
PROTECT: PRegnancy Outcomes using continuous glucose monitoring TEChnology in pregnant women with early-onset Type 2 diabetes: a multicentre randomised controlled trial – study protocol

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Tara T.M. Lee, Corinne Collett, Miranda Hayes, Matthew Hammond, Adam Wagner, Lee Shepstone, Jenny Myers, Madeleine Benton, Khalida Ismail, Shivani Misra, Neena Modi, Amanda Adler, Stephanie Stoway, Peter Calhoun, Robin Gal, Eleanor M. Scott & Helen R. Murphy

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Title: PROTECT: PRegnancy **O**utcomes using continuous glucose monitoring **TE**chnology in pregnant women with early-onset **T**ype 2 diabetes: A multicentre randomised controlled trial – study protocol

^{1,2}Tara T.M. Lee, ³Corinne Collett, ³Miranda Hayes, ³Matthew Hammond, ³Adam Wagner, ³Lee Shepstone, ⁴Jenny Myers, ⁵Madeleine Benton, ⁵Khalida Ismail, ⁶Shivani Misra, ⁶Neena Modi, ⁷Amanda Adler, ⁸Stephanie Stoway, ⁸Peter Calhoun, ⁸Robin Gal, ⁹Eleanor M. Scott[□] and ^{1,2}Helen R. Murphy[□]

[□]contributed equally

Corresponding author: Helen. R Murphy, helen.murphy@uea.ac.uk, Norwich Medical School, Floor 2, Bob Champion Research and Education Building, Rosalind Franklin Road, University of East Anglia, Norwich Research Park, Norwich, UK.

Authors' information: ¹Norwich Medical School, University of East Anglia, Norwich, UK. ²Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK. ³Norwich Clinical Trials Unit, Norwich Medical School, University of East Anglia, Norwich, UK. ⁴Maternal and Fetal Health Research Centre, University of Manchester, Manchester, UK. ⁵Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK. ⁶Imperial College London, London, UK. ⁷Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK, ⁸Jaeb Center for Health Research, Tampa, Florida, USA. ⁹Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK.

Abstract

Background: Early-onset type 2 diabetes (EOT2D), meaning type 2 diabetes diagnosed before the age of 40 disproportionately affects women from socially deprived and minority ethnic groups. EOT2D is now the most common form of pre-existing diabetes complicating pregnancy. These pregnancies carry high risks of congenital anomalies, stillbirth, neonatal death, and of both maternal and neonatal morbidity. Maternal glycaemia is the key modifiable risk factor yet remains suboptimal and is often accompanied by limited self-monitoring of blood glucose (SMBG). Continuous Glucose Monitoring (CGM) offers continuous real-time glucose

profiles, potentially enabling better dietary, lifestyle and therapy adjustments.

Methods / design: The PROTECT trial is a multicentre, randomised controlled trial designed to evaluate whether CGM improves maternal glucose and neonatal outcomes in women with EOT2D. The trial will recruit 422 pregnant participants (≤ 16 weeks 0 days' gestation, $\text{HbA1c} \geq 43$ mmol/mol) from around 20 UK NHS antenatal diabetes clinics. After a run-in phase with masked CGM, participants will be randomised to either real-time CGM (FreeStyle Libre 3) or standard SMBG. The primary maternal outcome is percentage of time in pregnancy-specific glucose target range (3.5–7.8 mmol/L). The primary neonatal outcome is a composite of neonatal care unit admission or death. Secondary outcomes include maternal HbA1c, glycaemic variability, insulin use, obstetric complications, neonatal morbidity, psychosocial measures, and cost-effectiveness. An internal pilot will assess recruitment feasibility, before proceeding to the full trial. Qualitative interviews with women and healthcare professionals will explore barriers and facilitators to CGM use. Statistical analyses will follow intention-to-treat principles.

Discussion: This is the largest trial to date investigating CGM in EOT2D pregnancy, aiming to generate robust evidence on clinical efficacy, lived experiences, and economic impact, informing future NHS policy and practice.

