BMJ Open

The Effectiveness of Real-Time Continuous Glucose Monitoring to Improve Glycaemic Control and Pregnancy Outcome in Patients with Gestational Diabetes Mellitus: A randomised controlled trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040498
Article Type:	Protocol
Date Submitted by the Author:	15-May-2020

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Keywords:	Diabetes in pregnancy < DIABETES & ENDOCRINOLOGY, Fetal medicine < OBSTETRICS, Maternal medicine < OBSTETRICS

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Study protocol

The Effectiveness of Real-Time Continuous Glucose Monitoring to Improve Glycaemic Control and Pregnancy Outcome in Patients with Gestational Diabetes Mellitus: A randomised controlled trial.

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Conflict of interest

The authors declare that there are no further financial or personal relationships with other people or organizations that could inappropriately influence the work reported or the conclusions, implications, or opinions stated.

KEY WORDS: Gestational diabetes mellitus, diagnosis, real-time continuous glucose monitoring, glycaemic control.

Short title: Continuous glucose monitoring to improve glycaemic control and pregnancy outcome in gestational diabetes.

Manuscript includes: 26 text pages (26 in total with front page, references)

1 Abstract

Introduction: Real-time continuous glucose monitoring (rt-CGM) systems provide users with information about current interstitial glucose levels and allows early detection of glycaemic excursions and accordingly timely adaptation by behavioural change or pharmacologic intervention. Randomized controlled studies adequately powered to evaluate the impact of long-term application of rt-CGM systems on the risk reduction of adverse obstetric outcomes are missing.

Methods and analysis: Open-label multicentre randomized controlled trial with two parallel groups including a total of 372 female patients with a recent diagnosis of gestational diabetes (GDM): 186 with rt-CGM (Dexcom G6) and 186 with self-monitored blood glucose (SMBG). Women with GDM will be consecutively recruited and randomized to rt-CGM or control (SMBG) group after a run-in period of 6 to 8 days. The third visit will be scheduled 8 to 10 days later and then every two weeks. At every visit, glucose measurements will be evaluated and all patients will be treated according to the standard care. From second to third visit as well as once for 10 days between gestational week 36+0 and 38+6 the control group will receive blinded CGM. Cord blood will be sampled immediately after delivery. A postpartum examination will be scheduled within 48 hours after delivery for assessment of neonatal biometry and maternal HbA1c, as well as between week 8 to 16 after delivery in all patients for a detailed re-examination of glucose metabolism including blinded CGM for 8 to 10 days in both groups. Primary outcome is the difference in the proportion of LGA newborns. Rate of neonatal hypoglycaemia, caesarean section, shoulder dystocia and neonatal anthropometry are secondary outcomes.

Ethics and dissemination: This study received ethical approval from the main ethic committee in Vienna. It was registered under www.ClinicalTrials.gov (NCT03981328). Data will be presented at international conferences and published in peer-reviewed journals.

Strengths and limitations of the study:

- This is a randomised controlled trial recruiting 372 pregnant women after the GDM diagnosis at 5 sites in Austria, Germany, Sweden and Switzerland.
- The study uses the newest version a of “real-time” CGM (rt-CGM) system which enables the user identify rapidly glycaemic excursions and allows timely adaptation by behavioural change or pharmacologic intervention.
- The study will increase knowledge about possible limitations of SMBG (routine care), such as undetected hyper- or hypoglycaemia.
- The study might show possible improvement of adverse perinatal outcome and particularly fetal macrosomia in offspring of mothers with GDM monitored by rt-CGM versus SMGB.

2 Introduction

The incidence of obesity and diabetes is rising worldwide even in younger populations. With a rise in maternal obesity also gestational diabetes mellitus (GDM) becomes more prevalent with a prevalence of up to 18% of pregnancies[1,2]. Previous studies found hyperglycaemia in pregnancy to be associated with gestational complications including macrosomia and neonatal hyperinsulinaemic hypoglycaemia[3] and an increased long-term risk for obesity or diabetes in the offspring's later life[4]. Large interventional trials provided evidence that obstetric and neonatal complications such as large for gestational age offspring (LGA, defined as birthweight >90th pctl) or shoulder dystocia can be significantly reduced by intensified treatment of even mild forms of maternal hyperglycaemia (e.g. by lifestyle modification or pharmacotherapy)[5–7].

Continuous glucose monitoring (CGM) has been shown to improve glycaemic control without increasing the risk of hypoglycaemia in patients with type 1 and 2 diabetes[8,9]. However, only a small number of studies evaluated the use of CGM in pregnancies affected by GDM: In the setting of a larger non-randomized observational study Yu et al.[10] found that mothers in the CGM group (use over 72 hours every 2 to 4 weeks) had improved glycaemic control as well as a lower amount of glycaemic variability as compared to a control group using self-monitored blood glucose (SMBG). In addition, the CGM-group showed lower birth weight percentiles associated with a lower risk for LGA offspring (13.7 vs. 25.8%) or neonatal hypoglycaemia (5.5 vs. 14%). Also a second observational study including 57 pregnant women with GDM indicated that CGM was more effectively detecting hyperglycaemic episodes as well as nocturnal hypoglycaemia than SMBG[11]. A study in 73 pregnant women with GDM, randomly assigned to either SMBG or CGM for a duration of 48h after diagnosis, found that CGM detected a markedly higher proportion of women requiring glucose lowering pharmacotherapy (31 vs 8%)[12]. Another randomized controlled trial on 106 women with GDM observed significantly lower weight gain associated with CGM. LGA cases were more often observed in the SMBG group (52.7 vs. 35.3%). However, the difference failed statistical significance as the study was not powered for obstetrical outcomes[13].

Unfortunately, both randomized controlled studies used older versions of a blinded CGM device, where glucose values were not directly visible for patients. In contrast, more recently developed "real-time" CGM (rt-CGM) systems provide users with information about current glucose levels and alert the patient before the upper or lower glucose threshold is reached or when glucose levels change rapidly. Hence, glycaemic excursions can be rapidly identified and accordingly adapted by behavioural change or pharmacologic intervention. A number of studies including non-pregnant patients showed superiority of rt-CGM over older blinded CGM versions in order to effectively empower and educate patients with diabetes to better understand how dietary habits, exercise or pharmacotherapy affects their glucose

levels[14]. A beneficial effect of rt-CGM in pregnancy was also supported by the CONCEPTT trial for pregnant women with type 1 diabetes[15]. Only one recent study compared SMBG with rt-CGM in women with GDM using a single application for 3 to 7 days within two weeks after diagnosis but it failed to demonstrate improvements in HbA1c or pregnancy outcomes, which was, however, likely due to the sample size and the short duration of intervention (single application)[16].

Taken together, larger randomized controlled studies adequately powered to evaluate the impact of long-term application of rt-CGM systems on the risk reduction of adverse obstetric outcomes are missing[17]. Of note, such studies are of high clinical relevance because of their guideline-changing potential. In addition, rt-CGM has the potential to reduce reported barriers to SMBG (such as inconvenience, pain or stigma of testing in public places) in order to improve poor reliability and adherence to glucose monitoring, which is a non-negligible problem in the treatment of GDM[18].

Hypotheses

The main hypothesis of the proposed study is that rt-CGM can effectively reduce the risk for neonatal and obstetric complications. It is further hypothesized that rt-CGM can improve maternal glycaemic control, body weight gain during pregnancy and (as rt-CGM potentially improves self-management strategies) has beneficial effects on maternal metabolism after pregnancy.

Primary and secondary outcomes

Primary objective: To assess differences in the proportion of LGA newborns (birth weight >90th pctl) in women with GDM using rt-CGM as compared to women with GDM using SMBG.

Secondary objectives: To assess differences in further obstetric or neonatal complications, neonatal hypoglycaemia, rate of caesarean section, shoulder dystocia and neonatal anthropometry will be assessed as secondary objectives. Further secondary outcomes are: differences in neonatal hyperinsulinemia, rt-CGM measures such as mean interstitial glucose, glycaemic variability, time in target (65 to 140 mg/dl [3.6 to 7.8 mmol/l]) as well as time spent in hyper- and hypoglycaemia (Time above and below range) (day-time: 07.01 to 22.59hr and night-time: 23.00 to 07.00hr), duration and frequency postprandial hyperglycaemic excursions, start and amount of glucose lowering therapy, HbA1c, glycosylated fibronectin, change in bodyweight during pregnancy and after delivery as well as glucose disposal at postpartum (markers of insulin sensitivity, insulin secretion and β-cell function assessed by a postpartum OGTT). Health-related quality of life (HRQoL) is a patient-reported outcome which has become as important in the evaluation of interventions as patient-relevant clinical outcomes. Therefore, HRQoL will be elicited. In addition, preferences will be assessed, and a health economic evaluation in terms of cost-effectiveness and cost-utility analysis will be performed.

