PRegnancy **O**utcomes using continuous glucose monitoring **TEC**hnology in pregnant women with early-onset **T**ype 2 diabetes

A multicentre randomised controlled trial of the clinical and cost-effectiveness of using continuous glucose monitoring (CGM) in pregnant women with early-onset type 2 diabetes

Version	3.0
Date	19th February 2025
Sponsor	University of East Anglia
Sponsor ID	R211139
Trial registration	ISRCTN12804317
IRAS project ID	331906

NIHR | National Institute for Health Research

Authorisation: Co-Chief Investigators:

Name	Professor Helen R Murphy	Professor Eleanor M Scott
Role	Co-Chief Investigator	Co-Chief Investigator
Signature	DocuSigned by: Helen R Murphy	DocuSigned by: Eleanor M Scott
Date	13 March 2025	17 March 2025

Authorisation: CTU Director or Representative

Name	Matt Hammond
Role	CTU Interim Director
Signature	Signed by: Matt Hammond
Date	13 March 2025

Authorisation: Trial Statisticians

Name	Professor Lee Shepstone	Dr Craig Kollman
Role	Trial Statistician Norwich Clinical Trials Unit	Trial Statistician Jaeb Center for Health Research
Signature	Signed by: Lee Shepstone	DocuSigned by: Craig Kollman
Date	13 March 2025	17 March 2025

1 Contents

2 Administrative information

This protocol was constructed using the Norwich Clinical Trials Unit (NCTU) Protocol Template, Version 4. It describes the PROTECT trial, sponsored by the University of East Anglia and coordinated by NCTU.

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, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to registered investigators in the trial. Sites entering participants for the first time should confirm they have the correct version through a member of the trial team at NCTU.

NCTU supports the commitment that its trials adhere to the SPIRIT guidelines. As such, the protocol template is based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2012 Statement for protocols of clinical trials[1]. The SPIRIT Statement Explanation and Elaboration document [2] can be referred to, or a member of NCTU Protocol Review Committee can be contacted for further detail about specific items.

2.1 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 Human Tissue (Quality and Safety for Human Application) Regulations 2007, the Data Protection Act 2018, the General Data Protection Regulation (GDPR) (EU) 2016/679, and the National Health Service (NHS) UK Policy Framework for Health and Social Care Research and other national and local applicable regulations. Agreements that include detailed roles and responsibilities will be in place between participating sites and NCTU.

Participating sites will inform NCTU as soon as they are aware of a possible serious breach of compliance, so that NCTU can fulfil its requirement to report the breach, if necessary, within the timelines specified in the UK Clinical Trials Regulations (currently 7 days). For the purposes of this regulation a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial.

2.2 Sponsor

The University of East Anglia is the trial sponsor and has delegated responsibility for the overall management of the PROTECT trial to the Chief Investigators and NCTU. Queries relating to sponsorship of this trial should be addressed to the Chief Investigators or via the trial team.

2.3 Structured trial summary

Primary Registry and Trial Identifying Number	ISRCTN12804317
Date of Registration	23/10/2023
Secondary Identifying Numbers	IRAS Project ID: 331906
Monetary or Material Support	NIHR Health Technology Assessment (HTA) Programme: NIHR150958. Devices supplied by Abbott Diabetes Care, Inc.
Sponsor	University of East Anglia
Contact for Public Queries	protect.trial@uea.ac.uk
Contacts for Scientific Queries	**Professor Helen R Murphy MBBChBAO, FRACP, MD** Honorary Consultant Physician, Norfolk and Norwich University Hospital NHS Foundation Trust / Professor of Medicine (Diabetes and Antenatal Care) **Tel: +44 (0)1603 591657** **Email: Helen.Murphy@uea.ac.uk** **Address:** Norwich Medical School, Floor 2, Bob Champion Research and Education Building, University of East Anglia, Norwich Research Park, Norwich, NR4 7UQ **Professor Eleanor Scott BM BS MD FRCP** Professor of Medicine (Diabetes and Maternal Health), Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds / Leeds Centre for Diabetes and Endocrinology, Leeds Teaching Hospitals NHS Trust **Tel: +44 (0)113 343 7762** **Email: E.M.Scott@leeds.ac.uk** **Address:** LICAMM, LIGHT Laboratories, Clarendon Way, University of Leeds, LS2 9JT
Short Title or Acronym	**PROTECT** – **PR**egnancy **O**utcomes using continuous glucose monitoring **TEC**hnology in pregnant women with early-onset **T**ype 2 diabetes
Scientific Title	A multicentre randomised controlled trial of the clinical and cost-effectiveness of using continuous glucose monitoring (CGM) in pregnant women with early-onset type 2 diabetes
Countries of Recruitment	United Kingdom
Health Condition Studied	Early-onset type 2 diabetes during pregnancy

Intervention	**Intervention arm**: A Real-Time Continuous Glucose Monitoring (CGM) system **Control arm**: Standard clinical care, which may be finger-prick Self-Monitoring Blood Glucose (SMBG) or continuous glucose monitoring.
Inclusion and Exclusion Criteria	**Inclusion criteria:** 1) Type 2 diabetes (T2D) 2) 16 years of age or over 3) Confirmed pregnancy 4) HbA1c of ≥43 mmol/mol (6.1%) in pregnancy (prior to randomisation) 5) Willingness to use the study devices throughout the trial 6) Able to provide informed consent 7) 4 days (aiming for ≥96 hours) of baseline CGM data before randomisation at no later than 16+0 weeks' gestation. In cases where 72-96 hours of CGM data is available, inclusion may be approved by the NCTU team. **Exclusion criteria:** 1) Non-type 2 diabetes 2) Women with chronic kidney disease (CKD) grade 4 or 5 (GFR <30ml/min)
Study Type	An open-label, interventional, multicentre, randomised, single-period, two-arm parallel group trial with Stage 1 (internal pilot) to test the feasibility of recruitment and randomisation followed by the Stage 2 (substantive study) if the progression criteria are met.
Target Sample Size	422 (211 per arm)
Primary Outcomes	**Primary maternal outcome:** The percentage time spent with maternal glucose levels within target range, as recorded by CGM Time-In-Range (TIR 3.5-7.8 mmol/L) across both arms from 20 until 38 weeks' gestation or until delivery, if delivery is earlier than 38 weeks' gestation. **Primary neonatal outcome:** Neonatal unit admission or death (stillbirth/neonatal death).
Secondary Outcomes	**Biomedical maternal:** 1. HbA1c & CGM mean glucose, GMI, frequency & duration of glycaemic excursions [%Time-Above-Range (>6.7 & >7.8 mmol/L), %Time-Below-Range (<3.5 & <3.0 mmol/L)], glycaemic variability (glucose SD, CV)] 2. Hypertensive disorders 3. Gestational weight gain

	4. Diabetes treatment (metformin & insulin use) 5. Hospital admissions & duration of stay 6. Severe hypoglycaemia, hyperosmolar hyperglycaemic state, and diabetic ketoacidosis episodes **Biomedical neonatal:** 1. Gestational age at birth 2. Birth weight for gestational age (SDS) (GROW customised birth weight, LGA birth weight >90th centile or SGA <10th centile) 3. Mode of delivery 4. Neonatal unit admission >24 hours (duration of stay, highest level care) 5. Adverse events (pregnancy loss <24 weeks, congenital anomaly (any), stillbirth, neonatal death) 6. Birth injury (spinal cord injury, clavicular, skull or bone fracture, shoulder dystocia, nerve palsy, subdural or intracerebral haemorrhage, hypoxic ischaemic encephalopathy) 7. Neonatal morbidity (treatment for neonatal hypoglycaemia, respiratory distress requiring treatment, neonatal jaundice requiring treatment) 8. Feeding at hospital discharge (exclusive breast-feeding / partial breast-feeding / exclusive formula feeding) **Patient Reported Outcomes:** 1. Diabetes distress, anxiety & depression and treatment satisfaction using short questionnaires at baseline & 32 weeks' gestation 2. Nested qualitative study to explore the acceptability, barriers, and facilitators for CGM use in T2D pregnancy. **Health Economic Outcomes:** 1. Incremental cost per quality-adjusted life year (QALY)

2.4 Roles and responsibilities

These membership lists are correct at the time of writing; please see terms of reference documentation in the Trial Master File for current lists.

2.4.1 Protocol Contributors

Name	Affiliation	Role
Professor Helen Murphy	UEA, Norfolk and Norwich University Hospitals NHS Foundation Trust (NNUH), Cambridge University Hospitals NHS Foundation Trust (CUHFT)	Co-Chief Investigator
Professor Eleanor Scott	University of Leeds (UoL), Leeds Teaching Hospitals NHS Trust (LTHT)	Co-Chief Investigator
Corinne Collett	University of East Anglia (UEA) – Norwich Clinical Trials Unit (NCTU)	Trial Manager

2.4.2 Trial Sponsor and Funders

Name	Affiliation	Role
Lindsey Harding	UEA	Sponsor Representative
Kirsty Lloyd-West	NIHR	Funder Representative

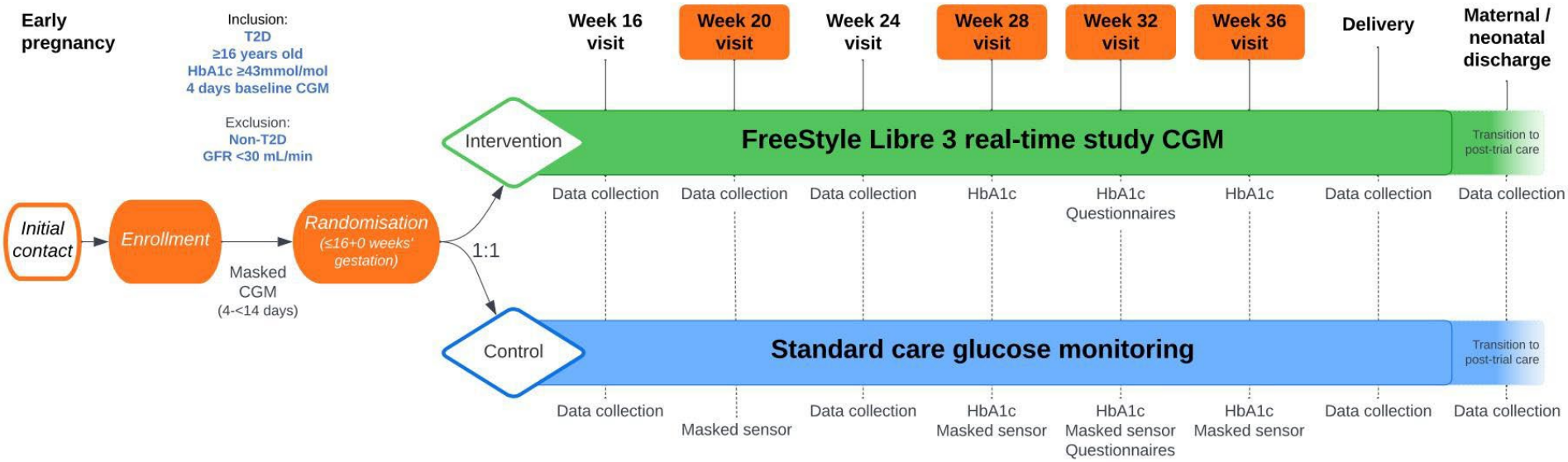
2.4.4 Trial Management Group

Name	Affiliation	Role and responsibilities
Professor Helen R Murphy*	UEA, NNUH, CUHFT	Co-Chief Investigator
Professor Eleanor M Scott*	UoL, LTHT	Co-Chief Investigator
Corinne Collett*	UEA – NCTU	Trial Manager
Alex Berry	Diabetes UK, National Diabetes Audit	PPI Co-Lead
Dr Jenny McLeish	Oxford National Perinatal Epidemiology Unit (NPEU)	PPI Co-Lead
Seema Hussain	Journalist, expert by experience	PPI
Sarah Dunkley	James Lind Alliance (JLA) Priority Setting Partnership (PSP) contributor, expert by experience	PPI
Prof Jenny Myers	Manchester Foundation NHS Trust	Obstetric / maternal fetal health expertise
Prof Khalida Ismail	King's College London	Process evaluation / qualitative research lead
Madeleine Benton	King's College London	Qualitative research expertise
Prof Neena Modi	Imperial College London	Neonatal expertise

Prof Amanda Adler	Diabetes Trials Unit, Oxford University	Health Economics Lead
Adam Wagner	UEA	Associate Professor in Health Economics
Dr Shivani Misra	Imperial College London	Type 2 diabetes expertise
Dr Tara T'Shieh Maey Lee	University of East Anglia	Obstetric /Technical CGM expertise
Prof Lee Shepstone	UEA – NCTU	Senior Trial Statistician
Dr Craig Kollman	Jaeb Centre for Health Research	Senior Trial Statistician
Robin Gal	Jaeb Centre for Health Research	JCHR Director of Research Operations
Antony Colles	UEA - NCTU	CTU Senior Data Programmer
Matthew Hammond	UEA – NCTU	CTU Deputy Director

*HRM, EMS and CC are also members of the Trial Team (refer to 6.11.4.4.1 for details)

3 Trial flow



4 Abbreviations

AE	Adverse Event
BMI	Body Mass Index
CE	Conformité Européenne (CE-mark)
CI	Chief Investigator
CI	Confidence Interval
CGM	Continuous Glucose Monitoring
CRF	Case Report Form
DDS	Diabetes Distress Scale
DKA	Diabetic ketoacidosis
DMC	Data Monitoring Committee
EOT2D	Early-Onset Type 2 Diabetes
EQ5D	Euro Health-Related Quality of Life Descriptive system
EU	European Union
GCP	Good Clinical Practice
GDM	Gestational diabetes mellitus
GMI	Glucose Management Indicator
HCP	Healthcare Professional
HHS	Hyperosmolar hyperglycaemic state
HRA	Health Research Authority
ITT	Intention to Treat
JCHR	Jaeb Center for Health Research
JLA	James Lind Alliance
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NCTU	Norwich Clinical Trials Unit
NNUH	Norfolk and Norwich University Hospitals NHS Foundation Trust
NPID	National Pregnancy in Diabetes
PI	Principal Investigator
PID	Participant Identification number
PIS	Participant Information Sheet
PIT	Participant Information Tool
PPI	Patient and Public Involvement
PROMS	Patient Reported Outcome Measures
QA	Quality Assurance
QC	Quality Control
QMMP	Quality Management and Monitoring Plan
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDS	Standard deviation score
SMBG	Self-monitored blood glucose
T2D	Type 2 Diabetes
TIR	Time In Range
TMG	Trial Management Group
TT	Trial Team
ToR	Terms of Reference
TSC	Trial Steering Committee
UEA	University of East Anglia

5 Introduction

5.1 Background and rationale

THE CLINICAL PROBLEM

The prevalence of EARLY-ONSET type 2 diabetes (EOT2D), diagnosed before 39 years old, is increasing with serious personal and public health consequences. EOT2D most typically affects WOMEN, those living in POORER communities and from MINORITY ETHNIC groups. Those with EOT2D have the highest risk of developing complications associated with T2D, and its associated co-morbidities of hypertension and hyperlipidaemia (1).