Trial registration: ISRCTN12804317 Registration Date: 23/10/2023

Background

Early-onset type 2 diabetes (EOT2D) diagnosed before 40 years of age, is more prevalent in women, those living in lower-income communities, and minority ethnic groups. Those living with EOT2D have the highest risk of developing diabetes-related complications and co-morbidities such as hypertension and hyperlipidaemia [1–3]. The prevalence of this condition is increasing, with a doubling in the proportion of pregnancies affected over the past 15–20 years [4–7]. It now the commonest form of pre-existing

diabetes diagnosed before pregnancy, accounting for 60% of diabetes pregnancies in the United Kingdom (UK), compared to 27% in 2002-03 [7, 8]. As up to 50% of women with gestational diabetes mellitus (GDM) will develop EOT2D within five years of a GDM pregnancy, the prevalence of EOT2D during pregnancy is expected to increase [9]. National pregnancy audit data highlights the striking healthcare inequalities faced by women with EOT2D in pregnancy: 90% are overweight or obese and 60% are from Asian, Black or mixed ethnic groups [4, 5, 7, 8]. Furthermore, there are seven times more EOT2D pregnancies in women from the most socially deprived communities [7].

EOT2D pregnancies are associated with an increased risk of obstetric and neonatal complications, including maternal hypertensive disorders, anxiety and depression, serious adverse pregnancy outcomes (congenital anomalies, stillbirth, neonatal death) as well as substantial neonatal morbidity (preterm birth, large and small birthweight babies, neonatal care unit admissions) [4-8]. During 2020-24, the rates of serious adverse pregnancy outcomes were 5.3%, with substantial neonatal morbidity (preterm births 24.8%, large and small for gestational age babies 25.4 and 15.2% respectively, neonatal care unit admissions 31.2%) [4, 7, 10, 11]. Maternal glycaemia is the key modifiable risk factor, with a three times higher odds ratio for neonatal morbidity and mortality where maternal HbA1c $\geq 43\text{mmol/mol}$ (6.1%) after 24 weeks' gestation [7].

Management of maternal glycaemia in EOT2D includes escalation of glucose lowering therapy with dietary advice, followed by metformin and then insulin, with doses titrated according to results from 4-7 daily "finger-prick" self-monitored blood glucose (SMBG) tests. However, finger-prick SMBG tests give only limited snapshots of glycaemia at the time of testing with little information of glucose excursions between tests. Continuous glucose monitoring (CGM) technology measures interstitial glucose levels every one to five minutes (up to around 1,440 measurements a day) and sends these readings to a display device, most typically the user's

smartphone. In doing so, CGM provides a more detailed picture of real-time glycaemia across the 24-hour day, which can help to inform food choices and exercise behaviours, contributing to a healthier lifestyle [12, 13].

Use of diabetes technologies in pregnancy was identified as a top-priority research question by patients and healthcare teams who contributed to the Diabetes Pregnancy James Lind Alliance Priority Setting Partnership [14]. The CONCEPTT trial demonstrated that CGM use in type 1 diabetes (T1D) pregnancy was associated with improved maternal glycaemia, with fewer neonatal complications of large for gestational age and neonatal intensive care admissions [15]. This led to changes in the NICE guidelines which recommend CGM as standard care in T1D pregnancies [16, 17]. Due to the stark differences in the patient characteristics and specialist diabetes care between women with T1D and EOT2D, we cannot extrapolate the benefits of CGM use from T1D to EOT2D pregnancy. Women with EOT2D receive comparatively very little diabetes support and are less likely to use insulin or monitor their glucose levels with CGM [18, 19].

Trials outside pregnancy comparing CGM to finger-prick SMBG in older-aged adults with T2D demonstrate consistent improvements in glucose levels independent of CGM device or diabetes treatment, which is consistent with our CONCEPTT findings in T1D pregnancy [13, 20, 21]. However, high-quality evidence regarding CGM use in those with EOT2D during pregnancy is lacking. A 2023 systematic review and meta-analysis identified only three small studies which included women with EOT2D, from the UK, Denmark and the Netherlands respectively [22]. With limited sample sizes, these studies and the systematic review lacked statistical power to evaluate the clinical effectiveness of CGM in EOT2D pregnancy [23-25].

The PROTECT trial aims to evaluate whether the use of real-time CGM can improve maternal glucose and reduce rates of serious neonatal morbidity and mortality compared to finger-prick SMBG in EOT2D pregnancy. It will include a nested qualitative study to explore barriers and facilitators to

CGM use and identify any variations by socio-demographic factors. The trial was designed in partnership with women with EOT2D, patient and public involvement (PPI) partners, NHS commissioners, healthcare teams working in maternity, neonatology, diabetes and mental health, as well as statisticians, health economists and clinical trialists.