Expected effects on the advancement of clinical practice

The aim of this proposal is to assess the ability of rt-CGM to improve glycaemic control (reduction of mean glucose, hyperglycaemic episodes and duration, improvement of glycaemic variability) in order to prevent adverse pregnancy outcomes and neonatal complications in women with GDM. The results of this study will contribute to:

- The improvement of clinical monitoring and management of glucose metabolism during pregnancy with GDM
- Increased knowledge about possible limitations of SMBG (routine care), such as undetected hyper- or hypoglycaemia, as well as to determine if comprehensive glucose data (as derived from rt-CGM) results in more or fewer women needing pharmacotherapy
- Possible improvement of adverse perinatal outcome and particularly fetal macrosomia in offspring of mothers with GDM

3 Methods and analysis

Participants and recruitment; Inclusion criteria

This study is designed as an open-label multicentre randomized controlled trial with two parallel groups including a total of 372 female patients (n=186 with rt-CGM, n=186 with SMBG) with a recent diagnosis of GDM. Diagnosis of GDM (i.e. diabetes first diagnosed in the second and third trimester and not clearly type 1 or type 2 diabetes[19]) is made in accordance with the IADPSG criteria after 24+0 weeks of gestation by a 2h 75g OGTT[20]. The study will be conducted at five academic hospitals in Austria, Switzerland, Sweden and Germany. All pregnant females (aged between 18 and 55 years) will be consecutively recruited after diagnosis of GDM until 31+6 weeks of gestation among women visiting the pregnancy outpatient departments (Division of Obstetrics and feto-maternal Medicine, Medical University of Vienna; Division of Obstetrics, University Hospital Basel; Department of Obstetrics, Charité-Universitätsmedizin Berlin) or the diabetes outpatient departments (Division of Endocrinology and Metabolic Diseases at the Heinrich Heine University, Düsseldorf; Department of Medicine, University Hospital, Örebro).

Exclusion criteria

Overt diabetes (i.e. pregestationally known type 1 or type 2 diabetes or fasting plasma glucose during the OGTT ≥126 mg/dl [7.0 mmol/l] or HbA1c ≥6.5% [44 mmol/l] or 2h post-load OGTT levels ≥200 mg/dl [11.1 mmol/l] assessed before 24+0 weeks of gestation, whereby results need to be confirmed by repeated testing in case of unequivocal hyperglycaemia according to the ADA standards[19]), history of bariatric surgery or other surgeries that induce malabsorption, long-term use (>2 weeks) of systemic steroids prior to enrolment, multiple pregnancy, patients already using glucose lowering medications (metformin or insulin) before study entry, fetal growth restriction due to placental dysfunction at study entry, inpatient psychiatric treatment up to 1 year before enrolment, participation in this study in previous pregnancy.

Study visits during pregnancy

A broad risk evaluation will be performed in participating females at the initial contact (V1) including: evaluation of maternal age, parity, history of GDM in previous pregnancies, detailed family history, ethnicity, preconceptional diseases, obstetric history. Height (stadiometer measured to the nearest centimeter) and actual weight (calibrated scales, light indoor clothing) will be additionally assessed. Moreover, an evaluation of preconceptional weight (self-reported) and body mass index (BMI) as well as measurement of blood pressure will be performed. All patients receive medical advice for nutrition (isocaloric diet containing 40-50% carbohydrates, 20% proteins and 30-35% fat, divided into three meals and three snacks) and regular physical exercising for 30 minutes per day following international recommendations. In addition, participanats are advised on capillary blood glucose measurement (fasting as well as

1h after starting each meal) at the initial visit (V1). Randomization will be done after a run-in period of 6 to 8 days (V2). The third visit (V3) will be scheduled 8 to 10 days after V2 and further follow-up visits every two weeks (i.e. 12 to 16 days after each visit). HbA1c and glycosylated fibronectin will be assessed at V2 as well as at the first visit between 36+0 and 38+6 weeks of gestation (12 ml, non-fasting state) (V4). Detailed fetal ultrasound examinations, a detailed examination of dietary intake as well as a blinded CGM (control group only) will be performed at V2 and V4. Body weight change and use of glucose lowering medications (amount of insulin units) will be examined at every visit. At every follow-up visit glucose measurements (SMBG or rt-CGM) and routine ultrasound examinations (fetal biometry and umbilical artery doppler) will be evaluated by the medical staff and all patients will be treated according to the standard of care for patients with GDM. This includes lifestyle modification and insulin therapy if recommended thresholds are exceeded. Both groups will be treated to be in the target range between 65 to 140 mg/dl [3.6 to 7.8 mmol/l] with at least 8h fasting glucose levels equal or below 95 mg/dl [5.3 mmol/l] and 1h postprandial glucose measurements equal or below 140 mg/dl [7.8 mmol/l] in accordance with the CONCEPTT study[15] and the ADA recommendations[21], respectively. Intermediate acting neutral protamine Hagedorn (NPH) insulin is started in the evening if ≥2 measurements of fasting glucose are equal or above 95 mg/dl [5.3 mmol/l] in a period of one week and rapid acting insulin analogues (Aspart or Lispro) if ≥2 measurements of 1h postprandial glucose (either after breakfast, lunch or dinner) are equal or above 140 mg/dl [7.8 mmol/l] in a period of one week. NPH is started with 6 to 10 IU and increased by 4 IU (or in case of higher doses i.e. >25 IU by 20%) and rapid acting insulin (bolus insulin) is started with 2 to 4 IU and increased by 2 to 4 IU if thresholds are not achieved within three days. Long acting insulin analogues such as glargine (U100/U300) or detemir can be used as an alternative to NPH if necessary. Patients are trained on insulin management and titration according to their glucose levels. Metformin can be used according to local practice guidelines (recommended in Sweden but not in Austria, Germany or Switzerland as first-line pharmacological intervention).

Study visits postpartum

Cord blood will be sampled and stored (at -80°C) immediately after delivery (VPP0). A postpartum examination will be scheduled within 48 hours after delivery (VPP1) for assessment of neonatal parameters and maternal HbA1c and glycosylated fibronectin (12 ml, non-fasting state), as well as between 8 to 16 weeks after delivery (VPP2) in all patients for a detailed re-examination of glucose homeostasis postpartum (including lifestyle and dietary pattern as well as HbA1c, glycosylated fibronectin as well as a blinded CGM for 10 days and an OGTT to assess the presence of prediabetic conditions after pregnancy with GDM). The postpartum OGTT is further used to provide estimates of insulin sensitivity, β-cell function and hepatic insulin extraction, the major physiological components of impaired glucose tolerance.

Randomization

Participants will be randomized to either treatment (rt-CGM augmented glucose monitoring) or control group (routine care SMBG) in a 1:1 ratio. The minimization method[22] with a 0.85 assignment probability will be used to minimize the imbalance between the groups according to week of gestation at study entry i.e. at V1 (three strata: 24+0 to 25+6, 26+0 to 27+6, 28+0 to 29+6, 30+0 to 31+6), previous pregnancy with GDM (two strata: yes or no) and preconceptional overweight/obesity status with three strata: i. normal weight (i.e. BMI below 25.0 kg/m²); ii. overweight (BMI 25.0 – 29.9 kg/m²); iii. obesity (BMI equal or above 30.0 kg/m²). Randomization will be performed at the second study visit (V2) by using a randomization software provided by the Medical University of Vienna.

Intervention

Patients randomized to the intervention group will be equipped with a rt-CGM sensor (Dexcom G6 sensor, a small flexible device that records interstitial glucose levels every five minutes) at V2. The sensor will be inserted into the subcutaneous tissue of the anterior abdominal wall (if this location is not tolerated by the pregnant patients, the upper buttock or posterior upper arm may be used instead). Additionally, patients will be advised to record capillary blood glucose values if glucose alerts or readings do not match with symptoms or expectations. Participants will be educated on how to exchange the sensor (has to be exchanged every ten days) and will be equipped with a real-time CGM monitor and instructed in its use. The monitor provides the user with information about current glucose levels and notifies the patient before her upper or lower glucose threshold are reached and when glucose levels change rapidly. All patients in the intervention group will be specially trained in the use of the system. As an alternative to the real-time monitor the patients' smart phone with an anonymized access to the CLARITY® mobile app can be used (details see below: "Intervention: Device description").

Intervention: Device description

The Dexcom G6 intended use is for the management of diabetes in persons aged 2 years and older. The Dexcom G6 System is intended to replace fingerstick blood glucose testing for diabetes treatment decisions. Interpretation of the Dexcom G6 System results should be based on the glucose trends and several sequential readings over time. The Dexcom G6 System also aids in the detection of episodes of hyperglycaemia and hypoglycaemia, facilitating both acute and long-term therapy adjustments. The Dexcom G6 System can be used alone or in conjunction with digitally connected medical devices for the purpose of managing diabetes.

The system consists of a sensor, transmitter, receiver, and mobile app. The sensor is a small, flexible wire inserted into subcutaneous tissue where it converts glucose into electrical current. The sensor incorporates an interferent layer that minimizes the effect of potential electroactive interferents, such as acetaminophen, by preventing it from reaching the sensor wire surface. The benefit of this interferent layer in blocking the effects of acetaminophen

prevents falsely high glucose readings. Thus, users may ingest acetaminophen while wearing the G6 CGM system. The transmitter, which is connected to the sensor and worn on the body, samples the electrical current produced by the sensor and converts the measurement into a glucose reading using an onboard algorithm. The receiver and/or the app displays the glucose reading along with a rate of change arrow and a trend graph. Additionally, the receiver and/or app issues alarms and alerts to notify the patient of glucose level changes and other important system conditions. The app provides the additional capability to share data with "followers" using the Dexcom Share service. The receiver can be put into a blinded mode using CLARITY® software. In this mode, users are unable to see the CGM data or receive CGM alerts.