There has been a DOUBLING in the proportion of pregnancies complicated by EOT2D during the past 15-20 years (2-5). EOT2D pregnancies now account for 54% of pregnancies complicated by pre-existing diabetes in the UK, compared to 27% in 2002-03(5, 6). National audit data reported 5,085 pregnancies in women with T2D and 4,175 in type 1 diabetes (T1D), meaning that EOT2D is now the commonest form of diabetes diagnosed before pregnancy (5). As 50% of women with gestational diabetes (GDM) will develop T2D within 5 years of a GDM pregnancy, the future prevalence of T2D pregnancy is expected to increase (7). GDM currently affects 10-20% of the pregnant population (8).

National audit data demonstrate the striking healthcare inequalities faced by women with EOT2D; 90% are overweight or obese (average pre-pregnancy weight 86kg), 70% live in the poorest communities and 60% are from Asian, Black or mixed ethnic groups (2, 3, 5, 6). There are SEVEN TIMES more EOT2D pregnancies in women from the most underprivileged communities (5).

Pregnancy in women with EOT2D is associated with an increased risk of complications for both mother and baby. For the mother, there are physical and mental health concerns with increased hypertension, preeclampsia and higher rates of anxiety and depression. EOT2D pregnancies have increased risk of birth defects (congenital anomaly), and of having a baby die before or during birth (stillbirth) or during the first month of life (neonatal death) (2, 3, 5, 6). EOT2D also increases the risk of serious obstetric and neonatal complications including preterm birth, large and small birthweight babies requiring admission to neonatal care units (2-4, 6). Adverse pregnancy outcomes (birth defects, stillbirth, neonatal death) and serious neonatal morbidity (neonatal unit admission>24hr) affect up to ONE in TWO BABIES of mothers with EOT2D (5).

Importantly, MATERNAL GLUCOSE is the KEY MODIFIABLE RISK FACTOR for neonatal morbidity and death (2, 5). National audit data reported 565 serious adverse outcomes in EOT2D mothers with above-target glucose compared to 105 in T2D mothers with in-target glucose levels. Serious neonatal morbidity (neonatal unit admissions >24 hour) and mortality are significantly reduced in babies of mothers who achieved target glucose levels (HbA1c <43 mmol/mol) after 24 weeks' gestation (5).

Neonatal care admissions separate mothers and babies, with immediate and longer-term consequences for maternal wellbeing, mother-baby bonding, and infant feeding. The average neonatal care admission in EOT2D pregnancy is 5 days, which at £9,463.70 (£1,892.74 daily) is a major cost burden for the NHS (9).

WHY IS THIS RESEARCH IMPORTANT NOW?

1) Understanding whether diabetes technology can improve pregnancy outcomes was the number one James Lind Alliance (JLA) Priority Setting Partnership (PSP) priority for diabetes pregnancy research(10). Listening to the priorities of pregnant women is particularly pertinent following the Ockenden report, where many women, especially from ethnic minorities and poorer communities reported poor experiences…*I felt frightened and not listened to*…" (9, 11, 12).

2) The burden of EOT2D pregnancy is high(2), and rapidly increasing with gestational diabetes (GDM) affecting one in seven women, half of whom will develop EOT2D within 5 years (7).

3) Nearly ONE in TWO BABIES born to mothers with EOT2D have serious health complications (birth defects, neonatal care admissions or death) with major impacts for women, families and the NHS(2, 5). We know that many adverse outcomes are potentially preventable by improving maternal glucose (2, 3, 13).

4) There are stark healthcare inequalities in access to diabetes technology. Currently, <15% of mothers with EOT2D (ethnically diverse, higher BMI, more deprived) are offered continuous glucose monitoring (CGM) compared to >90% of mothers with T1D (predominantly white, lower BMI, more affluent). Recent NICE guidance (31/03/22) highlighted the urgent need to address health inequalities in CGM access. Addressing inequalities by bringing high quality research to under-served communities is also a key NIHR priority.

5) The complications associated with EOT2D pregnancy carry high societal costs (pregnancy loss, stillbirth, neonatal death) and high NHS costs (preeclampsia £4656, neonatal care admission £9463 for 5-days, neonatal death £767)(14, 15).

Our study will examine whether real-time CGM is a viable tool to improve maternal glucose levels and reduce serious neonatal morbidity (neonatal care admissions or death) in EOT2D pregnancy.

REVIEW OF EXISTING EVIDENCE

National audit data confirm that background rates of neonatal morbidity and death are high (42.2% and 6.7%, respectively) during EOT2D pregnancy (2, 5, 16). However, they can be reduced if women achieve target glucose levels after 24 weeks' gestation. This is traditionally done by adjusting diabetes treatment (diet, insulin, metformin) according to 4-7 daily 'finger-prick' self-monitored blood glucose (SMBG) tests. Our Patient and Public Involvement (PPI) partners confirmed that many pregnant women find glucose testing extremely burdensome; *"having to monitor my bloods every single day was really tough" – "sneaking off into the toilet to do my sugars - it takes up so much time just thinking about it, planning it around meals and work".* SMBG also provides only limited glucose information, collected using unreliable methods (paper diaries), on which to adjust diabetes treatments.

CGM technology, which measures interstitial glucose from a device worn day and night, is revolutionizing how glucose levels are monitored and managed. Compared to HbA1c or finger-prick SMBG, CGM gives detailed information (1,440 glucose measures/day), describing glucose changes across the 24-hour day. Sensors, the size of a 1p coin, typically worn on the back of the arm, send interstitial glucose readings via Bluetooth, directly to a mobile phone (17, 18). CGM enables the user to assess how much time they spend in, above and below the target glucose range and alerts them if their glucose is too high or too low. Patients hold their CGM Time In Range (TIR) glucose information

on their mobile phones. They find glucose TIR information engaging because it provides immediate feedback on any changes they make to their diet or diabetes treatments (19, 20)·(21). The patient-centredness of TIR is strongly endorsed by a survey of 3,461 people with diabetes (70% with T2D) who ranked TIR as the factor, which after food choices, has the biggest impact on their daily lives. In contrast to SMBG, CGM data are easily shared remotely with the users, carers and health care professional (HCP) teams allowing diabetes treatment plans (diet, metformin, insulin) to be more precisely adjusted (22-25). This is especially relevant during pregnancy where there are frequent changes in gestational physiology and pharmacokinetics requiring timely personalized treatment adjustments (26, 27).

We performed an international randomised controlled trial (RCT) of CGM use in T1D pregnancy (CONCEPTT)(28). We demonstrated that compared to finger-prick SMBG, CGM use was associated with improved maternal glucose levels with higher CGM Time In Range (TIR) during the third trimester. It was changes in CGM TIR (68% vs 61%; p=0·0034) and neonatal health outcomes [large for gestational age (LGA) birthweight odds ratio 0·51, 95% CI 0·28 to 0·90; p=0·0210, neonatal unit admission >24h odds ratio 0·48; CI 0·26 to 0·86; p=0·0157, neonatal hypoglycaemia 0·45; CI 0·22 to 0·89; p=0·0250), 1-day shorter neonatal hospital stay (p=0·0091)] that led to changes in NICE guidelines and accelerated NHS implementation (Dec 2020)(29). Providing CGM in T1D pregnancy dominated management with finger-prick SMBG, by being less expensive and more effective(14, 15). For maternal outcomes, CGM use was clinically and cost effective. For neonatal outcomes, CGM cost less (-£2,612) while being more effective (QALYs 75.4 vs. 73.8) making it cost-saving with an incremental cost-effective ratio (ICER) of *minus* £1,571/QALY gained. This was driven, almost exclusively, by fewer neonatal admissions (14).

Based on our results, CGM is now standard care in T1D pregnancy, with NHS data demonstrating widespread uptake (30). We supported translation of CONCEPTT into real-world settings by developing accessible online CGM resources for patients and NHS teams (CGM user stories, YouTube videos, Top Tips). Due to stark differences in the characteristics of pregnant women with T1D and EOT2D we cannot extrapolate the benefits of CGM use in T1D to EOT2D pregnancy. Women with T1D receive extensive diabetes support with structured education & specialist care and are increasingly using diabetes technology before pregnancy. By contrast, women with EOT2D get very little diabetes support (31-33). Only 18% are treated with insulin and routinely monitor glucose levels before pregnancy (1, 2, 16, 34). Furthermore, as noted by our PPI partners, JLA PSP (>1,000 contributors) and patient survey (113 women with diabetes); most (84%) experience considerable stigma and negative emotions regarding their EOT2D. PPI partners wanted *more focus on the positivity of managing glucose levels and the results for my pregnancy/birth, for example being able to deliver naturally – proper support to manage diabetes without compromising my mental health and unborn baby.* The unrelenting emotional impact of maintaining safe glucose levels during pregnancy is associated with widespread symptoms of anxiety and depression (36% & 14% respectively) in women with EOT2D (35).

Trials comparing CGM to finger-prick SMBG in older-aged adults T2D (mean 63 years), show consistent improvements in glucose levels (higher TIR, lower HbA1c) (21, 36, 37). CGM benefits are independent of any particular CGM device or diabetes treatment, consistent with our CONCEPTT findings in T1D pregnancy (38). However, high quality evidence regarding CGM in those with EOT2D pregnancy is lacking. A 2019 Cochrane systematic review identified 4 RCTs (2 from our group) comparing CGM vs finger-prick SMBG; CONCEPTT and 3 RCTs which included small numbers of women with T2D (N=25

UK, N=31 Denmark, N=82 Netherlands)(39). These studies including ours (40), used older, larger CGM devices intermittently (40-42). We also recruited 50 CGM naïve pregnant women (39 GDM, 11 T2D); 98% reported that CGM was *'easy to use' 'less stressful'* and *'less painful'* than finger-prick SMBG. With limited sample sizes, these and the Cochrane review, lacked statistical power to evaluate the clinical effectiveness of CGM in EOT2D pregnancy.

Fewer than 5% of research participants with T2D are aged 18-39 years, with women who are pregnant or planning pregnancy often excluded from T2D trials (43). This is exacerbated by the relatively small numbers of pregnancies and recognised challenges of recruiting women from minority ethnicities and poorer backgrounds. The Metformin in Type 2 diabetes (MiTY) trial, the only high quality RCT in EOT2D pregnancy, required 7 years to recruit 500 participants. MiTY reported modest benefits of metformin and insulin on maternal glucose but no impact on serious neonatal morbidity and death which remained ~40% in both groups (44). Furthermore, improved maternal glucose outcomes, were accompanied by more small for gestational age (SGA) babies.

PROCESS EVALUATION

We previously conducted a number of qualitative studies evaluating the processes underlying the effectiveness of diabetes technology use in T1D pregnancy (17). Taken together, they suggest three key factors: firstly, HCP enthusiasm for health technology, secondly appropriate targeting to users needs and thirdly, women's and their partner's/families understanding of the crucial importance of maternal glucose levels for reducing EOT2D pregnancy risks. Our PPI partners emphasised that structural healthcare inequalities, stigma and previous negative healthcare interactions particularly impact on women with EOT2D; *'The diagnosis comes with a lot of guilt that we did something that could harm our babies'- 'I was made to feel so guilty, like it was entirely my fault, like I had and was failing my baby'*. We plan a pragmatic approach to identify and describe processes that assess the reach and uptake of CGM use in EOT2D, to aid the interpretation and translation of our findings. A nested qualitative study will explore barriers and facilitators to CGM use and identify any variations by socio-demographic factors.

This study has been co-produced with women with EOT2D, JLA PSP & PPI partners, NHS commissioners, and doctors and midwives working in maternity, neonatology, diabetes and mental health, as well as statisticians, health economists and clinical trialists.

5.1 Research aims

5.1.1 Research question

What is the clinical and cost-effectiveness of using continuous glucose monitoring (CGM) compared with standard care, for improving both maternal glucose and neonatal health outcomes in pregnant women with early-onset type 2 diabetes (EOT2D)?

We will examine whether using CGM improves maternal glucose and neonatal outcomes in EOT2D pregnancy. We will also measure its impact on maternal wellbeing, diabetes treatment satisfaction and cost effectiveness outcomes.

5.1.2 Explanation for choice of comparators

5.1.2.1 Intervention

The intervention being evaluated in this trial is a real-time Continuous Glucose Monitoring (CGM) system.

5.1.2.2 Control

The control for this study will be standard clinical care: Self-Monitoring Blood Glucose (SBMG) using finger-prick testing. It is expected that continuous glucose monitoring will be increasingly used in standard clinical care, particularly for women with EOT2D who are treated with insulin. Masked study CGM sensors will be applied to control group participants at 20, 28, 32, and 36 weeks' gestation to provide comparable outcome data.

