their diabetes as recommended by their healthcare team.

5.6 Outcomes

Primary outcomes:

- Proportion of participants with captured hypoglycaemia; within that group, the time spent in the hypoglycaemic range.

Secondary outcomes:

- Overall Time in Range; emergency department re-attendances and/or hospital re-admissions for falls, fractures, heart attacks, ischaemic strokes and death within 30 days.

5.7 Participants' timeline

Participants will remain in the study for 10 days to 2 weeks from providing consent:

- Receipt of information sheet whilst an inpatient at Norfolk and Norwich University Hospital or attending Older People's Emergency Department (OPED).
- If interested, the research team will fully explain the study and answer and questions. The chief investigator will assess whether there is any evidence of bruising, bleeding, cellulitis and/or skin tears on the upper arms or abdomen. Should that be the case, then the potential participant will not be eligible to take part in the study. We will provide an introduction to using the CGM device.
- We will give potential participants approximately two hours to consider whether or not to consent to take part. The CGM device will be used within its already approved licence and is supported by the NHS for people with diabetes, although older people generally do not qualify for NHS funding yet.
- Consent will be taken.
- Sensor will be fitted and worn for up to 10 days.

- After five days, the research team will contact the participant (or carer) to check how they are getting on with the CGM device and whether they are still happy to continue being part of the study. If not, the participant will be withdrawn, however, the data collected by the CGM device up to the date of withdrawal will still be analysed. The reason for withdrawal will be documented on the case record form (anonymised).
- After wearing the sensor for 10 days, members of the trial team will contact the participant to arrange a convenient time to remove the sensor and collect the smartphone. A member of the research team will travel to the place of residence to collect the equipment. When collecting the device, a member of the research team will stay outside the house, if this is preferred by the participant.
- CGM data will be analysed by the research team.
    - There will be a cross-specialty review of the CGM data: Diabetes (Dhatariya), Older People's Medicine (Mattishent) and Clinical Pharmacology (Loke).
    - The research team will write to the individual participants' GPs using the international consensus for clinical targets for CGM data interpretation (10):
        - If a participant spends around twelve hours between 3.9-10 mmol/L (time in range), then the research team will be able to provide reassurance regarding the current management regime.
        - If a participant spends more than 15 minutes <3.9mmol/L (time below range), then the research team will make recommendations to adjust the medication regime to try and reduce the time spent in the hypoglycaemic range.
        - If a participant spends more than 2 ½ hours per day >13.9 mmol/L (time above range), the research team will make recommendations to adjust the medication regime to try and reduce the time spent above range.
- End of study.

5.7.1 Withdrawal

Participants will have the right to withdraw from the study at any time without giving reason. Identifiable data already collected with consent will be retained and used in the study.

5.7.2 Participant transfers

If a participant moves from the area during the trial period, this will be considered a discontinuation from the study. Identifiable data already collected with consent will be retained and used in the study.

5.7.3 Trial closure

Trial closure will be after the last participant has returned the CGM device.

5.8 Sample size

We aim to recruit up to 30 participants. This is a size that the research team consider to be pragmatic and sufficient as indicative quantitative data upon which to base the sample size for a full trial.

5.9 Recruitment

Eligible participants will be identified and invited to participate whilst they either attend OPED or are admitted under AMU having presented with a fall or other symptoms suggestive of unrecognised hypoglycaemia.

Participant Information Sheets (PIS) will be handed out and interested patients will be consented by the research team.

No financial or non-financial incentives are offered to participants.

5.10 Data collection

Each participant will be given a unique trial Participant Identification Number (PIN).

The preferred method of data collection is direct online entry of data by trial staff onto the central database, stored on servers based at the University of East Anglia. Data may be entered onto paper Case Record Forms (CRFs) prior to entry onto the database (but this is not essential).

Data collection, data entry and queries raised by a member of the trial team will be conducted in line with the University of East Anglia's Data Management Standard Operating Procedure.