CGM Ancillary Devices Dexcom CLARITY® is an accessory for users of the Dexcom CGM system. It is a software program that allows the transfer of glucose data from the CGM system to Dexcom remote servers for data management to allow the use of the CGM data by the user and study clinicians. Target ranges of 65 to 140 mg/dl [3.6 to 7.8 mmol/l] will be set and the patients will be introduced in the use of alarm settings. Both participants and study sites will use CLARITY® to transfer glucose data between user and study site, whether CGM is used in blinded or real-time mode. A CLARITY® mobile app can be used for a retrospective review of glucose data on the smart device and can also be set up to allow receipt of push notifications of CGM data facilitating weekly data review. For all patients (intervention and control group) an anonymized CLARITY® account will be created by using a sequential study number which is allocated at randomization (sex will be female and birth date for each account will be set to 1.1.1990 for all accounts).

Intervention: Study proceedings

- For participants who have a supported phone, the G6 CGM app will be installed on participant's smart phone.
- An anonymized CLARITY® mobile account will be set up and linked to the research site.
- Participants will use CGM data for their diabetes management.
- A high alert threshold will be set at 140 mg/dl [7.8 mmol/l]. Low alert threshold and urgent low soon alerts will be turned off. If participants require insulin, the low alert will be turned on and the threshold set at 65 mg/dl [3.6 mmol/l]. In addition, the urgent low alert (55 mg/dl [3.1 mmol/l]), the urgent low soon alert (when glucose levels are falling fast and will be below 55 mg/dl [3.1 mmol/l] in less than 20 min) as well as alerts for rise and fall rate (3 mg/dl [0.17 mmol/l]) in addition to alerts for signal loss and no readings for more than 20 min will be enabled.
- Participants with applicable smart phones may have CLARITY® push notifications on the CLARITY® mobile app about weekly time in range comparison enabled during the study.
- For app users, the "Share and Follow" functionality will be discussed and encouraged (i.e. the study participants are able to invite followers to review their glucose levels).

- For participants using the receiver only, the receiver will be downloaded into the CLARITY® clinic account at each visit.
- For participants using real-time CGM data summary will be downloaded for documentation at V3 and V4 (between 36+0 and 38+6) as well as after delivery (VPP1).
- The research team will review the CGM in CLARITY® to inform lifestyle and therapy recommendations.
- The Dexcom G6 system will not be calibrated during the study period.

Control group

The participants of the control group will perform self-monitored blood glucose testing with a study-provided blood glucose meter, including testing supplies. They will perform capillary blood glucose monitoring as routinely used for patients with GDM, i.e., at least four capillary blood glucose values daily including measurements in a fasting state as well as 1h after starting each meal by using a routinely available blood glucose measurement device. The study participants will keep a logbook of their glucose values, which will be reviewed by clinicians from the study team at each visit and used for lifestyle and dietary recommendations as is routinely done in clinical practice. From V2 to V3 as well as once for ten days between gestational week 36+0 and 38+6 the control group receive blinded CGM; neither patients nor the treating medical staff will have access to the data recorded by the CGM sensor at this point in time. Instead, patients will control blood glucose levels based on SMBG, as is the routine procedure in current GDM treatment. Otherwise, the control group will receive the same study assessments as the intervention group. The blinded CGM will be removed and returned to Dexcom after the 10-day wear period after CGM data is uploaded to CLARITY® by an unblinded investigator who must not communicate about the results with patients or medical staff.

Each participant of the control group will be assigned a study blood glucose meter to measure and store their blood glucose values during the study. Therefore, the Contour® Next One system will be used. The meter has CE Mark clearance and is commercially available in Europe. Participants will receive an ample supply of meter test materials based on quantities routinely used. A commercially available desk-top software (Diabass® Pro) used in conjunction with Contour® Next One system glucose meter for blood glucose monitoring, will be utilized for downloading the meter data by the sites at V3 and V4 after checking that dates and times are correct.

Blood glucose meters used by the control group will be assessed to establish frequency of testing (overall and per week) as well as percentage of days with less than four measurements per day.

Analyses of CGM data

Rt-CGM data allows a detailed examination of the percentage of time in which glucose levels are in target range (time in target) (65 to 140 mg/dl [3.6 to 7.8 mmol/l]), hyperglycaemic episodes (glucose ≥140 mg/dl [7.8 mmol/l]) as well as mild (<65 mg/dl [3.6 mmol/l]), moderate (≤54 mg/dl [3.0 mmol/l]) or severe hypoglycemic episodes (requiring third party assistance) and their duration. To this purpose, several indices of the glucose control quality will be calculated, such as GRADE (Glycaemic Risk Assessment Diabetes Equation), some indices of hypoglycaemia and hyperglycaemia, and indices assessing the risk associated to both low and high glycaemic values, such as IGC (Index of Glycaemic Control) and ADRR (Average Daily Risk Range)[23]. Glycaemic variability will also be assessed, which can be quantified by standard deviation of the CGM data, or by more sophisticated indices, such as MAGE (Mean Amplitude Glucose Excursions), CONGA (Continuous Overlapping Net Glycaemic Action), Lability Index[23], as well as further indices that we developed internally, such as the Shape Index[24]. These will be compared between real-time CGM users and controls (i.e. from data obtained during the blinded CGM wear).

Assessment of dietary patterns

Dietary patterns will be assessed in all patients at V1, VPP1, and VPP2 via a published and validated Food-Frequency-Questionnaire (FFQ) proposed by the German Robert Koch Institute[25]. It was also previously used for the German DEGS project (www.degs-studie.de). Information from the FFQ will be analyzed quantitatively or summarized by eating scores proposed in the literature (such as the Healthy Eating Index 2010 or Alternate Healthy Eating Index 2010) reflecting diet quality based on actual guidelines[26,27]. In addition, all patients will be advised to conduct a nutritional protocol (seven days) from V2 to V3 as well as once at V4 (between 36+0 and 38+6 weeks of gestation). In a subgroup (only study site Vienna) dietary intake will also be assessed by performing 24-h-recalls by trained interviewers at V2, V4 and postpartum (VPP2): one face-to-face interview (approx. one hour) and the others as telephone interviews (approx. 30 minutes) during which data are entered simultaneously in GloboDiet. GloboDiet is a computerized program which was developed by the International Agency for Cancer Research (IARC) within the framework of the European Prospective Investigation into Cancer and Nutrition Study (EPIC-Study) for the conduction of harmonized and standardized 24-h-recalls[28]. This open-ended software was used in numerous previous studies and was validated within the EFCOVAL project[29–31]. In brief, GloboDiet is an interview-based dietary assessment instrument that allows obtaining a very detailed description and quantification of foods, recipes, and supplements consumed in the course of the preceding day and thus standardising data within and between countries. Probing questions and entering consumed foods in chronological order support the respondent's memory. The standardized structure prescribes – on the food group level – possibilities of description and quantification of food

items to choose from. Quantification of consumed foods is supported by the GloboDiet picture book that comprises coloured photographs of foods in different portion sizes, photographs of familiar household measures and schematic displays of forms (e.g. bread, cake). The software provides an automatic coding of food items and recipe ingredients as well as a rough calculation of nutrient intake meant for quality control of the interview. GloboDiet is characterized by the obtained standardization of dietary data within Europe, a large number of available foods and recipes, and a very detailed description of consumed foods. Currently, GloboDiet is one of the few dietary instruments providing comparable nutritional data within Europe. After finalization of the interviews, GloboDiet will be linked to the local nutrition database – the Bundeslebenmittelschlüssel (BLS) enhanced by the Austrian Nutrition Table (Österreichische Nährwerttabelle, ÖNWT), containing typical Austrian foods and recipes – allowing analyses on food ingredients level and to conduct precise energy and risk assessment.

Assessment of physical activity

Physical activity will be assessed at V1, VPP1, and VPP2 via the International IPAQ (Physical Activity Questionnaire, long-form). The IPAQ represents a well-accepted, validated instrument for monitoring population levels of physical activity in different settings and countries[32]. It will be analyzed via published guidelines for data processing and analysis at the IPAQ homepage Guidelines for data processing and analysis of the international physical activity questionnaire (IPAQ)[33]: In short, collected data will be summarized as median MET (metabolic equivalent of task) minutes per week, representing a continuous score for walking, moderate intensity activities, vigorous intensity activities and total activities, as recommended. In addition, the Pregnancy Physical Activity Questionnaire (PPAQ) will be performed to capture information on physical activity participation and sedentary behaviour during pregnancy[34].

Assessment of maternal intramyocellular and intrahepatocellular lipids

Intramyocellular (IMCL), and intrahepatocellular lipid contents (HCL) will be measured by using proton magnetic resonance spectroscopy (^{1}H MRS) in a subgroup of 40 patients (20 rt-CGM, 20 SMBG) at V3 and after delivery (VPP2) according to previously described methods[35–37]. The participants will be studied in supine position within a 3.0 Tesla whole-body magnet (Siemens or Philips). MRS is a non-invasive technique to evaluate tissue-specific metabolism and was shown to be safe and well tolerated by pregnant women in previous studies[38,39]. Patients will be positioned with a left pelvic tilt to avoid pressure on the inferior vena cava according to other studies in pregnancy[38]. For IMCL measurements, the calf muscle (right leg) will be positioned in a quadrature bird cage ^{1}H volume coil. A circular ^{1}H surface coil will be positioned over the liver for HCL measurement.