5.2 Objectives

Our main objective is to examine whether the use of CGM relative to standard care is clinically effective, cost effective and acceptable to pregnant women with EOT2D. Specific objectives are to:

1) Test the primary hypothesis that in pregnant women with EOT2D the use of real-time CGM is more effective than standard clinical care (finger-prick SMBG testing) for improving the percentage of time spent in the pregnancy target glucose range of 3.5-7.8 mmol/L and reducing clinically relevant neonatal morbidity (neonatal care admission) or perinatal death.
2) Estimate the incremental use of healthcare resources, costs and impact on health-related quality of life (measured using EQ-5D-5L questionnaire) associated with CGM relative to standard care.
3) Assess maternal acceptability of CGM use on diabetes treatment satisfaction, health-related quality of life and maternal wellbeing outcomes using qualitative interviews and validated questionnaires.
4) Examine the associations between maternal glycaemia (HbA1c and CGM Time-In-Range (TIR) metrics) with obstetric and neonatal health outcomes in EOT2D pregnancy.
5) Assess the proportion of women with EOT2D who give consent to be contacted for future studies.

5.2.2 Psychosocial objectives

To determine diabetes distress, anxiety & depression and treatment satisfaction using short, validated questionnaires at baseline (except for GMSS which is applicable only in late pregnancy) & 32 weeks' gestation:

- T2D Distress Scale (DDS)
- Glucose Monitoring Satisfaction Survey (GMSS)
- Patient Health Questionnaire 9-item depression scale (PHQ-9)
- Generalized Anxiety Disorder 7-item scale (GAD-7)
- EQ-5D-5L

The nested qualitative study will also explore the acceptability, barriers, facilitators as well as patient and HCP support needs for CGM use in EOT2D pregnancy.

5.2.3 Health economic objectives

To determine incremental cost per quality-adjusted life year (QALY) between treatment arms.

5.3 Trial design

An open-label, multicentre, randomised, single-period, two-arm parallel group trial with Stage 1 (internal pilot) to test the feasibility of recruitment and randomisation followed by the Stage 2 (substantive study) if the progression criteria are met.

422 pregnant women aged 16 years and over with EOT2D diagnosed prior to or during current pregnancy will be recruited through outpatient antenatal diabetes clinics. Women fulfilling the eligibility criteria will be randomised to real-time continuous glucose monitoring (CGM) or to continue with standard care self-monitoring blood glucose (SMBG) (finger-prick testing). It is expected that continuous glucose monitoring will be increasingly used in routine care for women with EOT2D, particularly for those who are treated with insulin. The study will take place within the home and NHS routine antenatal clinical settings.

5.3.1 Internal pilot

An internal pilot will recruit 142 women over 12 months to address the feasibility of recruiting and retaining pregnant women with T2D from geographically representative sites, and their willingness to use CGM.

The Trial Management Group (TMG) with PPI partner participation will review progress, reporting to the Data Monitoring Committee (DMC) and Trial Steering Committee (TSC). At the end of the 12-month pilot period, an assessment of CGM sensor usage, availability of CGM glucose data for the primary maternal outcome (CGM time-in-range) and the event rate for the neonatal composite outcome (neonatal care admission and perinatal mortality) for those who have given birth will be available for review. Acceptability of the trial processes will be considered.

6 Methods

6.1 Site selection

The trial sponsor has overall responsibility for site and investigator selection and has delegated this role to the CIs and NCTU.

6.1.1 Study setting

Recruitment for this study will take place in UK NHS antenatal diabetes clinics. Participants will use the CGM until after delivery of their babies, in their usual day-to-day setting, with support from their usual clinical care team.

Interviews will be conducted either by telephone, videocall or face to face at a mutually convenient location.

6.1.2 Site/Investigator eligibility criteria

20 NHS maternity clinics with specialist diabetes pregnancy teams serving mixed ethnic lower income groups representative of the diversity of pregnant women with T2D will be selected.

Trial sites will be issued with a copy of this protocol along with a pack of documentation needed by the Research and Development Department (R&D) of their Trust to enable the Trust to provide confirmation of capacity and capability to undertake the study.

6.1.2.1 Principal Investigator's (PI) qualifications and agreements

The investigators must be willing to sign an investigator statement to comply with the protocol for this trial (confirming their specific roles and responsibilities relating to the trial, and that their site is willing and able to comply with the requirements of the trial). This includes confirmation of appropriate qualifications and training, agreement to comply with the principles of GCP, to permit monitoring and audit as necessary at the site, and to maintain documented evidence of all staff at the site who have been delegated significant trial related duties.

6.1.2.2 Resourcing at site

The investigators should be able to demonstrate a potential for recruiting the required number of suitable participants within the agreed recruitment period (i.e., the investigators regularly treat the target population). They should also have an adequate number of qualified staff and facilities available for the foreseen duration of the trial to enable them to conduct the trial properly and safely.

Sites will be expected to complete a delegation of responsibilities log and provide staff contact details.

The site should have sufficient data management resources to allow prompt data return.

6.2 Site approval and activation

Each site will undergo site initiation. Following initiation and on receipt of the signed investigator statement, approved delegation of responsibilities log, staff contact details, and appropriate local approvals, written confirmation of site activation will be sent to the site PI. Sites will not be permitted to recruit any patients until a letter for activation has been issued. The Trial Manager or delegate will be responsible for issuing this after a green light to recruit process has been completed.

The site must conduct the trial in compliance with the protocol as agreed by the Sponsor, HRA and favourable opinion given by the Research Ethics Committee (REC). The PI or delegate must document and explain any deviation from the approved protocol and communicate this to the trial team at NCTU.

A list of activated sites may be obtained from the Trial Manager.

6.3 Participants

6.3.1 Participant recruitment

Potential participants will be identified by their clinical care team, provided with study information either in person or by post/email and invited to join the study. They may also contact the clinical care team directly. All women will be offered the opportunity to discuss the advantages and disadvantages of study participation with a member of the research team and/or their diabetes physician/diabetes educator/obstetric physician/obstetrician. They will usually have 24 hours or more to consider involvement prior to consenting, however due to the low-risk and routine nature of the intervention, and the need to keep the participant burden to a minimum, the participant may be consented at the initial contact if the hospital team feels that they are fully informed. There will be **NO EXCEPTIONS** (waivers) to eligibility requirements at the time of enrolment or randomisation. Questions about eligibility criteria should be addressed PRIOR to attempting to enrol the participant.

The eligibility criteria for this trial have been carefully considered and are the standards used to ensure that the study population are representative of those with T2D pregnancy and medically appropriate participants are entered. Participants not meeting the criteria should not be entered into the trial for their safety and to ensure that the trial results can be appropriately used to make future treatment decisions for other people with similar diseases or conditions. It is therefore vital that exceptions are not made to these eligibility criteria.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

6.3.1.1 Participant inclusion criteria

1. Type 2 diabetes (T2D)
2. 16 years of age or over
3. Confirmed pregnancy
4. HbA1c of ≥43 mmol/mol (6.1%) in pregnancy (prior to randomisation)
5. Willingness to use the study devices throughout the trial
6. Able to provide informed consent
7. 4 days (aiming for ≥96 hours) of baseline CGM data before randomisation at no later than 16+0 weeks' gestation. In cases where 72-96 hours of CGM data is available, inclusion may be approved by the NCTU team.

6.3.1.2 Participant exclusion criteria

1. Non-type 2 diabetes
2. Chronic kidney disease (CKD) grade 4 or 5 (GFR <30ml/min)

6.3.1.3 Inclusivity

For the purpose of this protocol, whilst we refer to pregnant women throughout, the study is inclusive of non-binary, gender-fluid, or any other pregnant persons.

6.3.1.4 Retention

Participants will remain in the trial for the duration of their pregnancy until maternal discharge after delivery, with data collected on their baby(ies) until neonatal discharge, if admitted (or 28 days post-delivery if admission prolonged). During pregnancy, participants will be seen by the clinical research team on a 4-weekly basis.

6.3.1.5 Co-enrolment guidance

Co-enrolment into interventional diabetes studies which could impact maternal glucose levels is not permitted, however co-enrolment is permitted for observational studies and / or studies which do not impact on maternal glucose, with approval from TMG.

6.3.2 Eligibility criteria for individuals performing the interventions

The intervention will be conducted by site staff who are experienced in working with pregnant women with T2D. Full training in the study procedures will be provided to the local study team.

6.3.3 Screening procedures and pre-randomisation investigations

Written informed consent to enter and be randomised into the trial must be obtained from participants after explanation of the aims, methods, benefits and potential hazards of the trial and **BEFORE** any trial-specific procedures. The only procedures that may be performed in advance of written informed consent being obtained are those that would be performed on all patients in the same situation as a usual standard of care.

6.3.3.1 Screening logs

Participating sites will be expected to maintain records of all patients screened for the trial, including those who are not entered (for whom ID numbers are not obtained) either due to ineligibility or because the patient declined to participate.

6.4 Interventions

Women fulfilling the eligibility criteria will be randomised to real-time study CGM or to continue with standard care glucose monitoring.

6.4.1 Intervention arm

6.4.1.1 Products

Women assigned to the intervention arm will monitor their glucose levels using a CE marked real-time CGM, **FreeStyle Libre 3** (Abbott Diabetes Care, Inc.), using the FreeStyle Libre apps installed on their smartphone. A mobile phone to host the apps will be provided if the participant does not have a compatible smartphone device.

6.4.1.2 Accountability

The local PI will ensure that adequate training is provided to the participants by the hospital team.

6.4.1.3 Treatment schedule

Participants will use the CGM throughout pregnancy until after delivery of their baby(ies). The CGM sensor will need to be replaced every 14 days. If participants lose the ability to access the CGM data during the trial they should revert to their pre-trial method of glucose monitoring.

The CGM glucose measures will be reviewed at study visits during pregnancy. As CGM data is uploaded and shared in real-time, measures may also reviewed by the clinical care and research teams at any time.

Ongoing care (post-delivery) will be at the discretion of the treating team.

6.4.2 Control arm

6.4.2.1 Products

Participants randomised to the control arm will wear a masked Freestyle Libre sensor (Pro, Libre 3, or equivalent) at 20, 28, 32 and 36 weeks' gestation to provide comparable outcome data. CGM data from masked sensors are available to researchers (CTU team, study statisticians, non-clinical members of the local research team) and will not routinely be available to participants or treating clinical teams.

6.4.2.3 Control schedule

Participants will continue to monitor their glucose via the **routine clinical care** method throughout pregnancy:

- SMBG (finger-prick testing) 4-7 times a day, recording in a paper or electronic diary format (as provided locally).

Participants using continuous glucose monitoring in later pregnancy will be asked to continue wearing masked sensors at the key timepoints, and may be asked to share their non-study sensor glucose data with the trial team.

6.4.3 Dispensing

Trial CGM sensors will be provided to the study team at each participating centre and additional devices should be requested by sites as appropriate. Sensors provided for use in the trial should be used for PROTECT participants only. Usage of devices will be monitored.

Participants will be able to keep any remaining CGM sensors at the end of the study.

6.4.4 Compliance and adherence

Compliance with CGM use will be monitored by the clinical care team during trial and standard antenatal visits which will take place either face-to-face or virtually 4-weekly between 12 weeks until delivery.

6.4.5 Concomitant care

Concomitant care will be as per usual clinical practice.

6.4.6 Treatment discontinuation

In consenting to the trial, participants are consenting to trial interventions, trial follow-up and data collection. However, an individual participant may stop treatment early or be stopped early for any of the following reasons (not exhaustive):

- Unacceptable adverse event
- Any change in the participant's condition that in the clinician's opinion justifies the discontinuation of treatment
- Withdrawal of consent for treatment by the participant
- Significant protocol violation or non-compliance

As participation in the trial is entirely voluntary, the participant may choose to discontinue trial treatment at any time without penalty or loss of benefits to which they would otherwise be entitled. Although not obliged to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights.

Participants who discontinue protocol treatment, for any of the above reasons, should remain in the trial for the purpose of follow up, and data collection (including masked CGM sensor data at key timepoints for both intervention and standard care participants), and analysis, if they are willing.

6.5 Outcomes

6.5.1 Primary outcomes

Primary maternal outcome: Percentage time spent with maternal glucose levels within the pregnancy target range, as recorded by CGM Time-In-Range (TIR 3.5-7.8 mmol/L) across both arms from 20 until 38 weeks' gestation, or until delivery, if delivery is earlier than 38 weeks' gestation.

Primary neonatal outcome: NICU admission or death (stillbirth/neonatal death) across both arms.

6.5.2 Secondary outcomes

Biomedical maternal:

1) HbA1c and CGM mean glucose, glucose management indicator (GMI), frequency and duration of glycaemic excursions [%Time-Above-Range (>6.7 & >7.8 mmol/L), %Time-Below-Range (<3.5 & <3.0 mmol/L)], glycaemic variability (glucose SD, CV)]
2) Hypertensive disorders
3) Gestational weight gain (from initial antenatal visit to 36 weeks' gestation)
4) Diabetes treatment (metformin and insulin use)
5) Hospital admissions and duration of stay
6) Severe hypoglycaemia, hyperosmolar hyperglycaemic state, and diabetic ketoacidosis episodes

Biomedical neonatal:

1) Gestational age at birth
2) Mode of delivery
3) Birth weight for gestational age (SDS) (GROW customised birth weight, LGA birth weight >90th centile or SGA <10th centile)
4) Neonatal care unit admission (duration of stay, highest level care)
5) Adverse events (pregnancy loss <24 weeks, congenital anomaly (any), stillbirth, neonatal death)
6) Birth injury (spinal cord injury, clavicular, skull or long bone fracture, shoulder dystocia, nerve palsy, subdural or intracerebral haemorrhage confirmed by computerized tomography (CT) or magnetic resonance imaging (MRI) scan, hypoxic ischaemic encephalopathy)
7) Neonatal morbidity (treatment for neonatal hypoglycaemia; treatment for respiratory distress; treatment for neonatal jaundice)
8) Feeding at hospital discharge (exclusive breast-feeding / partial breast-feeding / exclusive formula feeding)

Patient-reported outcome measures (PROMs):

Diabetes distress, anxiety and depression and treatment satisfaction using short questionnaires at baseline (except for GMSS which is applicable only in late pregnancy) and 32 weeks' gestation:

- T2D Distress Scale (DDS)
- Glucose Monitoring Satisfaction Survey (GMSS)
- Patient Health Questionnaire 9-item depression scale (PHQ-9)
- Generalized Anxiety Disorder 7-item scale (GAD-7)
- EQ-5D-5L (maternal)

The nested qualitative study will also explore the acceptability, barriers, facilitators as well as patient and HCP support needs for CGM use in T2D pregnancy.