For the purpose of this protocol and paper, whilst we refer to pregnant women throughout, the study is inclusive of non-binary, gender-fluid, or any other pregnant persons [26].

Methods / Design

Overall trial design

PROTECT is a multicentre, randomised, open-label, two-arm parallel group trial comparing CGM and finger-prick SMBG for pregnant women with type 2 diabetes.

Pregnant women with EOT2D who are ≤ 16 weeks and 0 days' gestation with a HbA1c of ≥ 43 mmol/mol ($\geq 6.1\%$) will be recruited via antenatal diabetes clinics from around 20 NHS Trusts across the UK. Trusts will be selected for their diverse patient populations. Participants will undergo a run-in phase of masked CGM (FreeStyle Libre3) to collect baseline data and ensure tolerance to the study devices. Participants with > 72 hours of baseline CGM data will be randomised on a 1:1 basis to the intervention CGM group (FreeStyle Libre3) or continue with finger-prick SMBG (control group). The primary maternal outcome is the percentage time spent with maternal glucose levels within the pregnancy target range (3.5-7.8 mmol/L), as recorded by CGM, from 20 until 38 weeks' gestation, or until delivery, if delivery is earlier than 38 weeks' gestation. The primary neonatal outcome is a composite outcome of neonatal care unit admission (reflecting clinically relevant neonatal morbidity), or death (stillbirth or neonatal death).

Internal pilot

An internal pilot will recruit 142 women over 12 months to address the feasibility of recruitment and retention of pregnant women from geographically representative sites, and their willingness to use finger-prick

SMBG or CGM. The Trial Management Group (TMG) together with PPI will review progress and report to the Data Monitoring Committee (DMC) and Trial Steering Committee (TSC). At the end of the 12-month internal pilot period, the trial will proceed to the full randomised controlled trial, subject to satisfactory progress.

Primary research questions

What is the clinical and cost-effectiveness of using CGM compared with finger-prick SMBG, for improving both maternal glucose and neonatal health outcomes in pregnant women with EOT2D?

Eligibility criteria

Participants are eligible if they fulfil the following inclusion criteria:

1. Type 2 diabetes
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. Chronic kidney disease grade 4 or 5 (GFR < 30 ml/min)

Recruitment

Potential participants will be provided with paper or digital study materials or both and invited to consider joining the trial. They will usually have 24 hours or more to consider taking part, however due to the low-risk nature of the intervention, and to minimise participant travel burden, the participant

may be consented at the initial contact. Written informed consent can be obtained until 15 weeks 3 days' gestation as determined by dating ultrasound scan.

Baseline data including basic socio-demographic data, past medical history and current diabetes management will be collected. A brief physical examination (blood pressure, height and weight measurements) will be performed. Participants will wear a study CGM to ensure the device is tolerated and provide a baseline assessment of glycaemia before randomisation. They will be asked to complete the following validated questionnaires: Type 2 Diabetes Distress Scale [27], Glucose Monitoring Satisfaction Survey [28], Patient Health Questionnaire 9-item depression scale [29], Generalized Anxiety Disorder 7-item scale [30] and Euroqol Five Dimensions Health-Related Quality of Life Questionnaire (EQ-5D) [31]. The relevant copyright permissions were sought and received for questionnaires.

Randomisation

After the run-in phase, participants are randomised to either CGM or finger-prick SMBG via a web-based randomisation system. If there are technical difficulties or inadequate CGM data, a further CGM sensor may be applied before 15 weeks 3 days' gestation. Participants will be allocated on a 1:1 basis with stratification per study site.

Intervention

CGM

Participants will be switched from their current glucose monitoring method to the trial CGM (FreeStyle Libre3) system, with face-to face training provided on sensor application, setting and responding to alarms; interpreting CGM data; sensor glucose targets (3.5-7.8 mmol/l) and diabetes therapy adjustment (metformin, insulin or both). These recommendations will be supported by written educational materials e.g. PROTECT trial "Top Tips" leaflets. Following training, participants will use CGM from

randomisation until after delivery, with CGM sensor data captured up to maternal hospital discharge.