Fetal biometry

Parameters of fetal anthropometry as determined by ultrasound as well as neonatal data including length, weight, gestational age at delivery will be included in the final analysis. A detailed fetal ultrasound examination will be performed at V2 and repeated at V4 (between 36+0 to 38+6 weeks of gestation) to assess fetal growth parameters including head circumference, biparietal diameter and abdominal circumference and abdominal fat thickness, femur length (measured and expressed as standardized gestational age related fetal growth percentiles[40]), amnion fluid index as well as size and location of the placenta and fetal subcutaneous tissue thickness. Moreover, fetal growth symmetry will be assessed by fetal head to abdomen circumference ratio and fetal doppler measurements (mainly umbilical artery and middle cerebral artery[41] and ductus venosus). Furthermore, fetal hepatic size (all hepatic diameters, such as area and volume) and umbilical venous volume flow and an echocardiac examination of the fetus will be performed in a subgroup (only study site Vienna).

Obstetric outcome

Obstetric outcome (caesarean section, birth injury, preterm birth before 37 completed weeks of gestation) stillbirth, small for gestational age (birth weight <10th pctl), large for gestational age infant (birth weight >90th pctl), shoulder dystocia, admitted to neonatal intensive care unit umbilical cord blood pH, Apgar score) will be recorded immediately after delivery. Length of hospital stay for mothers and offspring as well the duration of high-level neonatal care, respiratory distress, fetal hyperbilirubinemia and neonatal death ≤28 days will be further assessed. Calculations of age and sex adjusted percentiles will be performed by using international anthropometric standards according to those used in the CONCEPTT study[42]. Neonatal hypoglycaemia is defined as local blood glucose ≤31 mg/dl [1.7 mmol/l] in the first 24h after delivery and ≤45 mg/dl [2.5 mmol/l] after the first 24h after delivery or treatment with glucose infusion according to the HAPO study[3]. Additional anthropometric measures of the offspring include head, shoulder and abdominal circumference, length, upper and lower arm and leg circumference and skinfold measurements (suprailiac and subscapular, triceps, quadriceps) in accordance with previous studies[43–45]. Thereby skinfold measurements will be performed by using a validated instrument (Harpenden Skinfold Caliper) within 48h after delivery (VPP1).

Assessment of cord blood

17 ml umbilical cord blood (1x8 ml serum and 1x9 ml EDTA) will be taken immediately after delivery to examine cord-blood glucose, insulin and C-peptide.

Postpartum OGTT

The OGTT will be performed at VPP2 (i.e. 8 – 16 weeks after delivery): after collecting blood samples for measurements of glucose (2 ml blood), insulin and C-peptide (3 ml blood) in the

fasting state (at least 8 hours), participating females will receive a standardized 300 ml 75g glucose. Further blood samples of glucose, insulin and C-peptide measurements will be taken at 30, 60, 90, and 120 minutes after intake of glucose. Insulin sensitivity during the OGTT will be assessed by the oral glucose insulin sensitivity index (OGIS) according to Mari et al.[46]; this quantifies dynamic glucose clearance per unit change of insulin. The more recently developed PREDIM index will be used in addition[47]. The new index provides excellent prediction of clamp-derived insulin sensitivity from OGTT or meal data. As an approximation for hepatic insulin resistance the homeostasis model assessment of insulin resistance (HOMA-IR) will be used. Insulin secretion will be calculated by using the C-peptide deconvolution method[48]. β-cell function parameters, such as pancreatic glucose sensitivity and rate sensitivity, and potentiation of insulin secretion, will be computed by mathematical modelling[48].

Assessment of health-related quality of life and patients' preferences

Health-related quality of life will be elicited using the SF36 and the EQ-5D-5L[49]. It can be expected that adherence to lifestyle and dietary recommendations are associated with individual risk preferences. Hence, risk and time preferences will be elicited based on a lottery approach[50,51]. Participants will be asked to choose between two hypothetical lotteries that differ in expected outcomes which enables us to derive an individual classification of the risk type, i.e. risk-averse, risk-neutral or risk-loving individuals. Quality of life as well as risk and time preferences will be assessed at V1, VPP1, and VPP2. Obstetrical patient's satisfaction will be additionally assessed at VPP1 by using the Wijma score[52].

Patient and public involvement

Patients and public were not involved in the study design and will not be involved in the study conduct, recruitment and dissemination.

Health economic evaluation

For the evaluation of a complex intervention, a health economic evaluation is recommended as well[53,54]. In this study, a cost-effectiveness (CEA) and a cost-utility analysis (CUA) will be conducted from the perspective of the health insurance. The effect measure employed in the CEA will be the primary outcome of the main trial, i.e. avoided cases of LGA newborns. Due to the short intervention period quality-adjusted life-weeks (QALWs) will be used in the CUA . QALWs will be calculated based on either the EQ-5D-5L or the SF-6D[55] that derives preference-based scores from the SF-36. To receive utilities, quality of life will be evaluated by country-specific population based preferences separately for each country involved in the trial . Similarly, intervention costs as well as health care costs (direct costs) will be calculated separately for each country using local prices and adjusted for local purchasing power parity (PPP). Health care use will be assessed by a validated instrument that is adapted to the

requirements of the study[56]. Health care use will comprise resource use dedicated to the mother but not the child, e.g. clinical visits, outpatient contacts, contacts with therapists, and medication. Intervention associated costs are costs of devices, software, test strips, and costs due to education and training of study participants. Since the evaluation covers only the observation period alongside the trial, costs and effects will not be discounted. Comparing the outcomes and costs of the intervention group with the outcomes and costs of the control group yields the incremental cost-effectiveness ratio (ICER: additional cost per additional LGA newborn avoided) and the cost-utility ratio (ICUR: additional costs per additional QALW gained).

Reporting of adverse events

Any (serious) adverse events (AE/SAE) are recorded by the investigator using the specific AE/SAE sheet of the clinical report form (CRF). All SAE are reported to the responsible ethics committee within an appropriate time frame.

Sample Size and Statistical Analysis

Sample size

With a sample size of n=338 (169 pregnant women per group) we will be able to detect a difference between two independent proportions of LGA of 13.7% vs 25.8% (according to the results of a previous study[10]) with a power of 80% and a two-sided type 1 error of α=0.05 (calculated for Pearson's chi-square test). Considering a drop-out rate of 10% a total sample size of n=372 (186 women per group) is necessary for this study. This is in line with the sample size suggested by Kestilä et al.[12]. A blinded sample size review (the proportion of LGA cases in the sample is reviewed) and adaptation is planned after 50% of the patients have been investigated. The sample-size calculation was performed by using the software G*Power (V3.1.9.2)[57].

Analysis plan

Analyses should be conducted on the intention-to-treat principle. Categorical variables will be summarized by counts and proportions; continuous variables data will be summarized by means and standard deviations (SD) or by median and interquartile range in the case of strong deviations from the normal distribution. Pearson's chi-square test will be used to compare differences in the primary outcome (difference in proportion of LGA newborns) and for binary secondary outcomes (such as caesarean section rate, shoulder dystocia and neonatal hypoglycaemia). Bernard's test will be used as an alternative if an expected frequency in contingence tables is equal or less than 5 and the Cochran-Mantel-Haenszel method will be

used as sensitivity analysis to adjust for possible center specific effects. Continuous secondary outcome parameters (such as mean glucose, duration and amount of hyperglycaemia, glycaemic variability and other rt-CGM measures, postpartum OGTT data, HbA1c, glycosylated fibronectin or anthropometric data of the newborn) will be compared by student's t-test. Rank based inference (such as the Brunner-Munzel test[58]) will be used as an alternative in case of skewed distributed parameters. The association between HbA1c, rt-CGM measures and delivery and risk of LGA offspring will be assessed by binary logistic regression. There are many possible objectives for which further exploratory analysis could be performed in this study (e.g. functional principal components analysis for rt-CGM data). Hence, the present analysis plan represents only a selection of methods, which will be used for analysing the main objectives. Risk preferences will be analysed by non-parametric and parametric methods. In particular, we plan to classify study participants with respect to their risk tolerance (risk-aversion, risk-neutral, and risk-loving) and deriving CRRA (constant relative risk aversion) utility functions. Associations between risk preferences and behaviour (dietary patterns and physical activity) will be investigated. For the health economic evaluation, incremental cost-effectiveness ratios (ICER: Additional cost per additional LGA newborn avoided) and cost-utility ratios (ICUR: Additional cost per additional quality-adjusted life year gained) will be calculated. 95% confidence intervals will be analysed using bootstrap procedures[59]. To consider uncertainty, cost-acceptability curves will be calculated[60]. A two-sided p-value ≤0.05 is considered statistically significant. All analyses will be performed by using the statistic software R and contributing packages[61]. No further adjustment for multiplicity is planned for this study.

4. Ethics and dissemination

This study received ethical approval from the main ethic committee in Vienna (1863/2018). Ethics approval will be obtained by the local institutional review boards in Basel, Berlin, Dusseldorf, and Orebro. It was registered under www.ClinicalTrials.gov (NCT03981328). Data will be presented at international conferences and published in peer-reviewed journals.

Contribution to authorship

EH, KW, JJ, AI, JS, AT, MM, CSG designed the study. MM, AT, AI, MV, JM, CSG, PR will perform statistical analysis and data interpretation. EH, DE, KW, CK, KW, KS, GYS, IR, KC, JS, CSG will be responsible for patient management. PH, IH, MR, PR, HF, TF, MV, JM, BW, MD, GYS, CK, KS will make important contributions and critically reviewed this study protocol.