6.5.5 Health economic outcomes

A within-trial cost utility analysis comparing Freestyle Libre 3 CGM with standard care under the intention-to-treat principle. An NHS and personal social care perspective and a societal perspective will be adopted. The primary outcome measure of the health economics analysis will be incremental cost per quality-adjusted life year (QALY). The health-related quality of life instrument EQ-5D-5L collected at baseline and 32 weeks will provide maternal utility values for the calculation of QALYs.

6.6 Participant timeline

	Initial Contact	Recruitment visit	Randomis-ation visit	Routine antenatal appts	28-week visit	32-week visit	36-week visit	Delivery visit	Hospital discharge (infant)
	Early pregnancy	≥4 days prior to randomisation	≤16+0 weeks' gestation	16, 20 & 24 weeks' gestation	(+/- 2 weeks)	(+/- 2 weeks)	(+/- 2 weeks)		
Patient information provided (hard copy and/or electronic)	X								
Check inclusion / exclusion criteria		X							
Obtain written informed consent		X							
Height and weight, medical history		X							
HbA1c (local lab)		X†			X	X	X		
Bloods for metabolic phenotyping			X^						
Masked CGM sensor		X		X* (week 20 only)	X*	X*	X*		
Questionnaires		X	confirm completed			X			
Adverse event collection	Adverse Events of Special Interest (AESI) & Serious Adverse Events (SAEs) reported in line with section 7								
Randomisation			X						
CGM (Intervention arm only)**			Real-time CGM data uploaded via smartphone or receiver from randomisation to post-delivery						
Qualitative interviews (selected intervention participants)					Scheduled between researcher and participant during or after pregnancy				
! Trial data collection				X	X	X	X		
!! Data collection at delivery								X	
# Infant care and feeding data									X

†Only required if not previously performed in this pregnancy
^ Bloods for metabolic phenotyping to be taken at baseline, after written informed consent, or at any subsequent visit during pregnancy if not taken at baseline.
*Control participants and participants who have stopped trial CGM intervention only
** Participants in the control arm using continuous glucose monitoring may be asked to share their sensor glucose data with the trial team.
! Trial data: Maternal weight, blood pressure, glucose monitoring method(s), insulin delivery method, diabetes treatment, medication use, hospital admission, episodes of severe hypoglycaemia / hyperosmolar hyperglycaemic state / diabetic ketosis, adverse events.
!! Delivery data: Blood pressure, glucose monitoring method(s), medication use, hospital admission, episodes of severe hypoglycaemia / hyperosmolar hyperglycaemic state / diabetic ketosis, adverse events, pregnancy / diabetes complications, antenatal corticosteroids, method of delivery (vaginal or caesarean), infant birthweight, sex and gestational age, birth injury, length of hospital stay. Intrapartum and in-patient CGM data until maternal hospital discharge.
Infant data: High level neonatal care >24 hours, length of NICU stay, neonatal hypoglycaemia treated with buccal mucosa 40% glucose gel and/or iv dextrose, neonatal hyperbilirubinemia, respiratory distress, length of hospital stay.

6.6.1 Patient visits and assessments

6.6.1.1 Recruitment visit (between confirmed pregnancy and at least 4 days prior to randomisation)

- Checking inclusion and exclusion criteria
- Written informed consent
- Baseline socio-demographic data
- Relevant medical / obstetric history and present medical (diabetes, comorbidity, medication, and obstetric) information
- Body weight and height, calculation of BMI
- Early pregnancy HbA1c recorded (or performed if not previously done in this pregnancy)
- Bloods for metabolic phenotyping (C-peptide, autoantibodies, genetic risk score). If not taken at the recruitment visit, these can be taken at any time during pregnancy.
- Baseline questionnaire pack provided for participants to complete at home (either paper or electronically via link)
- Masked Freestyle Libre sensor insertion (at least 4 days prior to randomisation)

Ideally the sensor will be in place for around 7 days, however if necessary to meet timelines, **at least 4 days of CGM data** should be available prior to randomisation. If there are technical difficulties and/or inadequate CGM data a second CGM sensor may be provided (if possible within the required timeframes). Where only 72-96 hours of data are available, authorisation to randomise should be obtained from Norwich Clinical Trials Unit.

6.6.1.2 Randomisation visit (up to 16 weeks' 0 days' gestation)

- Masked CGM sensor review (to confirm adequate baseline data available, where possible).
- Collection / confirmation of completed baseline questionnaires
- Record diabetes treatment
- Randomisation via study website
- Participant training

6.6.1.2.1 Participant training – intervention arm

Patients randomised to the CGM arm will receive training (face to face or virtually) in the following:

- How to apply the sensor
- Understanding the FreeStyle Libre 3 apps, including sharing of data and setting alarms
- Interpreting CGM data
- Recommended targets and managing their diabetes in pregnancy (including 'Top Tips' guidance document)
- Metformin/insulin dose adjustment (if relevant)

The local study team will ensure that the participant has the skills and confidence required to proceed with CGM. If women are unable to demonstrate competency and/or compliance, their withdrawal from the study will be considered.

CGM training modules (non-trial specific) are available at https://abcd.care/dtn/diabetes-tech-pregnancy and can be accessed by trial participants and staff.

Participants will be encouraged to use CGM from randomisation until after delivery, with CGM sensor data captured up to maternal hospital discharge (or up to 14 days post-delivery, whichever is

sooner). Where the participant continues to wear intervention sensors following hospital discharge after delivery, data will continue to feed into the study LibreView account. Data post-hospital discharge will not be used in the analysis.

6.6.1.2.2 Participant training – control arm

Participants randomised to the control arm will receive training (face to face or virtually) in the following:

- Finger-prick SMBG training with a blood glucose meter (as per standard care). Participants will be asked to perform SMBG at least four values daily, including before breakfast (fasting state) and 1 hour after each meal.
- Recommended targets and managing diabetes in pregnancy (including 'Top Tips' guidance document)
- Metformin/insulin dose adjustment (if relevant)

6.6.1.6 Procedures following training

Following training, participants in the intervention arm will proceed to use CGM throughout pregnancy and delivery. Participants in the control arm will continue to use current methods of glucose monitoring and will keep a paper logbook or electronic diary of their glucose values, which will be reviewed as per routine care. Participants using continuous glucose monitoring will share their sensor glucose data directly with the trial team. Participants in the control arm will have masked study CGM sensors applied at 20, 28, 32 and 36 weeks' gestation to collect comparable outcome data (those using non-study continuous glucose monitoring will be asked to wear a masked study sensor alongside their own to allow comparable data to be collected).

Glucose targets for both groups are as follows:

- **fasting glucose levels 3.5-5.3 mmol/L**
- **1 hour post-prandial <7.8 mmol/L**
- **2 hours post-prandial <6.7 mmol/L**
- **HbA1c <43 mmol/mol**

Treatment should be adjusted by women and local HCP teams using metformin and/or insulin if glucose levels are out of range on three or more occasions and dietary intervention is unlikely to be adequate for optimal maternal glucose levels.

6.6.1.7 Study visits

Follow up visits will be every 4 weeks at ~16/40, 20/40, 24/40, 28/40, 32/40, 36/40 (+/- 2 weeks). It is expected that the majority of ongoing study visits will align with routine NHS antenatal clinic visits however virtual study visits (e.g., using phone or video calls) will be offered if appropriate, and data from community appointments may be used if needed.

At these visits the following data will be recorded on the study database:

- Weight
- Blood pressure
- Glucose monitoring method(s), frequency of glucose testing
- Insulin delivery method(s), dose and type, if relevant
- Other diabetes treatment

- Adverse events of special interest

In addition to the data collected above (6.6.1.7), the following will be performed at key visits:

- Masked CGM for control group participants (14 days data collection) at 20, 28, 32, and 36 weeks' gestation
- Blood collection for HbA1c at 28, 32, and 36 weeks' gestation
- Follow-up questionnaires at 32 weeks' gestation

6.6.1.9 Delivery visit

The following maternal, obstetric and neonatal outcomes will be collected:

- Maternal CGM sensor data
- Mode of delivery (vaginal, instrumental, elective/emergency caesarean section)
- Gestational age at delivery and indication for any preterm delivery <37 weeks
- Infant(s) birth weight
- Adverse events (pregnancy loss <24 weeks, stillbirth, neonatal death)

6.6.1.10 Neonatal follow up

Neonatal assessment is at hospital discharge (or 28 days if admission prolonged). The following data will be collected:

- Neonatal morbidity (treatment for neonatal hypoglycaemia, neonatal jaundice, respiratory distress)
- Neonatal care admission (duration of stay at each level of care: Level 3 intensive care, Level 2 high-dependency care, or Level 1 special care, recorded according to national guidance (BAPM 2010))
- Infant(s) feeding at hospital discharge (exclusive breast feeding/partial breast feeding/exclusive formula feeding)
- Neonatal readmission in the first 7 days after birth (e.g., for neonatal hyperbilirubinemia see section 9, outcome definitions)

6.6.1.11 Early pregnancy loss

In the event of early pregnancy loss, trial follow-up will end (with the exception of follow up of any CGM- or study-related SAEs). Participants on the intervention arm may be asked to return unused devices to the research team**.**

6.6.3 Blood sampling

HbA1c levels should be measured locally from blood samples.

At baseline (or at any time during pregnancy, if not taken at baseline), a blood sample will be taken and frozen, for later transfer to the Norwich Biorepository for metabolic phenotyping (assessment of maternal baseline pancreatic function: C-peptide and islet cell antibodies). A sample handling Work Instruction will be provided to all sites detailing sample collection and handling procedures. Appropriate tissue transfer agreements will be put in place prior to the transfer of relevant material.

6.6.2 Questionnaires

Participants will be asked to complete the following questionnaires at baseline and again at 32 weeks to assess diabetes distress, glucose monitoring satisfaction, anxiety & depression, and quality of life using short, validated questionnaires targeted as applicable for T2D:

- T2D Distress Scale (DDS)(45)
- Glucose Monitoring Satisfaction Survey (GMSS)(46)
- Patient Health Questionnaire 9-item depression scale (PHQ-9) (47)
- Generalized Anxiety Disorder 7-item scale (GAD-7) (48)
- EQ-5D (49)

These can be completed in participants' own homes electronically or on paper.

The **Type 2 Diabetes Distress Scale (DDS)** consists of 29 items and yields two sets of scores: an 8-item core distress score, reflecting overall diabetes-related emotional distress, and a 21-item set of seven source scores, reflecting seven different potential sources of distress. Responses are rated on a 5-point scale from 'not a problem' to 'a very serious problem'.

The **Glucose Monitoring Satisfaction Survey (GMSS)** is a 15-item self-report scale. The T2D version includes 4 subscales: openness, emotional burden, behavioural burden, and worthwhileness.

The **Patient Health Questionnaire 9-item depression scale (PHQ-9)** reflects the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) criteria, classifying symptoms on a scale of 0 (not at all) to 3 (nearly every day).

The **Generalized Anxiety Disorder 7-item scale (GAD-7)** consists of seven questions with response categories of 'not at all', 'several days', 'more than half the days', and 'nearly every day'. Scores are taken as cut-off points for mild, moderate, and severe anxiety.

The **EQ-5D Health-Related Quality of Life Questionnaire** is a self-rated health status using a visual analogue scale. It provides a self-reported description of current health in 5 dimensions i.e., mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The concept of health in EQ-5D also encompasses both positive aspects (well-being) and negative aspects (illness). The utility score is an expression of the Quality Adjusted Life Years (QALY).

6.6.4 Qualitative interviews

Participants will be purposively sampled by socio-demographic factors to understand how these affect CGM uptake (sensor wear and using CGM data to change diet/medication/insulin doses). To accommodate this breadth of representation, we will invite approximately 20-25 women to take part in the semi-structured interviews. Interviews will usually be scheduled at around 32-36 weeks' gestation, according to the participants convenience, including after birth if preferred. Interpreting will be offered to enable women to participate in other languages.

We will use the NIHR-INCLUDE Framework to achieve representation of underserved women. The topic guides will include themes relating to barriers and facilitators of CGM use, quality of the electronic, written and verbal information given by HCPs, quality of clinical interactions with HCP teams, extent of informal social support from partners, families, and support networks, impact of competing roles and responsibilities, T2D management strategies, stigma of living with overweight/obesity and EOT2D, psychological distress, and perceptions of medicalised pregnancy.

HCP focus group: We will conduct a focus group with HCPs from each NHS site to identify and describe HCP perceptions of the barriers and facilitators of CGM use. It will include topics on the learning from the study training programme, self-reported perception of skills, what they learned from problem solving and good practice sharing sessions and from patients and suggestions for what

further training and support would be needed for HCP teams and women with EOT2D if CGM use were to be rolled out in routine clinical care.

6.6.5 Early stopping of follow-up

If a participant chooses to discontinue their trial intervention, they should continue to be followed up as closely as possible to the follow-up schedule defined in the protocol, providing they are willing. They should be encouraged and facilitated not to leave the whole trial, even though they no longer use the allocated trial intervention. Should they choose to withdraw from the intervention only, they will be asked if would like to continue to provide outcome data (masked study CGM data / glucose data from other sources, delivery/neonatal/post-partum data and questionnaire data). If, however, the participant decides that they no longer wish to provide further data, we will respect her views and the participant withdrawn entirely from the trial. NCTU should be informed of the level of withdrawal via the study database. Data (and samples) already collected will be kept and included in analyses according to the intention-to-treat principle for all participants who stop follow up early.