Standard care

Participants will receive training on finger-prick SMBG testing with a blood glucose meter and will be requested to perform SMBG at least four times a day, including before breakfast (fasting level) and one hour after each meal. Training will also include NICE recommended SMBG glucose targets (<5.3 mmol/L fasting, <7.8 mmol/L at 1-hr post-meal), diabetes therapy adjustment (metformin, insulin or both), and PROTECT “Top Tips” leaflet.

Follow-up visits and data collection

Follow up study visits will be scheduled every four weeks (around 16-, 20-, 24-, 28-, 32- and 36-weeks’ gestation) to coincide with routine antenatal visits. The following data will be recorded: weight, blood pressure, glucose monitoring method(s), frequency of SMBG testing, diabetes treatment, medication use, details of any hospital admission, episodes of severe hypoglycaemia / hyperosmolar hyperglycaemic state / diabetic ketosis, and serious adverse events. For control arm participants, a masked CGM will be provided to collect at least 72hrs of comparable sensor glucose data at 20-, 28-, 32- and 36-weeks’ gestation. The questionnaires will be repeated at around 32 weeks’ gestation for all participants.

At delivery, data regarding obstetric and neonatal outcomes will be collected. Trial data will be recorded by trained staff at each site on a web-based database and associated with the participant’s initials and study ID.

Safety

Participants will be reviewed for use of study devices and adverse events at all study visits. Adverse Events of Special Interest (severe hypoglycaemia, hyperosmolar hyperglycaemia state and diabetic ketoacidosis) and Serious Adverse Events will be promptly notified to Norwich Clinical Trials Unit, and reported onwards to the trial sponsor, Research Ethics Committee or both as required.

Bloods

Blood collection for HbA1c levels will be performed at baseline to confirm eligibility (if no HbA1c in pregnancy), and where possible at 28-, 32- and 36-weeks' gestation, with optional biorepository samples taken for future metabolic studies in those that consent.

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 adjust diet/lifestyle and/or glucose lowering therapy). To accommodate this breadth of representation, we will invite approximately 20 women to take part in the semi-structured interviews. Interviews will usually be scheduled at around 32-36 weeks' gestation, but adjusted according to the participant's convenience, including after birth if preferred. Interpreting will be offered to enable women to participate in other languages.

An additional study of healthcare professionals across the NHS trial sites will identify and describe healthcare professionals' perceptions of the barriers and facilitators of CGM use. It will explore staff experiences of supporting pregnant women with EOT2D using CGM, and their views and suggestions for what further training and support would be needed for healthcare teams and women with EOT2D if CGM were to be rolled out in routine clinical care in this population.

In keeping with other investigations of user and healthcare professional experiences of diabetes technology, a flexible, open-ended approach will be used, allowing participants to raise issues they consider salient, including those unforeseen at the study outset. Interviews will be informed by topic guides, and data collection and analysis will occur concurrently so that findings identified in early interviews can inform the topics explored in later accounts.

Treatment discontinuation

In consenting to the trial, participants are consenting to trial intervention, follow-up and data collection. If a participant chooses to discontinue their trial intervention or control arm allocation, they will be asked if they would

be willing to provide outcome data (masked study CGM data, delivery and neonatal data and questionnaires). If, however, the participant decides that they no longer wish to provide further data, we will respect their views and the participant withdrawn entirely from the trial. Data (and samples) already collected will be included in analyses according to the intention-to-treat principle. The number of participants who stop trial follow-up early will be monitored across both arms.

Primary Outcomes

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

Primary neonatal outcome: Composite outcome of neonatal care unit admission or death (stillbirth or neonatal death)

Secondary Outcomes

Secondary outcomes include maternal glycaemic and insulin outcomes, obstetric and neonatal outcomes, safety outcomes, psychosocial outcomes and health economic outcomes.