Acknowledgements

Special thanks to all families who participate in this study.

Funding

This study is supported by Dexcom grant project number OUS-2018-027.

Competing interest statement

The authors declare that there are no further financial or personal relationships with other people or organizations that could inappropriately influence the work reported or the conclusions, implications, or opinions stated.

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym → title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry → page 3
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier → only in original protocol
Funding	4	Sources and types of financial, material, and other support → page18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors → page 2
	5b	Name and contact information for the trial sponsor → page 1/18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention → page 5-7 (Introduction)
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses → page 7 (Hypotheses)

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) → see Title
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained → page 8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) → page 8 (Eligibility criteria)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered → page 8/9 (Study procedure)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) → not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) → not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial → not applicable
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended → page 6 (Study outcomes)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) → page 8/9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations →page 17/18 (Sample size justification)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials) → page 9		

Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how –> not applicable
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial → not applicable
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol → page 13-15 (Study analysis plan)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) → page 15-19 (Other study measurements)

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct → see Reporting of adverse events, page 17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval → page 8 (Study settings/design)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial → page 9 (Data recording)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site → (page 3 (Conflict of interest)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions → page 18
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The Effectiveness of Real-Time Continuous Glucose Monitoring to Improve Glycaemic Control and Pregnancy Outcome in Patients with Gestational Diabetes Mellitus: A Study Protocol for a Randomised Controlled Trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040498.R1
Article Type:	Protocol
Date Submitted by the Author:	12-Aug-2020
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Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	Diabetes in pregnancy < DIABETES & ENDOCRINOLOGY, Fetal medicine < OBSTETRICS, Maternal medicine < OBSTETRICS, Clinical trials < THERAPEUTICS

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The Effectiveness of Real-Time Continuous Glucose Monitoring to Improve Glycaemic Control and Pregnancy Outcome in Patients with Gestational Diabetes Mellitus: A Study Protocol for a Randomised Controlled Trial

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Conflict of interest

The authors declare that there are no further financial or personal relationships with other people or organizations that could inappropriately influence the work reported or the conclusions, implications, or opinions stated.

Key Words

Gestational diabetes mellitus, diagnosis, real-time continuous glucose monitoring, glycaemic control.

Short title

Continuous glucose monitoring to improve glycaemic control and pregnancy outcome in gestational diabetes.

Word Count

Text: 6,244 Abstract: 426

Tables: 0 Figures: 1

1 ABSTRACT

Introduction: Real-time continuous glucose monitoring (rt-CGM) informs users about current interstitial glucose levels and allows early detection of glycaemic excursions and timely adaptation by behavioural change or pharmacologic intervention. Randomized controlled studies adequately powered to evaluate the impact of long-term application of rt-CGM systems on the reduction of adverse obstetric outcomes in women with gestational diabetes (GDM) are missing. We aim to assess differences in the proportion of large for gestational age (LGA) newborns in women using rt-CGM as compared to women with self-monitored blood glucose (primary outcome). Rates of neonatal hypoglycaemia, caesarean section and shoulder dystocia are secondary outcomes. A comparison of glucose metabolism and quality of life during and after pregnancy completes the scope of this study.

Methods and analysis: Open-label multicentre randomized controlled trial with two parallel groups including 372 female patients with a recent diagnosis of GDM (between 24+0 until 31+6 weeks of gestation): 186 with rt-CGM (Dexcom G6) and 186 with self-monitored blood glucose (SMBG). Women with GDM will be consecutively recruited and randomized to rt-CGM or control (SMBG) group after a run-in period of 6 to 8 days. The third visit will be scheduled 8 to 10 days later and then every two weeks. At every visit, glucose measurements will be evaluated and all patients will be treated according to the standard care. The control group will receive a blinded CGM for 10 days between the second and third visit and between week 36+0 and 38+6. Cord blood will be sampled immediately after delivery. 48 hours after delivery neonatal biometry and maternal HbA1c will be assessed, and between week 8 to 16 after delivery all patients receive a re-examination of glucose metabolism including blinded CGM for 8 to 10 days.

Ethics and dissemination: This study received ethical approval from the main ethic committee in Vienna. It was registered under www.ClinicalTrials.gov (NCT03981328). Data will be presented at international conferences and published in peer-reviewed journals.

Strengths and limitations of the study:

- This is a randomised controlled trial recruiting 372 pregnant women after the GDM diagnosis at 5 sites in Austria, Germany, Sweden and Switzerland.
- The study uses the newest version of a real-time CGM (rt-CGM) system which enables the user rapidly to identify glycaemic excursions and allows timely adaptation by behavioural change or pharmacologic intervention.
- The study will increase knowledge about possible limitations of SMBG (routine care), such as undetected hyper- or hypoglycaemia.
- The study might show possible improvement of adverse perinatal outcome and particularly fetal macrosomia in offspring of mothers with GDM monitored by rt-CGM versus SMGB.

2 INTRODUCTION

The incidence of obesity and diabetes is rising worldwide even in younger populations. With a rise in maternal obesity also gestational diabetes mellitus (GDM) becomes more prevalent with a prevalence of up to 18% of pregnancies[1,2]. Previous studies found hyperglycaemia in pregnancy to be associated with gestational complications including macrosomia and neonatal hyperinsulinaemic hypoglycaemia[3] and an increased long-term risk for obesity or diabetes in the offspring's later life[4]. Large interventional trials provided evidence that obstetric and neonatal complications such as large for gestational age offspring (LGA, defined as birthweight >90th pctl) or shoulder dystocia can be significantly reduced by intensified treatment of even mild forms of maternal hyperglycaemia (e.g. by lifestyle modification or pharmacotherapy)[5–7].

Continuous glucose monitoring (CGM) has been shown to improve glycaemic control without increasing the risk of hypoglycaemia in patients with type 1 and 2 diabetes[8,9]. In 2003, a study compared the glycaemic profile reflected by CGM and SMGB in 34 gravid patients with type 1 diabetes over a period of 3 days and found that on average more than 3 hours of hyperglycaemic episodes per day were undetected by SMBG and nocturnal hypoglycaemic episodes could be revealed by CGM 1-4 hours before showing clinical manifestations or being detected by SMBG.[10] However, only a small number of studies evaluated the use of CGM in pregnancies affected by GDM: In the setting of a larger non-randomized observational study Yu et al.[11] found that mothers in the CGM group (use over 72 hours every 2 to 4 weeks) had improved glycaemic control as well as a lower amount of glycaemic variability as compared to a control group using SMBG. In addition, the CGM-group showed lower birth weight percentiles associated with a lower risk for LGA offspring (13.7 vs. 25.8%) or neonatal hypoglycaemia (5.5 vs. 14%). Also a second observational study including 57 pregnant women with GDM indicated that CGM was more effectively detecting hyperglycaemic episodes as well as nocturnal hypoglycaemia than SMBG[12]. A study in 73 pregnant women with GDM, randomly assigned to either SMBG or CGM for a duration of 48h after diagnosis, found that CGM detected a markedly higher proportion of women requiring glucose lowering pharmacotherapy (31 vs 8%)[13]. Another randomized controlled trial on 106 women with GDM observed significantly lower weight gain associated with CGM. LGA cases were more often observed in the SMBG group (52.7 vs. 35.3%). However, the difference failed statistical significance as the study was not powered for obstetrical outcomes[14].

Unfortunately, both randomized controlled studies used older versions of a blinded CGM device, where glucose values were not directly visible for patients. In contrast, more recently developed "real-time" CGM (rt-CGM) systems provide users with information about current glucose levels and alert the patient before the upper or lower glucose threshold is

reached or when glucose levels change rapidly. Hence, glycaemic excursions can be rapidly identified and accordingly adapted by behavioural change or pharmacologic intervention. A number of studies including non-pregnant patients showed superiority of rt-CGM over older blinded CGM versions in order to effectively empower and educate patients with diabetes to better understand how dietary habits, exercise or pharmacotherapy affects their glucose levels[15]. A beneficial effect of rt-CGM in pregnancy was also supported by the CONCEPTT trial for pregnant women with type 1 diabetes[16]. Only one recent study compared SMBG with rt-CGM in women with GDM using a single application for 3 to 7 days within two weeks after diagnosis but it failed to demonstrate improvements in HbA1c or pregnancy outcomes, which was, however, likely due to the sample size and the short duration of intervention (single application)[17].

Taken together, larger randomized controlled studies adequately powered to evaluate the impact of long-term application of rt-CGM systems on the risk reduction of adverse obstetric outcomes are missing[18]. Of note, such studies are of high clinical relevance because of their guideline-changing potential. In addition, rt-CGM has the potential to reduce reported barriers to SMBG (such as inconvenience, pain or stigma of testing in public places) in order to improve poor reliability and adherence to glucose monitoring, which is a non-negligible problem in the treatment of GDM[19].

Hypotheses

The main hypothesis of the proposed study is that rt-CGM can effectively reduce the risk for LGA newborns (primary outcome) and other neonatal and obstetric complications. It is further hypothesized that rt-CGM can improve maternal glycaemic control, body weight gain during pregnancy and (as rt-CGM potentially improves self-management strategies) has beneficial effects on maternal metabolism after pregnancy.

Primary and secondary outcomes

Primary objective: To assess differences in the proportion of LGA newborns (birth weight >90th pctl) in women with GDM using rt-CGM as compared to women with GDM using SMBG.