The numbers of participants who stop trial follow-up early will be monitored across both arms.

6.6.6 Participant transfers

If a participant moves from the area making continued follow up at their consenting centre inappropriate, every effort should be made for them to be followed at another participating trial centre and / or remotely.

6.6.6.1 Transfer to another participating centre

Written consent should be taken at the new centre and then a copy of the participant's CRFs should be provided to the new centre. Responsibility for the participant remains with the original consenting centre until the new consent process is complete.

6.6.6.2 Transfer to a non-participating centre

Follow-up and data collection may continue remotely. CGM sensors may still be provided if this is in the best interests of the participant, and CGM data will continue to be collected remotely for the purposes of the trial. The original consenting centre should obtain outcome data from the new centre where possible. The participant's clinical care is the responsibility of the new centre.

6.6.6.3 Delivery at non-participating centres

Participants who deliver their babies at another centre or whose babies are in NICU at another centre should be followed up by the original consenting centre.

6.6.7 Loss to follow-up

Participants will be in contact with the clinical care team at 4-weekly intervals during the trial, or more frequently if clinically indicated.

6.6.8 Trial closure

The end of the trial is defined as 6 months following the last follow-up visit of the last patient, to allow for data entry and data cleaning activities to be completed.

6.7 Sample size

Assuming an anticipated neonatal care outcome incidence of 42.2% in the standard care group, based on national audit data (2, 5), a sample size of 422 would show a reduction from 42.2 to 26.0% at two-

sided 5% significance with 90% power and an assumed drop-out of 10%. An absolute reduction of 16.2% or odds ratio of 0.48 for neonatal unit admissions is based on our previous RCT data (28). The neonatal effect size in our earlier RCT (40) was higher (0.36)[40], so the most conservative estimate was chosen. A slightly smaller sample of 406 is required for the neonatal composite of neonatal admissions and death.

For the primary maternal outcome of CGM Time-in-Range (TIR) from 20 weeks until 38 weeks or delivery, 188 participants are required to detect a clinically relevant 10% increase from 60 to 70% TIR with 90% power. Using a sample size of 422 (380 analysable 14-day CGM profiles), provides 90% power to detect a CGM TIR difference of 6.65% which is deemed to be a clinically important difference. The expected maternal TIR outcome of 60% TIR (SD 20%) in the control group is based on limited EOT2D data (40-42).

The trial is powered on the neonatal unit admission outcome (involving separation of the newborn from their mother). A superiority analysis of the composite endpoint will be performed.

Table 1: Sample size estimations

Sample size								
Outcome	**Power**	**Significance**	**Control**	**Interven-tion**	**Difference**	**SD**	**Drop-outs**	**Total**
Neonatal care	90%	5% (2-sided)	42.2%	26.0%	OR 0.48 Absolute 16.2%	N/A	10%	422
Neonatal composite	90%	5% (2-sided)	48.8%	31.7%	OR 0.48 Absolute 17.2%	N/A	10%	406
CGM TIR*	90%	5% (2-sided)	60.0%	70.0%	10.0%	20%	10%	188

*A sample size of 422 provides 90% power to detect a CGM TIR difference of 6.6% which is clinically important

6.8 Assignment of intervention

6.8.1 Allocation

6.8.1.1 Sequence generation

Eligible participants will be randomised via a web-based randomisation system hosted by the Norwich Clinical Trials Unit (University of East Anglia (UEA)). Women will be allocated on a 1:1 basis to either the intervention arm (real time CGM) or control arm (routine clinical care). Randomisation is stratified by site.

6.8.1.2 Allocation concealment mechanism

The allocation is computer generated so will not be known prior to the participant being randomised. The patient will be allocated a participant number at time of consent. When all pre-designated questions have been completed in the CRF, the research staff will have access to the randomisation process for that participant. The treatment allocation will be revealed and linked to that participant number. Allocation is concealed prior to randomisation to prevent treatment bias.

6.8.1.3 Allocation implementation

Eligible participants will be randomised using central randomisation software using computer generated blocks of random sizes.

6.8.2 Blinding

This is an unblinded trial. Both participants and their clinical care team will be aware of the allocation.

6.9 Data collection, management and analysis

6.9.1 Data collection methods

Each participant will be given a unique trial Participant Identification Number (PID) at the recruitment visit. Data will be collected from this point at the time-points indicated in section 6.6.

The preferred method of data collection is direct online entry of data onto the central database, stored on servers based at NCTU, by members of the PROTECT trial team working within each research site. Data may be entered onto paper Case Record Forms (CRFs) prior to entry onto the database (but this is not an essential step). Staff will receive training on data collection and use of the online system.

Safety data and other data requiring expedited reporting will be reported directly to NCTU via email using supplied paper CRFs in accordance with section 7.

CGM data will be collected via web-based diabetes management software intended for use with the FreeStyle Libre CGM system (Abbott Diabetes Care, Inc.). Digital glucose data from non-study glucose monitoring systems may be collected in linked-anonymised form.

Data collection, data entry and queries raised will be conducted in line with the NCTU and trial specific Data Management Standard Operating Procedure.

Clinical trial team members will receive trial protocol training. All data will be handled in accordance with the General Data Protection Regulation (GDPR) (EU) 2016/679 and the Data Protection Act 2018.

6.10.2 Data management

Data will be entered under the participant's PID onto the central database stored on the servers based at NCTU. Access to the database will be via unique, individually assigned (i.e. not generic) usernames and passwords, and only accessible to members of the PROTECT trial team at NCTU, and external regulators if requested. The servers are protected by firewalls and are patched and maintained according to best practice. The physical location of the servers is protected physically and environmentally in accordance with University of East Anglia's General Information Security Policy 3 (GISP3: Physical and environmental security).

The database and associated code have been developed by NCTU Data Management, in conjunction with the PROTECT trial team. The database software provides a number of features to help maintain data quality, including maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests, and search facilities to identify validation failure/ missing data.

Data will be shared with the Jaeb Center for Health Research (JCHR) in accordance with a data sharing agreement, in order for them to carry out statistical analyses.

After completion of the trial the database will be retained on the servers of NCTU for on-going analysis of secondary outcomes. The database will be archived a minimum of one year after the publication of primary outcome.

Identification, screening and enrolment logs, linking participant identifiable data to the pseudoanonymised PID, will be held locally by the trial site. This will either be held in written form in a locked filing cabinet or electronically in password protected form on hospital computers. After completion of the trial the identification, screening and enrolment logs will be stored securely by the sites for 10 years unless otherwise advised by NCTU.

6.10.3 Non-adherence and non-retention

Every effort will be made to record the reasons for non-adherence (e.g. discontinuation of intervention due to harms or lack of efficacy) and non-retention (i.e. consent withdrawn; loss to follow up) as this information can influence the handling of missing data and interpretation of results.

6.10.4 Statistical methods

6.10.4.1 Primary outcome analysis

Maternal glucose:

The primary analysis will evaluate the change in the time spent in the target glucose range (CGM TIR 3.5-7.8 mmol/L) between the intervention and control arm between 20 weeks' gestation and 38 weeks or until delivery (if delivered earlier), based on 4 x 14-day CGM assessments, at 20-22, 28-30, 32-34 and 36-38 weeks. The median gestation of delivery in T2D pregnancy is 38 weeks. A linear mixed effects regression model will be fit with CGM TIR from 20 weeks' gestation until delivery as the dependent variable adjusting for baseline CGM TIR, and subject as random effects. A point estimate, 95% confidence interval and p-value will be reported for the treatment effect based on the linear regression model. Residual values will be examined for an approximate normal distribution. If values are highly skewed, then a transformation or robust statistical methods will be used instead.

Neonatal outcomes:

The primary neonatal outcome is a composite of neonatal unit admission or death in line with section 6.10.4.3.

6.10.4.2 Secondary outcome analyses

The same approaches as in 6.10.4.1 will be applied to secondary CGM metrics including:

- Mean CGM glucose
- Glucose management indicator (GMI)
- Time above range (TAR >6.7 & >7.8 mmol/L) and time below range (<3.5 & <3.0 mmol/L)

For all above mentioned secondary analyses, the false discovery rate will be controlled using an appropriate statistical procedure. Measures of glucose variability (SD and CV) have skewed distributions and will be compared between groups using a logarithmic transformation.

The analysis of HbA1c data will use the data collected at baseline, 28, 32 and 36 weeks in a longitudinal analysis over the entire study period. The planned linear mixed effects model will include baseline HbA1c as the dependent variable. This analysis focuses on whether the slope of change in HbA1c over the three follow-up time points is different between the treatment groups. The estimated correlation matrix between the intercept and slope of the random effects will be examined to assess whether larger rates of decreases in HbA1c are associated with higher initial values.

6.10.4.3 Dichotomous outcomes

For severe hypoglycaemia / hyperosmolar hyperglycaemic state (HHS) / DKA episodes, and rarer outcomes such as birth defect / stillbirth / neonatal deaths, proportions will be compared between treatment groups using Fisher's exact test. For any events which occur in at least 30 participants, logistic regression will be used to compare treatment groups and explore other factors contributing to obstetric and neonatal risks.

- Maternal target glucose attainment (HbA1c <43 mmol/mol, CGM time-in-range international consensus targets)
- Severe hypoglycaemia, hyperosmolar hyperglycaemic state, and diabetic ketoacidosis episodes
- Incident gestational hypertension or preeclampsia

- Pregnancy loss: miscarriage, congenital anomaly, stillbirth, neonatal death (death ≤28 days of life)
- Preterm birth (<37 weeks and early preterm <34 weeks)
- Birth injury (spinal cord injury, clavicular, skull or long bone fracture, shoulder dystocia, nerve palsy, subdural or intracerebral haemorrhage confirmed by computerized tomography (CT) or magnetic resonance imaging (MRI) scan, hypoxic ischaemic encephalopathy)
- Birth weight >90th centile using customized centiles
- Birth weight <10th centile using customized centiles
- Mode of delivery
- Infant feeding

6.10.4.4 Continuous outcomes

Linear regression will be used to compare treatment groups

- Maternal glucose outcomes (HbA1c, CGM mean glucose, TIR, TAR, GMI)
- Maternal gestational weight gain (from initial antenatal visit to 36 weeks' gestation)
- Neonatal gestational age at delivery
- Birth weight SDS

Time to event outcomes: Length of hospital stay for the mother and length of hospital stay for the baby will be compared between groups using a log-rank test.

6.10.4.5 Safety evaluation

Serious Adverse Events will be tabulated by treatment group and statistical tests performed as appropriate.

6.10.4.6 Patient Reported Outcome Measures (PROMS) evaluation

Except for the Glucose Monitoring Satisfaction Survey (applicable in late pregnancy after all participants have used SMBG or CGM), questionnaire scores will be available both at baseline and at follow-up for both groups. We will compare EQ-5D summary score between randomised groups using an analysis of covariance (ANCOVA) approach. The final EQ-5D score will be the outcome variable and the baseline EQ-5D score and treatment group the co-variates. The treatment group parameter in this model estimates the treatment effect. We will summarise scores from all other questionnaires by group and the analyses will primarily be descriptive.

6.10.4.7 Statistical analysis

A detailed statistical analysis plan (SAP) for the primary and secondary outcomes will be written and approved before database lock and commencement of data analyses. We will report data in line with the Consolidated Standards of Reporting Trials (CONSORT) statement showing attrition rates and loss to follow-up. Analyses will be conducted using the intention-to-treat principle, incorporating data from all participants according to randomised group. Every effort will be made to follow up participants for outcome assessments including those who withdraw from trial interventions.

Descriptive statistics within each randomised group will be presented for baseline values. These will include counts and percentages for binary and categorical variables, and means and standard deviations (SD), or medians with lower and upper quartiles (IQR), for continuous variables, along with minimum and maximum values and counts of missing values. There will be no tests of statistical significance or confidence intervals for differences between randomised groups on baseline variables.

Treatment effects on biomedical outcomes will be estimated using linear mixed models fitted to outcome variables, adjusted for individual baseline where available, and study site as a random factor to account for potential between site differences. Where variables are measured at multiple timepoints, mixed linear models will be used to utilize data at all time points. Treatment effect on the primary neonatal endpoint will be expressed as an odds ratio with 95% CI estimated from a logistic regression model. For the primary maternal endpoint, the comparison between the two treatment arms is based on a general mixed effects regression model. The two primary endpoints will be treated as fixed effects in mixed models.

6.10.4.8 Missing data

To handle missing maternal glucose data (HbA1c or CGM) on women who withdraw from the study, we will use a multiple imputation procedure, imputing missing values from a regression model that includes earlier HbA1c or CGM values. In a sensitivity analysis, we will use an imputation procedure that assumes the data are missing-not-at-random and impute values from either the low end or high end of the observed range.

6.10.5 Qualitative analyses

Reach will be assessed as participation and attrition bias. We will assess intervention uptake by CGM sensor usage.

The interview/focus group data will be analysed qualitatively using a thematic framework approach (55-57). These analyses will be conducted primarily by members of the qualitative research team. We will explore relationships between the patient reported outcomes (anxiety, depression, diabetes distress, glucose monitoring satisfaction), maternal glucose outcomes (CGM TIR, HbA1c) and participants engagement with CGM and antenatal care (CGM sensor usage, antenatal clinic visits).

Interview transcripts will be transcribed verbatim; transcripts that require translation will be back translated to ensure accuracy and quality. Patient and HCP data will be analysed and reported separately. Data will be managed in NVIVO v12™.

6.10.6 Within-trial economic analysis

A within-trial economic evaluation will be conducted, based on an NHS cost perspective with a 28-day horizon beyond birth. Resource use associated with both the CGM intervention and standard care will be measured (including diabetes treatment**,** nurse intervention, CGM sensor and reader device/phone, and SMBG meter, lancets, and test strips) along with maternal/baby hospital care e.g., antenatal visits, duration of hospitalization and neonatal care unit admission. We will collect data on outpatient consultations, medications, and maternal inpatient admissions and length of stay. All resource use data will be costed using national databases such as the National Schedule of Reference costs.