Data for the primary outcome will be collected by downloading reports from the CGM device. This will be done through the dedicated Dexcom G6 Clarity diabetes management software (available as a free download). These reports will capture the glucose readings during the 10-day period when the CGM device was used.

The research team will also collect the following patient data through access of hospital records:

Baseline data:

- Medication use at start of study period;
- Baseline demographics and co-morbidities;
- Duration of diabetes (if available from the notes);
- HbA1c.

Follow-up data:

- ED attendances and/or hospital admissions for falls, fractures, heart attacks, ischaemic strokes and death within 30 days of removal of the participant's sensor.

Participant identification logs, screening logs and enrolment logs will be kept at the trial site in a locked cabinet within a secured room. Clinical trial team members will receive trial protocol training. Regular central monitoring will assess data quality and completeness during progression of the trial. All data will be handled in accordance with the Data Protection Act 1998.

5.11 Data management

All data will be stored in a database on a secure server, provided and maintained by the University. The server environment is protected by a firewall and is patched and maintained according to best practice. The physical location of the server is protected by CCTV and security door access. Access to the database will be controlled via unique, personally attributable (i.e. not generic) usernames, password protected, and accessible only to members of the trial team, and external regulators if requested.

Data will be entered in the approved database by a member of the trial team. After completion of the trial the database will be retained on the servers of University for on-

going analysis. The identification, screening and enrolment logs, linking participant identifiable data to the pseudo-anonymized PIN, will be stored securely at the database, with access controlled on a per-user basis. Access to identifiable and pseudo-anonymized data will be stored separately within the database and permissioned accordingly.
Participant contact details will be collected by a member of the research team at the time that the participant calls to express an interest in being part of the study.

5.12 Analysis plan

Baseline characteristics for each participant will be presented in a Table. For categorical variables, the number and percentage will be presented. For continuous variables, the mean (and standard deviation) or median (and interquartile range) will be presented depending on the distribution.
The aim of the study is to determine if the primary outcomes can be captured, and to obtain an idea of effect sizes and their boundaries. This will inform conduct and design of future larger studies.
For participants who commenced wearing the CGM device whilst an inpatient, the research team will analyse the inpatient data separately to data captured in the community.

5.13 Data Monitoring

5.13.1 Data Monitoring Committee

This study is looking into the capture of hypoglycaemic episodes through the use of CGM in older people with diabetes. It carries minimal or no risks. The device simply enables glucose concentrations to be recorded in a less invasive and more frequent manner than conventional finger-prick testing.

This study does not involve delivery of a therapeutic intervention that exerts physiological effect. The medical device has already received CE mark/approval for people with diabetes and can be purchased from the Dexcom website: (https://www.dexcom.com/en-GB).

Any adverse events reports will be assessed by the Independent Expert Advisor. Therefore, the trial team submit that a separate data monitoring committee is not necessary.

5.13.2 Data monitoring for harm

Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg Investigator's Brochure for an unauthorised product or summary of product characteristics (SPC) for an authorised product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any AE or AR that: results in death is life threatening* requires hospitalisation or prolongs existing hospitalisation** results in persistent or significant disability or incapacity or is another important medical condition***
* the term life threatening here refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (eg a silent myocardial infarction) ** Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for pre-existing conditions (including elective procedures that have not worsened) do not constitute an SAE *** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. Important AEs or ARs that may not be immediately life threatening or result in death or hospitalisation, but may seriously jeopardise the participant by requiring intervention to prevent one of the other outcomes listed in the table	

Adverse events include: pain at the insertion site of the sensor, skin reaction to the adhesive of the sensor.

All non-serious AEs and ARs, whether expected or not, should be recorded in the patient's medical notes and reported in the toxicity (symptoms) section of the Follow-up Form. SAEs and SARs should be notified immediately the investigator becomes aware of the event (in no circumstance should this notification take longer than 24 hours).