Maternal glycaemic and insulin outcomes

1. Change in maternal HbA1c based on blood samples taken at baseline, 28-, 32- and 36-weeks' gestation
2. The percentage of time spent with CGM glucose levels above target range (>6.7 & >7.8 mmol/L)
3. The percentage of time spent with CGM glucose levels below target range (<3.5 & <3.0 mmol/L)
4. Change in CGM mean glucose
5. Glucose management indicator (GMI)
6. Glycaemic variability: glucose standard deviation (SD) and coefficient of variation (CV)
7. Diabetes treatment (metformin and insulin use)

Obstetric outcomes

1. Hypertensive disorders
2. Gestational weight gain (from initial antenatal visit to 36 weeks' gestation)
3. Mode of delivery
4. Gestational age at delivery and indication of preterm delivery (<37 weeks' gestation)
5. Maternal hospital admissions and length of hospital stay

Neonatal outcomes

1. Adverse pregnancy outcomes (pregnancy loss <24 weeks, congenital anomaly (any), stillbirth, neonatal death)
2. Birth injury
3. Neonatal morbidity (characterised by treatment for neonatal hypoglycaemia, respiratory distress and/or neonatal jaundice)
4. Infant birthweight for gestational age (customised birth weight percentile: GROW customised birth weight, large for gestational age birthweight >90th centile and small for gestational age birthweight <10th centile)
5. Neonatal care unit admission (length of stay, highest level care)
6. Feeding at hospital discharge (exclusive breast-feeding / partial breast-feeding / exclusive formula feeding)

Safety outcomes

1. Severe hypoglycaemia
2. Hyperosmolar hyperglycaemic state
3. Diabetic ketoacidosis episodes

Psychosocial outcomes

1. Questionnaires during early and late pregnancy
2. Qualitative interviews:
 - Women randomised to the CGM intervention arm
 - Trial healthcare staff from the trial sites

Health economic outcomes

A within-trial cost utility analysis comparing FreeStyle Libre 3 CGM with finger-prick SMBG 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.

Statistical Analysis

Analyses will be performed according to intention-to-treat principles. For the primary maternal outcome, summary statistics for time in range 3.5-7.8 mmol/L at baseline and follow-up will be tabulated by treatment group. The outcome will be compared between treatment groups using a linear mixed effects model with time in range 3.5-7.8 mmol/L at follow-up as the dependent variable adjusting for time in range 3.5-7.8 mmol/L at baseline, BMI, and race (White and non-White) as fixed effects and clinical site as a random effect. If any participants are enrolled for subsequent pregnancies, the model will also include a random participant effect. A point estimate, 95% confidence interval and p-value will be reported for the treatment effect based on the linear regression model.

The primary neonatal outcome is the composite of neonatal care unit admission (between birth and neonatal hospital discharge) or death (stillbirth or neonatal death). The proportion of pregnancies resulting in one of these outcomes will be tabulated by group. A mixed effects logistic regression model will be used for formal group comparison adjusting for time in range 3.5-7.8 mmol/L at baseline, BMI, race, and clinical site as a random effect. If any participants are enrolled for multiple pregnancies, the model will also include a random participant effect. The treatment effect will be expressed as an Odds Ratio (OR), reported with 95% confidence intervals and values.

For both primary maternal and neonatal outcomes, missing data will be handled using multiple imputation assuming missing-at-random for the primary analysis.

The analysis of the continuous secondary outcomes will parallel the primary analyses described above. For the binary secondary outcomes, the number and percent of participants meeting each category will be tabulated by treatment group at baseline (where available) and follow-up. The treatment effect will be expressed as an Odds Ratio (OR), reported with 95% confidence intervals and values. For binary outcomes with at least 30 events combined between the two treatment groups, outcomes will be compared between treatment groups using a mixed effects logistic regression model adjusting for the BMI, race (White and non-White), outcome at baseline (where available) and site as a random effect. For neonatal outcomes, if any participants are enrolled for multiple pregnancies, the models will also include a random participant effect. Missing data will be handled using multiple imputation.

For binary outcomes with fewer than 30 events combined between the two treatment groups, outcomes will be compared using Barnard's exact test without covariate adjustment or handling of missing data.

Sample size estimation

Assuming an anticipated neonatal care outcome incidence of 42.2% in the standard care group, based on national audit data [4, 7], 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 care unit admissions is based on our previous randomised controlled trial data [15]. The neonatal effect size in our earlier randomised controlled trial [23] was higher (0.36), 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 pregnancy-specific target range from 20 weeks until 38 weeks' gestation or delivery, 188 participants are required to detect a clinically relevant 10% increase from 60 to 70% time in range with 90% power. A sample size of 422 (380 analysable CGM profiles), provides 90% power to detect a CGM time in range difference of 6.65% which is deemed to be a clinically important difference. The expected maternal time in range outcome of 60% time in range (SD 20%) in the control group is based on limited EOT2D data [23–25].