Secondary objectives: To assess differences in further obstetric or neonatal complications, neonatal hypoglycaemia, rate of caesarean section, shoulder dystocia and neonatal anthropometry will be assessed as secondary objectives. Further secondary outcomes are: differences in neonatal hyperinsulinemia, rt-CGM measures such as mean interstitial glucose, glycaemic variability, time in target (65 to 140 mg/dl [3.6 to 7.8 mmol/l]) as well as time spent in hyper- and hypoglycaemia (Time above and below range) (day-time: 07.01 to 22.59hr and night-time: 23.00 to 07.00hr), duration and frequency postprandial hyperglycaemic excursions, start and amount of glucose lowering therapy, HbA1c, glycosylated fibronectin, change in bodyweight during pregnancy and after delivery as well as glucose disposal at postpartum (markers of insulin sensitivity, insulin secretion and β-cell function assessed by a postpartum

OGTT). Health-related quality of life (HRQoL) is a patient-reported outcome which has become as important in the evaluation of interventions as patient-relevant clinical outcomes. Therefore, HRQoL will be elicited. In addition, preferences will be assessed, and a health economic evaluation in terms of cost-effectiveness and cost-utility analysis will be performed.

Expected effects on the advancement of clinical practice

The aim of this proposal is to assess the ability of rt-CGM to improve glycaemic control (reduction of mean glucose, hyperglycaemic episodes and duration, improvement of glycaemic variability) in order to prevent adverse pregnancy outcomes and neonatal complications in women with GDM. The results of this study will contribute to:

- The improvement of clinical monitoring and management of glucose metabolism during pregnancy with GDM
- Increased knowledge about possible limitations of SMBG (routine care), such as undetected hyper- or hypoglycaemia, as well as to determine if comprehensive glucose data (as derived from rt-CGM) results in more or fewer women needing pharmacotherapy
- Possible improvement of adverse perinatal outcome and particularly fetal macrosomia in offspring of mothers with GDM

3 METHODS AND ANALYSIS

Participants and recruitment; Inclusion criteria

This study is designed as an open-label multicentre randomized controlled trial with two parallel groups including a total of 372 female patients (n=186 with rt-CGM, n=186 with SMBG) with a recent diagnosis of GDM. Diagnosis of GDM (i.e. diabetes first diagnosed in the second and third trimester and not clearly type 1 or type 2 diabetes[20]) is made in accordance with the IADPSG criteria after 24+0 weeks of gestation by a 2h 75g OGTT[21]. The study will be conducted at five academic hospitals in Austria, Switzerland, Sweden and Germany. All pregnant females (aged between 18 and 55 years) will be consecutively recruited after diagnosis of GDM between 24+0 and 31+6 weeks of gestation among women visiting the pregnancy outpatient departments (Division of Obstetrics and feto-maternal Medicine, Medical University of Vienna, Austria; Division of Obstetrics, University Hospital Basel, Switzerland; Department of Obstetrics, Charité-Universitätsmedizin Berlin, Germany) or the diabetes outpatient departments (Division of Endocrinology and Metabolic Diseases at the Heinrich Heine University, Düsseldorf, Germany; Department of Medicine, University Hospital, Örebro, Sweden).

Exclusion criteria

Overt diabetes (i.e. pregestationally known type 1 or type 2 diabetes or fasting plasma glucose during the OGTT ≥126 mg/dl [7.0 mmol/l] or HbA1c ≥6.5% [44 mmol/l] or 2h post-load OGTT levels ≥200 mg/dl [11.1 mmol/l] assessed before 24+0 weeks of gestation, whereby results need to be confirmed by repeated testing in the absence of unequivocal hyperglycaemia according to the ADA standards[20]), history of bariatric surgery or other surgeries that induce malabsorption, long-term use (>2 weeks) of systemic steroids prior to enrolment, multiple pregnancy, patients already using glucose lowering medications (metformin or insulin) before study entry, fetal growth restriction due to placental dysfunction at study entry, inpatient psychiatric treatment up to 1 year before enrolment, participation in this study in previous pregnancy.

Study visits during pregnancy

A flow-diagram of the study visits is provided in Figure 1. A broad risk evaluation will be performed in participating females at the initial contact (V1) including: evaluation of maternal age, parity, history of GDM in previous pregnancies, detailed family history, ethnicity, preconceptional diseases, obstetric history. Height (stadiometer measured to the nearest centimetre) and actual weight (calibrated scales, light indoor clothing) will be additionally assessed. Moreover, an evaluation of preconceptional weight (self-reported) and body mass index (BMI) as well as measurement of blood pressure will be performed. All patients receive

medical advice for nutrition (isocaloric diet containing 40-50% carbohydrates, 20% proteins and 30-35% fat, divided into three meals and three snacks) and regular physical exercising for 30 minutes per day following international recommendations. In addition, participants are advised on capillary blood glucose measurement (fasting as well as 1h after starting each meal) at the initial visit (V1). Randomization will be done after a run-in period of 6 to 8 days when patients get used to SMBG (V2). The third visit (V3) will be scheduled 8 to 10 days after V2 and further follow-up visits every two weeks (i.e. 12 to 16 days after each visit). HbA1c and glycosylated fibronectin will be assessed at V2 as well as at the first visit between 36+0 and 38+6 weeks of gestation (12 ml, non-fasting state) (V4). Detailed fetal ultrasound examinations, a detailed examination of dietary intake as well as a blinded CGM (control group only) will be performed at V2 and V4. Body weight change and use of glucose lowering medications (amount of insulin units) will be examined at every visit. At every follow-up visit glucose measurements (SMBG or rt-CGM) and routine ultrasound examinations (fetal biometry and umbilical artery doppler) will be evaluated by the medical staff and all patients will be treated according to the standard of care for patients with GDM. This includes lifestyle modification and insulin therapy if recommended thresholds are exceeded. Both groups will be treated to be in the target range between 65 to 140 mg/dl [3.6 to 7.8 mmol/l] with at least 8h fasting glucose levels equal or below 95 mg/dl [5.3 mmol/l] and 1h postprandial glucose measurements equal or below 140 mg/dl [7.8 mmol/l] in accordance with the CONCEPTT study[16] and the ADA recommendations[22], respectively. Intermediate acting neutral protamine Hagedorn (NPH) insulin is started in the evening if ≥2 measurements of fasting glucose are equal or above 95 mg/dl [5.3 mmol/l] in a period of one week and rapid acting insulin analogues (Aspart or Lispro) if ≥2 measurements of 1h postprandial glucose (either after breakfast, lunch or dinner) are equal or above 140 mg/dl [7.8 mmol/l] in a period of one week. NPH is started with 6 to 10 IU and increased by 4 IU (or in case of higher doses i.e. >25 IU by 20%) and rapid acting insulin (bolus insulin) is started with 2 to 4 IU and increased by 2 to 4 IU if thresholds are not achieved within three days. Long acting insulin analogues such as glargine (U100/U300) or detemir can be used as an alternative to NPH. Patients are trained on insulin management and titration according to their glucose levels. Metformin can be used according to local practice guidelines (recommended in Sweden but not in Austria, Germany or Switzerland as first-line pharmacological intervention).

Study visits postpartum

Cord blood will be sampled and stored (at -80°C) immediately after delivery (VPP0). A postpartum examination will be scheduled within 48 hours after delivery (VPP1) for assessment of neonatal parameters and maternal HbA1c and glycosylated fibronectin (12 ml, non-fasting state), as well as between 8 to 16 weeks after delivery (VPP2) in all patients for a detailed re-examination of glucose homeostasis postpartum (including lifestyle and dietary

pattern as well as HbA1c, glycosylated fibronectin as well as a blinded CGM for 10 days and an OGTT to assess the presence of prediabetic conditions after pregnancy with GDM). The postpartum OGTT is further used to provide estimates of insulin sensitivity, β-cell function and hepatic insulin extraction, the major physiological components of impaired glucose tolerance.

Randomization

Participants will be randomized to either treatment (rt-CGM augmented glucose monitoring) or control group (routine care SMBG) in a 1:1 ratio. The minimization method[23] with a 0.85 assignment probability will be used to minimize the imbalance between the groups according to week of gestation at study entry i.e. at V1 (three strata: 24+0 to 25+6, 26+0 to 27+6, 28+0 to 29+6, 30+0 to 31+6), previous pregnancy with GDM (two strata: yes or no) and preconceptional overweight/obesity status with three strata: i. normal weight (i.e. BMI below 25.0 kg/m²); ii. overweight (BMI 25.0 – 29.9 kg/m²); iii. obesity (BMI equal or above 30.0 kg/m²). Randomization will be performed at the second study visit (V2) by using a randomization software provided by the Medical University of Vienna.

Intervention

Patients randomized to the intervention group will be equipped with a rt-CGM sensor (Dexcom G6 sensor, a small flexible device that records interstitial glucose levels every five minutes) at V2. The sensor will be inserted into the subcutaneous tissue of the anterior abdominal wall (if this location is not tolerated by the pregnant patients, the upper buttock or posterior upper arm may be used instead). Additionally, patients will be advised to record capillary blood glucose values if glucose alerts or readings do not match with symptoms or expectations. Participants will be educated on how to exchange the sensor (has to be exchanged every ten days) and will be equipped with a real-time CGM monitor and instructed in its use. The monitor provides the user with information about current glucose levels and notifies the patient before her upper or lower glucose threshold are reached and when glucose levels change rapidly. All patients in the intervention group will be specially trained in the use of the system. As an alternative to the real-time monitor the patients' smart phone with an anonymized access to the CLARITY® mobile app can be used (details see below: "Intervention: Device description").