The primary outcome measure of the health economics analysis will be incremental cost per quality-adjusted life year (QALY). The health-related quality of life instrument EQ-5D-5L collected at baseline and 32 weeks' gestation will provide maternal utility values for the calculation of QALYs. The valuation of EQ-5D-5L responses will follow the latest guidance from NICE's manual for health technology evaluation. Additionally, costs will also be assessed in relation to the primary outcomes of maternal

glucose (costs per 5% increase in CGM TIR) and neonatal care admission or death (stillbirth/neonatal death).

A Health Economic Analysis Plan will be produced prior to the outcome analysis, where the incremental cost and incremental effect for trial outcomes associated the CGM intervention, compared to standard SMBG testing, will be estimated. To assess value for money, assuming dominance does not occur (where one option is more effective and less costly than the other option), the incremental cost-effectiveness ratio associated with the CGM intervention will be estimated for each outcome and assessed in relation to available cost-effectiveness thresholds e.g., £20,000-£30,000 per QALY 58. The associated level of uncertainty will also be characterised by using bootstrapping and by estimating the cost-effectiveness acceptability curve and by conducting sensitivity analysis.

The cost utility analysis comparing CGM with SMBG will be performed under the intention-to-treat principle. An NHS and personal social care perspective and a societal perspective will be adopted. If applicable, the results of the economic evaluation will also be presented using a cost-consequence analysis framework where the primary, selected secondary outcomes and costs from each trial arm will be presented in a disaggregated manner over the trial period.

We will report descriptive statistics for resource use, costs, and EQ-5D-5L utilities at each follow-up time point using complete data. We will estimate differences in cost and utilities between trial arms using mixed effects linear regression models to allow for multiple follow-ups clustered within participants. Missing data will be addressed using best practice in cost-effectiveness studies. We will undertake mean imputation of baseline data and multiple imputation of follow-up costs and of EQ-5D values, if appropriate after examining the patterns of missing data. We will use predictive mean matching to create a total number of imputed datasets as the proportion of data missing across all time periods.

Following multiple imputation, we will estimate the total costs and QALYs for each participant in the trial. On each imputed dataset, we will estimate incremental costs and QALYs using separate linear regression models controlling for treatment allocation and other variables. These estimates will be combined using Rubin's rule to produce the mean difference in costs and QALYs of CGM relative to SMBG. Incremental cost-effectiveness ratio (ICER) will be estimated by dividing the difference in costs by the difference in QALYs of CGM and SMBG with results depicted on the cost-effectiveness plane. This will be interpreted as the additional costs/savings associated to the additional QALY benefits from CGM compared to SMBG. The joint uncertainty around incremental costs and QALYs will be estimated using bootstrapping from each imputed dataset, running the estimation models and extracting the estimated treatment effects. This will allow capturing the correlation between the two treatment effects (on costs and QALYs) and estimate the probability of CGM being cost-effective at a maximum willingness to pay of £20,000 to £30,000 per QALY gained. This will be calculated by estimating the proportion of bootstrap replicates with a net monetary benefit (NMB) above 0 for each threshold value, where the NMB is obtained by the product of the mean difference in QALYs and the threshold value minus the mean difference in costs.

6.10.7 Analysis of tissue samples

Blood samples will be taken at 4 collection points (baseline, 28 weeks', 32 weeks' and 36 weeks' gestation) for local lab measurement of HbA1c levels.

In addition, a sample will be taken and transferred to the Norwich Biorepository for metabolic phenotyping (assessment of maternal baseline pancreatic function: C-peptide and islet cell antibodies).

A laboratory manual will be developed.

6.11 Data monitoring

6.11.1 Data Monitoring Committee

Further details of the roles and responsibilities of the Data Monitoring Committee (DMC), including membership, relationships with other committees, decision making processes, and the timing and frequency of interim analyses (and description of stopping rules and/or guidelines where applicable) are described in detail in the PROTECT DMC Terms of Reference (ToR).

6.11.2 Interim analyses

There will be no formal interim analyses however the following will be reviewed at the end of the internal pilot phase:

- CGM sensor usage (i.e. percentage time spent using CGM)
- Availability of CGM glucose data for the primary maternal outcome
- Event rate for the neonatal composite outcome

6.11.3 Data monitoring for harm

Adverse events will be collected as per section 7 and analysed according to the Statistical Analysis Plan. Serious Adverse Events (SAEs) by treatment group will be reviewed by the DMC as described in their terms of reference.

6.11.4 Quality assurance and control

6.11.4.1 Risk assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the PROTECT trial are based on the standard NCTU Quality Management Policy that includes a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the trial and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on: the rights and safety of participants; project concept including trial design, reliability of results and institutional risk; project management; and other considerations.

QA is defined as all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial related activities are fulfilled.

6.11.4.2 Central monitoring at NCTU

NCTU staff will review electronic Case Report Form (eCRF) data for errors and missing key data points. The trial database will also be programmed to generate reports on errors and error rates. Essential trial issues, events and outputs, including defined key data points, will be detailed in the trial Data Management Plan.

6.11.4.3 On-site monitoring

A risk-based monitoring approach will be adopted, and on-site monitoring is not expected to be undertaken unless central monitoring processes flag concerns. The frequency, type and intensity of triggered on-site monitoring will be detailed in the PROTECT Quality Management and Monitoring Plan (QMMP). The QMMP will also detail the procedures for review and sign-off of monitoring reports. In the event of a request for a trial site inspection by any regulatory authority, NCTU must be notified as soon as possible.

6.11.4.3.1 Direct access to participant records

Participating investigators must agree to allow trial related monitoring, including audits, REC review and regulatory inspections, by providing access to source data and other trial related documentation as required. Participant consent for this will obtained as part of the informed consent process for the trial.

6.11.4.4 Trial oversight

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harms; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in the compliance section of the protocol. Independent trial oversight complies with the NCTU trial oversight policy.

In multi-centre trials this oversight is considered and described both overall and for each recruiting centre by exploring the trial dataset or performing site visits as described in the PROTECT Quality Management and Monitoring Plan.

6.11.4.4.1 Trial Team

The Trial Team (TT) will be set up to assist with developing the design, coordination, and day to day operational issues in the management of the trial, including budget management. The Trial Team will comprise the CIs and UEA trial management team, who will meet 1-2 weekly..

6.11.4.4.2 Trial Management Group

A Trial Management Group (TMG) will be set up to assist with developing the design, coordination, and strategic management of the trial. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMG terms of reference.

6.11.4.4.3 Trial Steering Committee

The Trial Steering Committee (TSC) is the group responsible for oversight of the trial, in order to safeguard the interests of trial participants. The TSC provides advice to the CI, NCTU, the funder and sponsor on all aspects of the trial through its independent Chair. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TSC terms of reference.

6.11.4.4.4 Data Monitoring Committee

The Data Monitoring Committee (DMC) is the only oversight body that has access to unblinded accumulating comparative data. The DMC comprises independent members and is responsible for

safeguarding the interests of trial participants, monitoring the accumulating data, and making recommendations to the TSC on whether the trial should continue as planned. The membership, frequency of meetings, activity (including review of trial conduct and data) and authority will be covered in the DMC terms of reference. The DMC will consider data in accordance with the statistical analysis plan and will advise the TSC through its Chair.

6.11.4.4.5 Trial Sponsor

The UEA is the trial sponsor. The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage, and finance the trial. The Sponsor is responsible for ensuring that the study meets the relevant standards and makes sure that arrangements are put and kept in place for management, monitoring and reporting. The UEA has delegated some Sponsor's activities to the CI and NCTU, these are documented in the Sponsor's form for delegated activities.

7 Safety reporting

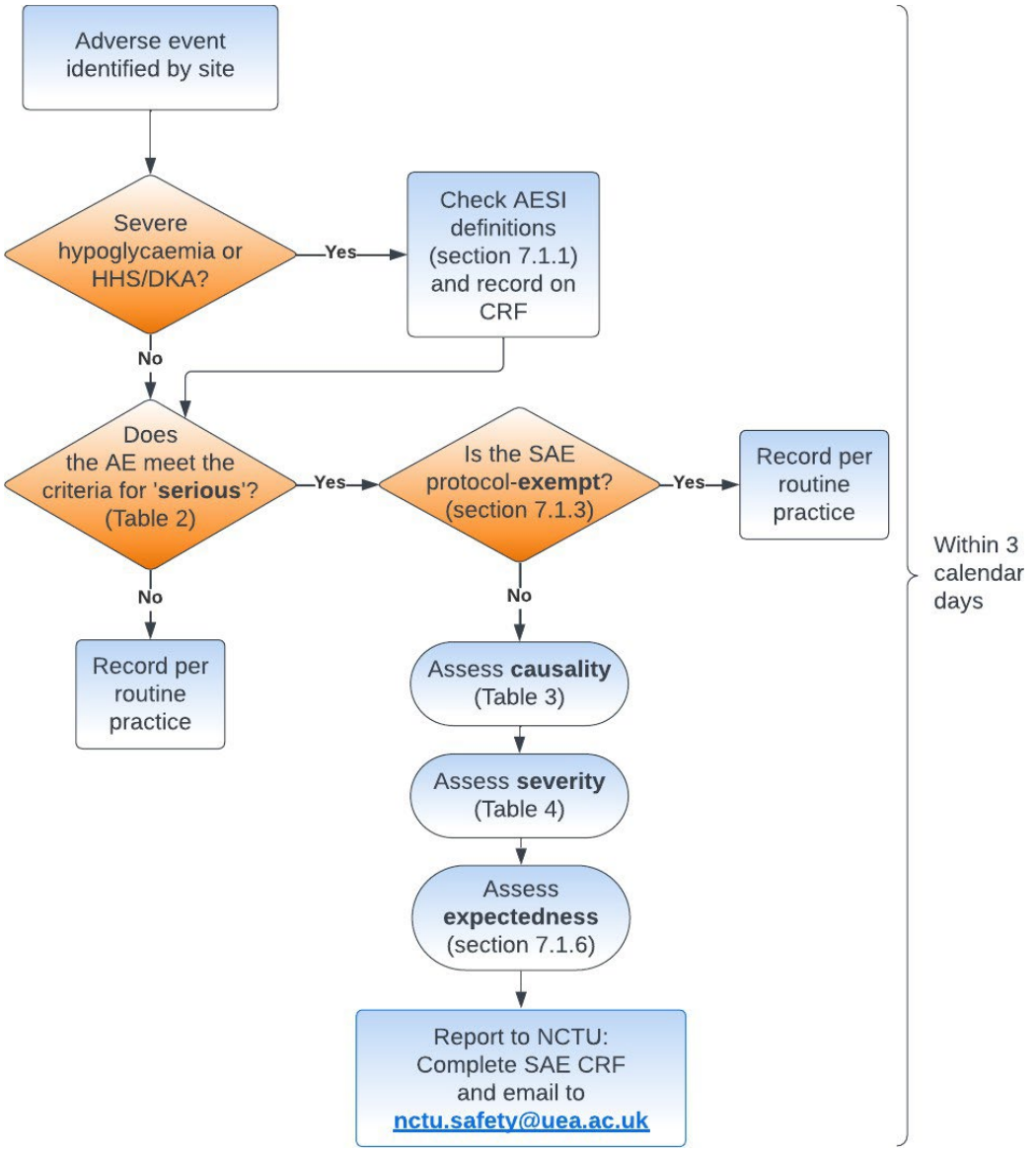
Definitions of the EU Directive 2001/20/EC Article 2 based on the principles of ICH GCP apply.

Table 2: Adverse event definitions

Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including an abnormal laboratory finding) in a participant, whether or not related to the intervention. This definition includes events related to the intervention, the comparator, and the study procedures.
Adverse events include: • *an exacerbation of a pre-existing illness* • *an increase in the frequency or intensity of a pre-existing episodic event or condition* • *a condition (regardless of whether present prior to the start of the trial) that is detected after trial procedures / intervention. (This does not include pre-existing conditions recorded as such at baseline)* • *continuous persistent disease or a symptom present at baseline that worsens following administration of the trial treatment* *Adverse events do NOT include:* • *Medical or surgical procedures: the condition that leads to the procedure is the adverse event* • *Pre-existing disease or a condition present before treatment that does not worsen* • *Hospitalization where no untoward or unintended response has occurred e.g., elective cosmetic surgery*	
Serious Adverse Event (SAE)	Any AE that: • results in death • is life threatening* • requires hospitalization or prolongs existing hospitalization** • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • is otherwise considered medically significant by the investigator
** 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* *** Hospitalization is defined as an in-patient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. Hospitalization for pre-existing conditions (including elective procedures that have not worsened) or planned hospitalization for a pre-existing condition or a procedure required by the protocol without serious deterioration in health do not constitute SAEs.*	

7.1 Investigator responsibilities relating to safety reporting

Participants will be reviewed for adverse events at all study visits. Non-serious AEs do *not* need to be reported to NCTU, however should be recorded per local policies. SAEs and Adverse Events of Special Interest (AESI), should be reported to NCTU in line with the below:



7.1.1 Adverse Events of Special Interest

The following Adverse Events of Special Interest (AESI) should be reported using the relevant eCRF:

Severe hypoglycaemia: An event requiring assistance of another person actively to administer carbohydrate, glucagon, or other resuscitative actions. Severe hypoglycaemia will be categorised as treated at home with rescue carbohydrates and/or glucagon, requiring ambulance or paramedic call out, and/or requiring hospital admission.

Hyperosmolar hyperglycaemic state (HHS) / Diabetic ketoacidosis (DKA): requiring hospital admission and treated with intravenous insulin infusion (as defined by the Joint British Diabetes Societies).

7.1.2 Seriousness assessment

When an AE occurs, the investigator responsible for the care of the participant must assess whether or not the event is 'serious' using the definition given in Table 2.