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

Trial and data management

The University of East Anglia is the trial sponsor and has delegated responsibility for the overall management of the trial to the Chief Investigator and Norwich Clinical Trials Unit, including the trial design, coordination, monitoring and analysis and reporting of results. A Trial Management Group (TMG) has been set up to assist with developing the design, co-ordination and strategic management of the trial.

Statistical analysis

Statistical analyses will be handled by the Jaeb Center for Health Research, Tampa, Florida, United States of America in conjunction with Norwich Clinical Trials Unit, Norwich, United Kingdom.

Trial Steering Committee

The Trial Steering Committee (TSC) is responsible for oversight of the trial in order to safeguard the interests of trial participants. The TSC will meet

approximately 6-monthly to review progress of the trial and provide advice to the Chief Investigator, Norwich Clinical Trials Unit, funder and sponsor.

Data Monitoring Committee

The independent Data Monitoring Committee (DMC) 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. They are planned to meet on six-monthly basis. There will be no formal interim analyses but updates will be provided for the DMC on a regular basis. The DMC is the only oversight body that has access to unblinded accumulating comparative data.

Discussion

This trial aims to evaluate the clinical efficacy of continuous glucose monitoring in pregnant women with early onset type 2 diabetes. It will also provide insights into women's lived experiences of using CGM in EOT2D pregnancy and healthcare professionals' experiences of supporting its use in this population. Furthermore, estimates of its cost-effectiveness and cost-utility will inform provision of CGM in EOT2D pregnancy in NHS healthcare settings. It may be able to assess whether CGM has an effect on obstetric and neonatal outcomes.

This is the largest randomised study to examine the use of CGM in pregnancies complicated by EOT2D. It will inform patients, caregivers, healthcare professionals and funding agencies regarding the use of CGM in pregnant women with EOT2D.

Dissemination

A report will be written for the funding bodies and for peer-reviewed publication and will be disseminated to international lay and scientific audiences.

Abbreviations

CGM: continuous glucose monitoring

CONCEPTT: Continuous glucose monitoring in pregnant women with type 1 diabetes (randomised controlled trial)

CV: coefficient of variation

EOT2D: early-onset type 2 diabetes

EQ-5D: Euroqol Five Dimensions Health-Related Quality of Life Questionnaire

GMI: Glucose Management Indicator

HbA1c: Haemoglobin A1c

DMC: Data Monitoring Committee

NICE: National Institute for Health and Care Excellence

PPI: Patient and Public Involvement

QALY: quality-adjusted life year

TMG: Trial Management Group

TSC: Trial Steering Committee

Declarations

Ethics approval and consent to participant

This clinical study protocol was given favourable opinion by South Central - Berkshire B Research Ethics Committee (reference 23/SC/0315) and approved by the Health Research Authority (HRA) for participating NHS organisations in England. Each participant is required to sign a consent form prior to participating in the study.

Consent for publication

Not applicable

Availability of data and materials

After completion of the study, requests for access to trial data and stored samples will be considered, and approved in writing where appropriate, after formal application to the TSC. Inquiries for data should be addressed to the principal investigator Prof Helen R. Murphy.

Competing interests

HRM has previously sat on a scientific advisory board for Medtronic (CGM manufacturer) and reports receiving research support (CGM devices at

reduced or no cost) from Abbott Diabetes Care and from Dexcom (reduced cost CGM devices), and speakers fees from Abbott, Dexcom, Novo Nordisk, Sanofi and Ypsomed. EMS reports personal fees from Abbott Diabetes Care and Lilly Diabetes, unrelated to the present work. Abbott Diabetes Care are supplying CGM systems free of charge for the purposes of the study.

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Authors' contributions

TTML and HRM co-wrote the first draft of the manuscript, with input from EMS and CC. The statistical analysis plan was written with input from LS, SS, PC and RG. All authors (TTML, CC, MiH, MaH, AW, LS, JM, MB, KI, SM, NM, AA, SS, PC, RG, EMS and HRM) contributed to the conception and/or development of the study and read and approved the final manuscript.

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