Intervention: Device description

The Dexcom G6 intended use is for the management of diabetes in persons aged 2 years and older. The Dexcom G6 System is intended to replace fingerstick blood glucose testing for diabetes treatment decisions. Interpretation of the Dexcom G6 System results should be based on the glucose trends and several sequential readings over time. The Dexcom G6 System also aids in the detection of episodes of hyperglycaemia and hypoglycaemia, facilitating both acute and long-term therapy adjustments. The Dexcom G6 System can be used alone or in conjunction with digitally connected medical devices for the purpose of managing diabetes.

The system consists of a sensor, transmitter, receiver, and mobile app. The sensor is a small, flexible wire inserted into subcutaneous tissue where it converts glucose into electrical current. The sensor incorporates an interferent layer that minimizes the effect of potential electroactive interferents, such as acetaminophen, by preventing it from reaching the sensor wire surface. The benefit of this interferent layer in blocking the effects of acetaminophen prevents falsely high glucose readings. Thus, users may ingest acetaminophen while wearing the G6 CGM system. The transmitter, which is connected to the sensor and worn on the body, samples the electrical current produced by the sensor and converts the measurement into a glucose reading using an onboard algorithm. The receiver and/or the app displays the glucose reading along with a rate of change arrow and a trend graph. Additionally, the receiver and/or app issues alarms and alerts to notify the patient of glucose level changes and other important system conditions. Also, alarms will be provided if the receiver detects loss of connection to the sensor. The app provides the additional capability to share data with "followers" using the Dexcom Share service. The receiver can be put into a blinded mode using CLARITY® software. In this mode, users are unable to see the CGM data or receive CGM alerts.

CGM Ancillary Devices Dexcom CLARITY® is an accessory for users of the Dexcom CGM system. It is a software program that allows the transfer of glucose data from the CGM system to Dexcom remote servers for data management to allow the use of the CGM data by the user and study clinicians. Target ranges of 65 to 140 mg/dl [3.6 to 7.8 mmol/l] will be set and the patients will be introduced in the use of alarm settings. Both participants and study sites will use CLARITY® to transfer glucose data between user and study site, whether CGM is used in blinded or real-time mode. A CLARITY® mobile app can be used for a retrospective review of glucose data on the smart device and can also be set up to allow receipt of push notifications of CGM data facilitating weekly data review. For all patients (intervention and control group) an anonymized CLARITY® account will be created by using a sequential study number which is allocated at randomization (sex will be female and birth date for each account will be set to 1.1.1990 for all accounts). CLARITY® also provides metrics to check for patient compliance.

Intervention: Study proceedings

- For participants who have a supported phone, the G6 CGM app will be installed on participant's smart phone.
- An anonymized CLARITY® mobile account will be set up and linked to the research site.
- Participants will use CGM data for their diabetes management.
- A high alert threshold will be set at 140 mg/dl [7.8 mmol/l]. Low alert threshold and urgent low soon alerts will be turned off. If participants require insulin, the low alert will be turned on and the threshold set at 65 mg/dl [3.6 mmol/l]. In addition, the urgent low alert (55 mg/dl [3.1 mmol/l]), the urgent low soon alert (when glucose levels are falling fast and will be below 55

mg/dl [3.1 mmol/l] in less than 20 min) as well as alerts for rise and fall rate (3 mg/dl [0.17 mmol/l]) in addition to alerts for signal loss and no readings for more than 20 min will be enabled.

- Participants with applicable smart phones may have CLARITY® push notifications on the CLARITY® mobile app about weekly time in range comparison enabled during the study.
- For app users, the "Share and Follow" functionality will be discussed and encouraged (i.e. the study participants are able to invite followers to review their glucose levels).
- For participants using the receiver only, the receiver will be downloaded into the CLARITY® clinic account at each visit.
- For participants using real-time CGM data summary will be downloaded for documentation at V3 and V4 (between 36+0 and 38+6) as well as after delivery (VPP1).
- The research team will review the CGM in CLARITY® to inform lifestyle and therapy recommendations.
- The Dexcom G6 system does not require calibration during the study period.

Control group

The participants of the control group will perform self-monitored blood glucose testing with a study-provided blood glucose meter, including testing supplies. They will perform capillary blood glucose monitoring as routinely used for patients with GDM, i.e., at least four capillary blood glucose values daily including measurements in a fasting state as well as 1h after starting each meal by using a routinely available blood glucose measurement device. The study participants will keep a logbook of their glucose values, which will be reviewed by clinicians from the study team at each visit and used for lifestyle and dietary recommendations as is routinely done in clinical practice. From V2 to V3 as well as once for ten days between gestational week 36+0 and 38+6 the control group receive blinded CGM; neither patients nor the treating medical staff will have access to the data recorded by the CGM sensor at this point in time. Instead, patients will control blood glucose levels based on SMBG, as is the routine procedure in current GDM treatment. Otherwise, the control group will receive the same study assessments as the intervention group. The blinded CGM will be removed and returned to Dexcom after the 10-day wear period after CGM data is uploaded to CLARITY® by an unblinded investigator who must not communicate about the results with patients or medical staff.

Each participant of the control group will be assigned a study blood glucose meter to measure and store their blood glucose values during the study. Therefore, the Contour® Next One system will be used. The meter has CE Mark clearance and is commercially available in Europe. Participants will receive an ample supply of meter test materials based on quantities routinely used. A commercially available desktop software (Diabass® Pro) used in conjunction with Contour® Next One system glucose meter for blood glucose monitoring, will be utilized for

downloading the meter data by the sites at V3 and V4 after checking that dates and times are correct.

Blood glucose meters used by the control group will be assessed to establish frequency of testing (overall and per week) as well as percentage of days with less than four measurements per day.

Analyses of CGM data

Rt-CGM data allows a detailed examination of the percentage of time in which glucose levels are in target range (time in target) (65 to 140 mg/dl [3.6 to 7.8 mmol/l]), hyperglycaemic episodes (glucose ≥140 mg/dl [7.8 mmol/l]) as well as mild (<65 mg/dl [3.6 mmol/l]), moderate (≤54 mg/dl [3.0 mmol/l]) or severe hypoglycaemic episodes (requiring third party assistance) and their duration. To this purpose, several indices of the glucose control quality will be calculated, such as GRADE (Glycaemic Risk Assessment Diabetes Equation) some indices of hypoglycaemia and hyperglycaemia, such as the HBGI (High Blood Glucose Index) and LBGI (Low Blood Glucose Index), and indices assessing the risk associated to both low and high glycaemic values, such as IGC (Index of Glycaemic Control) and ADRR (Average Daily Risk Range). Glycaemic variability will also be assessed, which can be quantified by standard deviation of the CGM data, or by more sophisticated indices, such as MAGE (Mean Amplitude Glucose Excursions), CONGA (Continuous Overlapping Net Glycaemic Action), Lability Index[24,25], as well as further indices that we developed internally, such as the Shape Index[26]. These will be compared between real-time CGM users and controls (i.e. from data obtained during the blinded CGM wear).

Assessment of dietary patterns

Dietary patterns will be assessed in all patients at V1, VPP1, and VPP2 via a published and validated Food-Frequency-Questionnaire (FFQ) proposed by the German Robert Koch Institute[27]. It was also previously used for the German DEGS project (www.degs-studie.de). Information from the FFQ will be analysed quantitatively or summarized by eating scores proposed in the literature (such as the Healthy Eating Index 2010 or Alternate Healthy Eating Index 2010) reflecting diet quality based on actual guidelines[28,29]. In addition, all patients will be advised to conduct a nutritional protocol (seven days) from V2 to V3 as well as once at V4 (between 36+0 and 38+6 weeks of gestation). In a subgroup (only study site Vienna) dietary intake will also be assessed by performing 24-h-recalls by trained interviewers at V2, V4 and postpartum (VPP2): one face-to-face interview (approx. one hour) and the others as telephone interviews (approx. 30 minutes) during which data are entered simultaneously in GloboDiet. GloboDiet is a computerized program which was developed by the International Agency for Cancer Research (IARC) within the framework of the European Prospective Investigation into Cancer and Nutrition Study (EPIC-Study) for the conduction of harmonized and standardized

24-h-recalls[30]. This open-ended software was used in numerous previous studies and was validated within the EFCOVAL project[31–33]. In brief, GloboDiet is an interview-based dietary assessment instrument that allows obtaining a very detailed description and quantification of foods, recipes, and supplements consumed in the course of the preceding day and thus standardising data within and between countries. Probing questions and entering consumed foods in chronological order support the respondent's memory. The standardized structure prescribes – on the food group level – possibilities of description and quantification of food items to choose from. Quantification of consumed foods is supported by the GloboDiet picture book that comprises coloured photographs of foods in different portion sizes, photographs of familiar household measures and schematic displays of forms (e.g. bread, cake). The software provides an automatic coding of food items and recipe ingredients as well as a rough calculation of nutrient intake meant for quality control of the interview. GloboDiet is characterized by the obtained standardization of dietary data within Europe, a large number of available foods and recipes, and a very detailed description of consumed foods. Currently, GloboDiet is one of the few dietary instruments providing comparable nutritional data within Europe. After finalization of the interviews, GloboDiet will be linked to the local nutrition database – the Bundeslebenmittelschlüssel (BLS) enhanced by the Austrian Nutrition Table (Österreichische Nährwerttabelle, ÖNWT), containing typical Austrian foods and recipes – allowing analyses on food ingredients level and to conduct precise energy and risk assessment.