The following ARE considered Serious Adverse Events:

- Severe maternal hypoglycaemic event requiring paramedic assistance, emergency department assessment and/or hospital admission.
- Admissions with HHS/DKA requiring inpatient treatment with fixed or variable rate intravenous insulin infusion
- Maternal death
- Stillbirth / neonatal death
- Severe skin reaction requiring hospital admission
    - Note: Itchiness, redness, bleeding, and bruising at the insertion site may occur as well as local tape allergies. Only where a skin reaction is classified as potentially life-threatening and requiring hospital admission will a Serious Adverse Event Form be required to be completed.

7.1.3 Exempted Serious Adverse Events

The following are likely to be related to the underlying condition or disease or likely to represent concomitant illness and **will not be considered to be reportable as SAEs** in this study:

- Hospitalization for fetal monitoring during delivery, or hospitalization for delivery (including preterm delivery)
- Hospitalisation for unstable blood glucose/increased hypoglycaemia, and decreased insulin requirements, necessitating fetal monitoring and delivery.
- Hospitalization for maternal indications common to type 2 diabetes pregnancy:
    - Hypertensive disorders of pregnancy (gestational hypertension, worsening of pre-existing hypertension, preeclampsia)
    - Hyperemesis
    - Pregnancy loss: miscarriage or termination before 24 weeks
    - Severe adverse peripartum outcomes: abruption, post-partum haemorrhage, 3rd degree tears, postnatal readmission with wound complications
    - Other obstetric reason for admission unrelated to diabetes
    - Preterm labour or birth
    - Severe hypoglycaemia without paramedic call-out, emergency department assessment or hospital admission
    - Admission for hyperglycaemia or ketosis not requiring treatment with fixed or variable rate intravenous insulin infusion
- Infant outcomes known to type 2 diabetes pregnancy:
    - Birth injury
    - Congenital or chromosomal anomalies
    - Admission to neonatal unit
    - Neonatal hypoglycaemia (including hypoglycaemic seizures)
    - Hyperbilirubinemia
    - Respiratory distress
    - Shoulder dystocia

7.1.4 Causality

The investigator must assess the causality of all reportable serious adverse events in relation to the trial intervention or procedures using the definitions in Table 4.

Table 3: Causality definitions

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely to be related	There is little evidence to suggest that there is a causal relationship. There is another reasonable explanation for the event (e.g. the participant's clinical condition or other concomitant treatment)
Possibly related	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition or other concomitant treatment)
Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out

7.1.5 Severity of adverse events

The severity of all reportable SAEs should be graded using the following table:

Table 4: AE severity grading

Intensity	Definition
Mild	Participant is aware of signs and symptoms, but they are easily tolerated
Moderate	Signs / symptoms cause sufficient discomfort to interfere with usual activities
Severe	Participant is incapable of working or performing usual activities

NB. The term "severe" is often used to describe the intensity (severity) of a specific event. This is not the same as 'serious', which is based on patient/event outcome or action criteria (see definition in Table 2).

7.1.6 Expectedness

If there is at least a possible relatedness to the trial intervention or procedures, the Chief Investigator must assess the expectedness of the event. An unexpected event is one that is not reported in the protocol, or one that is more frequently reported or more severe than previously reported.

The following are 'expected' maternal events:

- Hypoglycaemia (including severe hypoglycaemia)
- Hyperglycaemia, ketosis, HHS, DKA

The following are 'expected' events in the infant:

- Birth injury
- Congenital or chromosomal anomalies
- Admission to neonatal unit
- Neonatal hypoglycaemia (including hypoglycaemic seizures)
- Hyperbilirubinemia
- Respiratory distress
- Shoulder dystocia

7.3 Notifications

7.3.1 Notifications by the Investigator to NCTU

If the event meets the criteria for 'serious' (Table 2) then a SAE form must be completed and forwarded to NCTU. This should be **immediately, and in no circumstances later than 3 calendar days** after the Investigator becomes aware of the event.

Investigators should notify NCTU of related SAEs occurring from consent until maternal post-partum hospital discharge. If the participant discontinues with the intervention, SAEs considered related to the intervention should still be reported.

The SAE form must be signed off by the Principal Investigator (PI) or other investigator with delegated responsibility, with attention paid to the severity and causality of the event. In the absence of the PI (or delegate), the SAE form should be completed and signed by a member of the site trial team and emailed as appropriate within the timeline. The PI/delegate should check the SAE form at the earliest opportunity, make any changes necessary, sign and then email to NCTU. Detailed written reports should be completed as appropriate. Systems will be in place at the site to enable the PI to check the form for clinical accuracy as soon as possible.

The minimum criteria required for reporting an SAE are the trial number and date of birth, name of reporting person and sufficient information on the event to confirm seriousness. Any further information regarding the event that is unavailable at the time of the first report should be sent as soon as it becomes available.

The SAE form must be scanned and sent by email to the NCTU central safety email account (nctu.safety@uea.ac.uk).

Participants must be followed up until clinical recovery is complete / laboratory results have returned to normal or baseline values, or until the event has stabilised. Follow-up should continue after completion of protocol intervention and/or trial follow-up if necessary. Follow-up SAE forms (clearly marked as follow-up) should be completed and emailed to NCTU as further information becomes available. Additional information and/or copies of test results etc. may be provided separately. The participant must be identified by trial number, date of birth and initials only. The participant's name should not be used on any correspondence and should be blacked out and replaced with trial identifiers on any test results.

7.3.2 Reporting procedures for SAEs

A Co-Chief Investigator (or a medically qualified delegate) will review all SAE reports received. In the event of disagreement between the causality assessment given by the local investigator and the Co-CI (or delegate), both opinions and any justifications will be provided in subsequent reports.

The delegated staff at NCTU will cross reference the SAE against expected events specified in the protocol to determine onward reporting requirements. This expectedness assessment will be reviewed and signed off by a Co-CI.

SAEs considered to be related to the CGM system will be reported to the manufacturer in line with the contract.

SAEs should be reported to the main REC within 15 days of the NCTU becoming aware if, in the opinion of the CI, the event was both:

- Related to the study – i.e., resulted from the administration of the CGM or trial procedures
- Unexpected – i.e., not listed in the protocol as an expected occurrence.

NCTU will keep investigators informed of any safety issues that arise during the course of the trial.

7.3.3 Other safety monitoring

7.3.3.1 Suicidal ideation or a risk of self-harm on a self-reported PHQ-9 Questionnaire

The eCRF will be designed to immediately flag the entry of data that indicates suicidal ideation or a risk of self-harm (defined as any participant scoring 1 ('several days') or above on item 9 of PHQ-9 ('How often in the past two weeks have you had thoughts that you would be better off dead or of hurting yourself in some way?).

In the event of the above, an email will be generated by the eCRF and sent to the PI and local site team.

The recruiting site should follow its standard local mental health procedures to ensure the safety and wellbeing of the participant is maintained.

8 Ethics and dissemination

8.1 Research Ethics and Health Research Authority approval

Before initiation of the trial at any clinical site, the protocol, all informed consent forms, and trial-specific material to be given to the prospective participant will be submitted to the relevant REC and to HRA for approval. 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 must be respected. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the participant. The reasons for doing so must be recorded. After randomisation, the participant must remain within the trial for the purpose of follow up and data analysis according to the treatment option to which they have been allocated. However, 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.

8.2 Other approvals

Documentation will need to be submitted to the R&D Department at each NHS Trust in order to gain confirmation of capacity and capability (for English sites) or local R&D approval (for non-English sites) prior to the study being initiated at that Trust.

A copy of the local capacity and capability / R&D approval must be forwarded to the NCTU, before participants are randomised to the trial.

The protocol has received formal approval and methodological, statistical, clinical and operational input from the NCTU Protocol Review Committee.

8.4 Amendments

Amendments to the protocol and other documents (e.g., changes to eligibility criteria, outcomes, sample size calculations, analyses) will be agreed by the CIs and / or TMG for more notable changes. Such amendments will be forwarded to the Sponsor for confirmation as to whether it is either substantial or non-substantial and will then be submitted to the Health Research Authority and Ethics Committee for categorisation and approval. Once the amendment has been categorised it will be sent to relevant sites for consideration in accordance with standard HRA processes and timescales. Amendments must not be implemented until HRA approval is received and sites have either confirmed acceptance or, no objection has been received within the defined timescale. Notification will be sent by NCTU to trial personnel to confirm when an amendment can be implemented.

8.5 Consent or assent

Patients will be provided with the patient information (paper or digital Patient Information Sheet (PIS)) and given time to read it fully. Following a discussion with a medical qualified investigator or suitable trained and authorised research team member, any questions will be satisfactorily answered and if the participant is willing to participate, written informed consent will be obtained. During the consent process, it will be made completely and unambiguously clear that the participant is 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.

Consent will be re-sought if new information becomes available that affects the participant's consent in any way. This will be documented in a revision to the patient information sheet and the participant will be asked to sign an updated consent form. These will be approved by the ethics committee prior to their use.

Consent will be taken (optional) for potential future metabolic and National Pregnancy in Diabetes (NPID) linkage studies.

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

8.5.1 Consent or assent in ancillary studies

Consent will be taken for potential metabolic and National Pregnancy in Diabetes (NPID) data linkage studies.

8.6 Confidentiality

Any paper copies of personal trial data will be kept at the participating site in a secure location with restricted access. This information will be securely destroyed 10 years after the end of the trial.

Confidentiality of patient's personal data is ensured by not collecting patient names on CRFs and limiting access to personal information held on the database. At trial enrolment, the patient will be issued a participant identification number and this will be the primary identifier for the patient, with secondary identifiers of date of birth and initials.

The patient's consent form will carry their name and signature. These will be kept at the trial site, with a copy uploaded to the study database for monitoring purposes. This copy will be deleted once checks are complete.

8.7 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.

8.8 Indemnity

The NHS indemnity scheme will apply to the potential liability of the sponsor for harm to participants arising from the management and conduct of the research. UEA holds insurance to cover harm to participants arising from the design of the study.

8.9 Finance

PROTECT is fully funded by an NIHR Health Technology Assessment (HTA) grant ID NIHR150958. Trial CGM devices are supplied free of charge from Abbott Diabetes Care, Inc.

8.10 Archiving

The investigators agree to archive and/or arrange for secure storage of PROTECT trial materials and records for 10 years after the close of the trial unless otherwise advised by the NCTU.

8.11 Access to data

Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TMG/TSC. Considerations for approving access are documented in the TMG/TSC Terms of Reference.

8.12 Ancillary and post-trial care

Devices will be provided to the participants for the duration of the trial. Post-trial care is at the discretion of the woman and her treating clinical team.

8.13 Publication policy

8.13.1 Trial results

Data will be published in internationally peer-reviewed scientific journals; members of the investigator group and clinical collaborators will be included as co-authors as appropriate.

The results of the trial will be disseminated regardless of the direction of effect.

8.13.2 Authorship

Authorship will be determined by a publication policy which will be agreed by the TMG.

8.13.3 Reproducible research

The trial will be registered on the ISRCTN website, granting public access to the trial outcomes. In addition, the clinical study protocol will be submitted for publication. Every effort will be made to grant access to the participant-level dataset subject to TSC approval.

9 Outcome definitions

Early onset type 2 diabetes: T2D diagnosed before 39 years of age.

Booking appointment: first antenatal visit following confirmation of pregnancy.

Birth injury: includes spinal cord injury, clavicular fracture, basal skull fracture, depressed skull fracture, long bone fracture (humerus, radius, ulna, femur, tibia or fibula), shoulder dystocia, peripheral nerve / brachial plexus injury, subdural or intracerebral haemorrhage confirmed by computerized tomography (CT) or magnetic resonance imaging (MRI) scan, hypoxic ischaemic encephalopathy.

Neonatal hyperbilirubinemia: Significant jaundice based on bilirubin levels requiring treatment with either phototherapy, or an exchange transfusion, or receiving intravenous gamma globulin or requiring readmission into hospital during the first 7 days of life due to hyperbilirubinemia.

Neonatal hypoglycaemia: A capillary glucose <2.2mmol/L on one or more occasions, within the first 48 hours after delivery starting at least 30 minutes after birth and necessitating treatment either with 40% glucose gel administered to the buccal mucosa and/or with intravenous glucose.

Respiratory distress: Respiratory difficulties requiring supplemental oxygen and/or any positive pressure ventilation, beyond resuscitation period (10 minutes), and /or given surfactant within 72 hours after birth.

Levels of neonatal care based on BAPM 2011 Categories of Care:

- **Transitional care** is provided in some units, where the mother is resident with her baby and providing care with minimal support from a midwife/healthcare professional. E.g., low birth-weight babies, babies receiving antibiotics or phototherapy.
- **Special Care** is for babies who require additional care but do not require either Intensive or High Dependency care. E.g., oxygen by nasal cannula, feeding by nasogastric, jejunal tube or gastrostomy, continuous physiological monitoring (excluding apnoea monitors only), care of a stoma, presence of IV cannula, baby receiving phototherapy, special observation of physiological variables at least 4 hourly
- **High Dependency Care** is for babies who require highly skilled staff but where the ratio of nurse to patient is less than intensive care. E.g., requiring non-invasive respiratory support (e.g., nasal CPAP, SIPAP, BIPAP, HHFNC); parenteral nutrition; continuous infusion of drugs (except prostaglandin &/or insulin); presence of a central venous or long line (PICC); presence of a tracheostomy; presence of a urethral or suprapubic catheter, presence of trans-anastomotic tube following oesophageal atresia repair, presence of NP airway/nasal stent, observation of seizures / CF monitoring, barrier nursing, ventricular tap.
- **Intensive Care** is for the most unwell babies, typically those delivered preterm and/or needing respiratory support, or other high-level care.

Preterm birth: Preterm birth (<37 weeks and early preterm <34 weeks).

Shoulder dystocia: Defined as a vaginal cephalic delivery that requires additional obstetric manoeuvres to deliver the fetus after the head has delivered and gentle traction has failed (https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg42/).

Hyperglycaemia: high blood sugar (glucose level).

Hyperosmolar hyperglycaemic state: hyperglycaemia ≥30 mmol/L, hyperosmolality (effective serum osmolality usually ≥320 mOsm/kg), and volume depletion in the absence of significant ketoacidosis.