When an AE or AR occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in Table 1. If the event is classified as 'serious' then an SAE form must be completed and notification sent within one working day.

The investigator must assess the causality of all serious events or reactions in relation to the trial therapy using the definitions below.

Causality definitions

Relationship	Description	Event type
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely to be related	There is little evidence to suggest that there is a causal relationship (eg the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (eg the participant's clinical condition or other concomitant treatment)	Unrelated SAE
Possibly related	There is some evidence to suggest a causal relationship (eg because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (eg the participant's clinical condition or other concomitant treatment)	SAR
Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely	SAR
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

5.14 Trial team

The Trial Team will be set up to assist with developing the design, co-ordination and day to day operational issues in the management of the trial, including budget management.

5.15 Independent Expert Advisor

The Independent Expert Advisor is the independent advisor responsible for oversight of the trial to safeguard the interests of trial participants.

5.16 Trial Sponsor

The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the trial.

6 Ethics and Dissemination

6.1 Research Ethics Approval

Before initiation of the trial, the protocol, all informed consent/declaration forms and any material given to the prospective participant/consultee will have been approved by the relevant REC. Any subsequent amendments to these documents will be submitted for further approval.

The rights of the participant to refuse to participate in the trial without giving a reason will be respected. The participant remains free to change their mind at any time about the protocol treatment and follow-up without giving a reason and without prejudicing their further treatment.

6.2 Protocol Amendments

The chief investigator is responsible for communicating any regulatory approved substantial protocol amendments (e.g. changes to eligibility criteria, outcomes, sample size calculations, analyses) to all principal investigators in all participating centres, trial registries, journals and regulators. Relevant parties will be informed by postal letter containing an amended version of the protocol for storing in the trial master file.

6.3 Consent or Consultation

Patients will be provided with a Participant Information Sheet (PIS) and given time to read it fully. Following a discussion with a medical qualified investigator or suitably trained and authorised delegate, any questions will be satisfactorily answered and if the participant is willing to participate, written informed consent will be obtained.

Members of the trial team seeking consent will be fully trained in Good Clinical Practice (GCP). During the consent process, it will be made completely and unambiguously clear to participants they are free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment.

A copy of the approved consent form is available from the trial team.

6.4 Confidentiality

All patients will be recorded on an identification log with pseudo-anonymised identifiers of initials and trial ID. This log will be compiled by trial research staff and stored in either locked cabinets in swipe card access officers and on hospital or university password access computers in swipe card access offices. All potential participants are allocated a participant identification number (PIN) to replace their name. Personal information is collected by trial staff trained in the principals of GCP. Only members of the trial team will have access to the database, identification and screening logs.

6.5 Declaration of Interests

The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the trial.

6.6 Indemnity

UEA holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UEA has been negligent.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of UEA or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to UEA's insurers, via the Sponsor's office.

6.7 Finance

This study is funded by the Norfolk Diabetes Trust (NDT). It is not expected that any further external funding will be sought

6.8 Archiving

The investigators agree to archive and/or arrange for secure storage of trial materials and records for a minimum of 10 years after the close of the trial.

6.9 Access to data

Access to the final trial dataset will be granted to the trial team, the independent expert advisor and any regulatory authorities. Access by any other parties will require approval from the CI and the independent advisor. Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the independent expert advisor.

6.10 Ancillary and post-trial care

Following completion of the trial, CGM will not be prescribed to participants using research funding. Patients and carers will have to go through conventional funding channels if they wish to continue using the medical device.

6.11 Publications policy

The Chief Investigator will co-ordinate the writing of abstracts and full publications and send these to all co-investigators before submission to scientific meetings and peer review journals for comments and approval. Following full publication, relevant papers will be sent to the appropriate patient groups, and participants who have requested this.

Any trial related publications will include co-investigators, who in the opinion of the Chief Investigator, have made a significant contribution to the: design, conduct, analysis, funding application and report writing of the trial.

7 Protocol Amendments

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