Hypoglycaemia: low blood sugar (glucose level).

Severe hypoglycaemia: An event requiring assistance of another person actively to administer carbohydrate, glucagon, or other resuscitative actions. Severe hypoglycaemia will be categorised as treated at home with rescue carbohydrates and/or glucagon, requiring ambulance or paramedic call out, requiring hospital admission.

Diabetic ketoacidosis (DKA): requiring hospital admission and treated with intravenous insulin infusion (as defined by the Joint British Diabetes Societies)

Maternal hypertensive disorders: includes gestational hypertension, worsening of pre-existing hypertension, and/or preeclampsia defined as:

- Gestational hypertension: Systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on at least two occasions four hours apart, developing after 20 weeks of gestation in previously normotensive women.
- Pre-eclampsia: Hypertension accompanied by proteinuria ≥300 mg in 24 hours, or two readings of at least ++ on dipstick analysis of urine or documentation of pre-eclampsia in the delivery or antenatal records.
- Preeclampsia superimposed on chronic hypertension: Preeclampsia (as defined above) developing after 20 weeks of gestation in women with known chronic hypertension (history of hypertension before conception or the presence of hypertension at the booking visit before 20 weeks' gestation in the absence of trophoblastic disease).

10 References

1. Today Study Group, Bjornstad P, Drews KL, Caprio S, Gubitosi-Klug R, Nathan DM, et al. Long-Term Complications in Youth-Onset Type 2 Diabetes. N Engl J Med. 2021;385(5):416-26.
2. Murphy HR, Howgate C, O'Keefe J, Myers J, Morgan M, Coleman MA, et al. Characteristics and outcomes of pregnant women with type 1 or type 2 diabetes: a 5-year national population-based cohort study. Lancet Diabetes Endocrinol. 2021;9(3):153-64.
3. Murphy HR, Bell R, Cartwright C, Curnow P, Maresh M, Morgan M, et al. Improved pregnancy outcomes in women with type 1 and type 2 diabetes but substantial clinic-to-clinic variations: a prospective nationwide study. Diabetologia. 2017;60(9):1668-77.
4. Mackin ST, Nelson SM, Kerssens JJ, Wood R, Wild S, Colhoun HM, et al. Diabetes and pregnancy: national trends over a 15 year period. Diabetologia. 2018;May;61(5):1081-8.
5. National Pregnancy in Diabetes (NPID) Audit Report 2020. https://digitalnhsuk/data-and-information/publications/statistical/national-pregnancy-in-diabetes-audit/2019-and-2020. 2021;United Kingdom.
6. Macintosh MC, Fleming KM, Bailey JA, Doyle P, Modder J, Acolet D, et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. Bmj. 2006;333(7560):177.
7. Vounzoulaki E, Khunti K, Abner SC, Tan BK, Davies MJ, Gillies CL. Progression to type 2 diabetes in women with a known history of gestational diabetes: systematic review and meta-analysis. BMJ. 2020;369:m1361.
8. Saravanan P, Diabetes in Pregnancy Working G, Maternal Medicine Clinical Study G, Royal College of O, Gynaecologists UK. Gestational diabetes: opportunities for improving maternal and child health. Lancet Diabetes Endocrinol. 2020;8(9):793-800.
9. Ockenden D. Findings, conclusions and essential actions from the independent review of maternity services and the Shrewsbury and Telford Hospital NHS Trust. 2022. https://assetspublishingservicegovuk/government/uploads/system/uploads/attachment_data/file/1064302/Final-Ockenden-Report-web-accessiblepdf. 2022.
10. Ayman G, Strachan JA, McLennan N, Malouf R, Lowe-Zinola J, Magdi F, et al. The top 10 research priorities in diabetes and pregnancy according to women, support networks and healthcare professionals. Diabet Med. 2021;38(8):e14588.
11. Knight M, Stanford S. Ockenden: another shocking review of maternity services. BMJ. 2022;377:o898.
12. Sibley M. Ockenden report: the refusal of our healthcare service to take patient experience seriously. BMJ. 2022;377:o875.
13. Yamamoto JM, Murphy HR. Treating to Target Glycaemia in Type 2 Diabetes Pregnancy. Curr Diabetes Rev. 2022.
14. Murphy HR, Feig DS, Sanchez JJ, de Portu S, Sale A, Group CC. Modelling potential cost savings from use of real-time continuous glucose monitoring in pregnant women with Type 1 diabetes. Diabet Med. 2019;36(12):1652-8.
15. Ahmed RJ, Gafni A, Hutton EK, Hu ZJ, Sanchez JJ, Murphy HR, et al. The cost implications of continuous glucose monitoring in pregnant women with type 1 diabetes in 3 Canadian provinces: a posthoc cost analysis of the CONCEPTT trial. CMAJ Open. 2021;9(2):E627-E34.
16. Murphy HR, Moses RG. Pregnancy Outcomes of Young Women With Type 2 Diabetes: Poor Care and Inadequate Attention to Glycemia. Diabetes Care. 2022;45(5):1046-8.
17. Farrington C. Wearable technologies and stigma in diabetes: the role of medical aesthetics. Lancet Diabetes Endocrinol. 2016;4(7):566.
18. Scott EM, Bilous RW, Kautzky-Willer A. Accuracy, User Acceptability, and Safety Evaluation for the FreeStyle Libre Flash Glucose Monitoring System When Used by Pregnant Women with Diabetes. Diabetes Technol Ther. 2018;20(3):180-8.

19. Scott EM, Feig DS, Murphy HR, Law GR, Group CC. Continuous Glucose Monitoring in Pregnancy: Importance of Analyzing Temporal Profiles to Understand Clinical Outcomes. Diabetes Care. 2020;43(6):1178-84.
20. Law GR, Ellison GT, Secher AL, Damm P, Mathiesen ER, Temple R, et al. Analysis of Continuous Glucose Monitoring in Pregnant Women With Diabetes: Distinct Temporal Patterns of Glucose Associated With Large-for-Gestational-Age Infants. Diabetes Care. 2015.
21. Ehrhardt N, Al Zaghal E. Continuous Glucose Monitoring As a Behavior Modification Tool. Clin Diabetes. 2020;38(2):126-31.
22. Yamamoto JM, Murphy HR. Benefits of Real-Time Continuous Glucose Monitoring in Pregnancy. Diabetes Technol Ther. 2021;23(S1):S8-S14.
23. Murphy HR. Continuous glucose monitoring targets in type 1 diabetes pregnancy: every 5% time in range matters. Diabetologia. 2019;62(7):1123-8.
24. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care. 2017;40(12):1631-40.
25. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care. 2019;42(8):1593-603.
26. Murphy HR, Rayman G, Duffield K, Lewis KS, Kelly S, Johal B, et al. Changes in the glycemic profiles of women with type 1 and type 2 diabetes during pregnancy. Diabetes Care. 2007;30(11):2785-91.
27. Goudie RJ, Lunn D, Hovorka R, Murphy HR. Pharmacokinetics of insulin aspart in pregnant women with type 1 diabetes: every day is different. Diabetes Care. 2014;37(6):e121-2.
28. Feig DS, Donovan LE, Corcoy R, Murphy KE, Amiel SA, Hunt KF, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet. 2017;390(10110):2347-59.
29. Murphy HR. 2020 NICE guideline update: Good news for pregnant women with type 1 diabetes and past or current gestational diabetes. Diabet Med. 2021;38(6):e14576.
30. Murphy HR. Managing Diabetes in Pregnancy Before, During, and After COVID-19. Diabetes Technol Ther. 2020;22(6):454-61.
31. Roland JM, Murphy HR, Ball V, Northcote-Wright J, Temple RC. The pregnancies of women with Type 2 diabetes: poor outcomes but opportunities for improvement. Diabet Med. 2005;22(12):1774-7.
32. Clausen TD, Mathiesen E, Ekbom P, Hellmuth E, Mandrup-Poulsen T, Damm P. Poor pregnancy outcome in women with type 2 diabetes. Diabetes Care. 2005;28(2):323-8.
33. Murphy HR, Temple RC, Ball VE, Roland JM, Steel S, Zill EHR, et al. Personal experiences of women with diabetes who do not attend pre-pregnancy care. Diabet Med. 2010;27(1):92-100.
34. Lee TTM, Collett C, Man MS, Hammond M, Shepstone L, Hartnell S, et al. AiDAPT: automated insulin delivery amongst pregnant women with type 1 diabetes: a multicentre randomized controlled trial - study protocol. BMC Pregnancy Childbirth. 2022;22(1):282.
35. Asbjornsdottir B, Vestgaard M, Do NC, Ringholm L, Andersen LLT, Jensen DM, et al. Prevalence of anxiety and depression symptoms in pregnant women with type 2 diabetes and the impact on glycaemic control. Diabet Med. 2021;38(3):e14506.
36. Martens T, Beck RW, Bailey R, Ruedy KJ, Calhoun P, Peters AL, et al. Effect of Continuous Glucose Monitoring on Glycemic Control in Patients With Type 2 Diabetes Treated With Basal Insulin: A Randomized Clinical Trial. JAMA. 2021;325(22):2262-72.
37. Beck RW, Riddlesworth TD, Ruedy K, Ahmann A, Haller S, Kruger D, et al. Continuous Glucose Monitoring Versus Usual Care in Patients With Type 2 Diabetes Receiving Multiple Daily Insulin Injections: A Randomized Trial. Ann Intern Med. 2017;167(6):365-74.
38. Karter AJ, Parker MM, Moffet HH, Gilliam LK, Dlott R. Association of Real-time Continuous Glucose Monitoring With Glycemic Control and Acute Metabolic Events Among Patients With Insulin-Treated Diabetes. JAMA. 2021;325(22):2273-84.

39. Jones LV, Ray A, Moy FM, Buckley BS. Techniques of monitoring blood glucose during pregnancy for women with pre-existing diabetes. Cochrane Database Syst Rev. 2019;5:CD009613.
40. Murphy HR, Rayman G, Lewis K, Kelly S, Johal B, Duffield K, et al. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: randomised clinical trial. Bmj. 2008;337:a1680.
41. Secher AL, Ringholm L, Andersen HU, Damm P, Mathiesen ER. The Effect of Real-Time Continuous Glucose Monitoring in Pregnant Women With Diabetes: A randomized controlled trial. Diabetes Care. 2013;36(7):1877-83.
42. Voormolen DN, DeVries JH, Sanson RME, Heringa MP, de Valk HW, Kok M, et al. Continuous glucose monitoring during diabetic pregnancy (GlucoMOMS): A multicentre randomized controlled trial. Diabetes Obes Metab. 2018;20(8):1894-902.
43. Sargeant JA, Brady EM, Zaccardi F, Tippins F, Webb DR, Aroda VR, et al. Adults with early-onset type 2 diabetes (aged 18-39 years) are severely underrepresented in diabetes clinical research trials. Diabetologia. 2020;63(8):1516-20.
44. Feig DS, Donovan LE, Zinman B, Sanchez JJ, Asztalos E, Ryan EA, et al. Metformin in women with type 2 diabetes in pregnancy (MiTy): a multicentre, international, randomised, placebo-controlled trial. Lancet Diabetes Endocrinol. 2020;8(10):834-44.
45. Polonsky WH, Fisher L, Earles J, Dudl RJ, Lees J, Mullan J, et al. Assessing psychosocial distress in diabetes: development of the diabetes distress scale. Diabetes Care. 2005;28(3):626-31.
46. Polonsky WH, Fisher L, Hessler D, Edelman SV. Development of a New Measure for Assessing Glucose Monitoring Device-Related Treatment Satisfaction and Quality of Life. Diabetes Technol Ther. 2015;17(9):657-63.
47. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606-13.
48. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166(10):1092-7.
49. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. BMJ. 1998;316(7133):736-41.

11 Amendments to protocol

V1.0 to V2.0; 7th December 2023

1. Severe visual impairment removed from exclusion criteria. This will be left to Investigator discretion as to appropriateness of the devices.
2. Contact updates. Deletion of Sponsor contact from protocol signature page as not required by Sponsor.
3. Clarification that control arm standard of care is finger-prick glucose testing.
4. Clarification that Freestyle Libre Pro (or equivalent sensors) will be used in the control arm.
5. Minor typographical corrections throughout.
6. Data will be shared with the Jaeb Center for Health Research (JCHR) in accordance with a data sharing agreement, in order for them to carry out statistical analyses on CGM data.
7. Clarification that consent forms will be uploaded to the study database for central review.

V2.0 to V3.0; 19th February 2025

1. Inclusion criteria simplified to ensure participants aren't excluded for arbitrary reasons. Participants may be entered providing they have a confirmed pregnancy, HbA1c ≥43 mmol/mol confirmed prior to randomisation, and enough time and opportunity to collect 4-days (aiming for 96 hours) of baseline CGM data prior to randomisation by 16 weeks gestation.
2. Contact updates: Sponsor contact, Trial Statisticians, TMG.
3. Clarification that the participant may be consented on the same day as being given the trial information to minimise participant burden (as approved in the original IRAS application).
4. Qualitative interviews will be carried out once, without requiring baseline and follow-up assessments to minimise participant burden. Interviews will be scheduled according to participants convenience, usually during late pregnancy, but can be performed in the early post-partum phase (0-12 weeks).
5. Bloods for metabolic phenotyping may be taken at the recruitment visit, or at any time up to 36 weeks' gestation.
6. Clarity added around transfers. Where a participant moves to a non-participating centre, trial follow up will continue remotely. To ensure that the participant is not disadvantaged or put at risk, CGM sensors can continue to be provided.
7. DTN training website links updated.
8. SAE exemption added for clarity, where hospitalisation is for fetal monitoring / delivery, as a result of increased hypoglycaemia / decreasing insulin requirements.
9. Clarification that randomisation is stratified by site.
10. Removal of reference to Trial Team Terms of Reference.
11. Corrected parameters for secondary CGM analyses from ≥6.7, ≥7.8, ≤3.5, and ≤3.0 mmol/L to >6.7, >7.8, <3.5, and <3.0 mmol/L.