Assessment of physical activity

Physical activity will be assessed at V1, VPP1, and VPP2 via the International IPAQ (Physical Activity Questionnaire, long-form). The IPAQ represents a well-accepted, validated instrument for monitoring population levels of physical activity in different settings and countries[34]. It will be analysed via published guidelines for data processing and analysis at the IPAQ homepage Guidelines for data processing and analysis of the international physical activity questionnaire (IPAQ)[35]: In short, collected data will be summarized as median MET (metabolic equivalent of task) minutes per week, representing a continuous score for walking, moderate intensity activities, vigorous intensity activities and total activities, as recommended. In addition, the Pregnancy Physical Activity Questionnaire (PPAQ) will be performed to capture information on physical activity participation and sedentary behaviour during pregnancy[36].

Assessment of maternal intramyocellular and intrahepatocellular lipids

Intramyocellular (IMCL), and intrahepatocellular lipid contents (HCL) will be measured by using proton magnetic resonance spectroscopy (^{1}H MRS) in a subgroup of 40 patients (20 rt-CGM, 20 SMBG) at V3 and after delivery (VPP2) according to previously described methods[37–39]. The participants will be studied in supine position within a 3.0 Tesla whole-body magnet (Siemens or Philips). MRS is a non-invasive technique to evaluate tissue-specific metabolism

and was shown to be safe and well tolerated by pregnant women in previous studies[40,41]. Patients will be positioned with a left pelvic tilt to avoid pressure on the inferior vena cava according to other studies in pregnancy[41]. For IMCL measurements, the calf muscle (right leg) will be positioned in a quadrature bird cage ^{1}H volume coil. A circular ^{1}H surface coil will be positioned over the liver for HCL measurement.

Fetal biometry

Parameters of fetal anthropometry as determined by ultrasound as well as neonatal data including length, weight, gestational age at delivery will be included in the final analysis. A detailed fetal ultrasound examination will be performed at V2 and repeated at V4 (between 36+0 to 38+6 weeks of gestation) to assess fetal growth parameters including head circumference, biparietal diameter and abdominal circumference and abdominal fat thickness, femur length (measured and expressed as standardized gestational age related fetal growth percentiles[42]), amnion fluid index as well as size and location of the placenta and fetal subcutaneous tissue thickness. Moreover, fetal growth symmetry will be assessed by fetal head to abdomen circumference ratio and fetal doppler measurements (mainly umbilical artery and middle cerebral artery[43] and ductus venosus). Furthermore, fetal hepatic size (all hepatic diameters, such as area and volume) and umbilical venous volume flow and an echocardiography of the foetus will be performed in a subgroup (only study site Vienna).

Obstetric outcome

Obstetric outcome (caesarean section, birth injury, preterm birth before 37 completed weeks of gestation) stillbirth, small for gestational age (birth weight <10th pctl), large for gestational age infant (birth weight >90th pctl), shoulder dystocia, admitted to neonatal intensive care unit umbilical cord blood pH, Apgar score) will be recorded immediately after delivery. Length of hospital stay for mothers and offspring as well the duration of high-level neonatal care, respiratory distress, fetal hyperbilirubinemia and neonatal death ≤28 days will be further assessed. Calculations of age and sex adjusted percentiles will be performed by using international anthropometric standards according to those used in the CONCEPTT study[44]. Neonatal hypoglycaemia is defined as local blood glucose ≤31 mg/dl [1.7 mmol/l] in the first 24h after delivery and ≤45 mg/dl [2.5 mmol/l] after the first 24h after delivery or treatment with glucose infusion according to the HAPO study[3]. Additional anthropometric measures of the offspring include head, shoulder and abdominal circumference, length, upper and lower arm and leg circumference and skinfold measurements (suprailiac and subscapular, triceps, quadriceps) in accordance with previous studies[45–47]. Thereby skinfold measurements will be performed by using a validated instrument (Harpenden Skinfold Caliper) within 48h after delivery (VPP1).

Assessment of cord blood

17 ml umbilical cord blood (1x8 ml serum and 1x9 ml EDTA) will be taken immediately after delivery to examine cord-blood glucose, insulin and C-peptide.

Postpartum OGTT

The OGTT will be performed at VPP2 (i.e. 8 – 16 weeks after delivery): after collecting blood samples for measurements of glucose (2 ml blood), insulin and C-peptide (3 ml blood) in the fasting state (at least 8 hours), participating females will receive a standardized 300 ml 75g glucose. Further blood samples of glucose, insulin and C-peptide measurements will be taken at 30, 60, 90, and 120 minutes after intake of glucose. Insulin sensitivity during the OGTT will be assessed by the oral glucose insulin sensitivity index (OGIS) according to Mari et al.[48]; this quantifies dynamic glucose clearance per unit change of insulin. The more recently developed PREDIM index will be used in addition[49]. The new index provides excellent prediction of clamp-derived insulin sensitivity from OGTT or meal data. As an approximation for hepatic insulin resistance the homeostasis model assessment of insulin resistance (HOMA-IR) will be used. Insulin secretion will be calculated by using the C-peptide deconvolution method[50]. β-cell function parameters, such as pancreatic glucose sensitivity and rate sensitivity, and potentiation of insulin secretion, will be computed by mathematical modelling[50].

Assessment of health-related quality of life and patients' preferences

Health-related quality of life will be elicited using the SF36 and the EQ-5D-5L[51]. It can be expected that adherence to lifestyle and dietary recommendations are associated with individual risk preferences. Hence, risk and time preferences will be elicited based on a lottery approach[52,53]. Participants will be asked to choose between two hypothetical lotteries that differ in expected outcomes which enables us to derive an individual classification of the risk type, i.e. risk-averse, risk-neutral or risk-loving individuals. Quality of life as well as risk and time preferences will be assessed at V1, VPP1, and VPP2. Obstetrical patient's satisfaction will be additionally assessed at VPP1 by using the Wijma score[54].

Patient and public involvement

Patients and public were not involved in the study design and will not be involved in the study conduct, recruitment and dissemination.

Health economic evaluation

For the evaluation of a complex intervention, a health economic evaluation is recommended as well[55,56]. In this study, a cost-effectiveness (CEA) and a cost-utility analysis (CUA) will be conducted from the perspective of the health insurance. The effect measure employed in

the CEA will be the primary outcome of the main trial, i.e. avoided cases of LGA newborns. Even if the effect parameter of the intervention group will not be superior to the control group, a health economic evaluation will be performed to inform about efficiency since costs might be lower in the intervention group [57]. Due to the short intervention period quality-adjusted life-weeks (QALWs) will be used in the CUA. QALWs will be calculated based on either the EQ-5D-5L or the SF-6D[58] that derives preference-based scores from the SF-36. To receive utilities, quality of life will be evaluated by country-specific population-based preferences separately for each country involved in the trial. Similarly, intervention costs as well as health care costs (direct costs) will be calculated separately for each country using local prices and adjusted for local purchasing power parity (PPP). Health care use will be assessed by a validated instrument that is adapted to the requirements of the study[59]. Health care use will comprise resource use dedicated to the mother but not the child, e.g. clinical visits, outpatient contacts, contacts with therapists, and medication. Intervention associated costs are costs of devices, software, test strips, and costs due to education and training of study participants. Since the evaluation covers only the observation period alongside the trial, costs and effects will not be discounted. Comparing the outcomes and costs of the intervention group with the outcomes and costs of the control group yields the incremental cost-effectiveness ratio (ICER: additional cost per additional LGA newborn avoided) and the cost-utility ratio (ICUR: additional costs per additional QALW gained).

Reporting of adverse events, data and safety monitoring

Any (serious) adverse events (AE/SAE) are recorded by the investigator using the specific AE/SAE sheet of the clinical report form (CRF). All SAE are reported to the responsible ethics committee within an appropriate time frame.

Data safety and accuracy as well as patient safety will be monitored by local data and safety monitoring committees for clinical trials (e.g. the KKS – competence centre for clinical trials – in Austria).

Sample Size and Statistical Analysis

Sample size

With a sample size of n=338 (169 pregnant women per group) we will be able to detect a difference between two independent proportions of LGA of 13.7% vs 25.8% (according to the results of a previous study[11]) with a power of 80% and a two-sided type 1 error of α=0.05 (calculated for Pearson's chi-square test). Considering a drop-out rate of 10% a total sample size of n=372 (186 women per group) is necessary for this study. This is in line with the sample size suggested by Kestilä et al.[13]. A blinded sample size review (the proportion of LGA cases in the sample is reviewed) and adaptation is planned after 50% of the patients have been

investigated. The sample-size calculation was performed by using the software G*Power (V3.1.9.2)[60].

Analysis plan

Analyses should be conducted on the intention-to-treat principle. Categorical variables will be summarized by counts and proportions; continuous variables data will be summarized by means and standard deviations (SD) or by median and interquartile range in the case of strong deviations from the normal distribution. Pearson's chi-square test will be used to compare differences in the primary outcome (difference in proportion of LGA newborns) and for binary secondary outcomes (such as caesarean section rate, shoulder dystocia and neonatal hypoglycaemia). Bernard's test will be used as an alternative if an expected frequency in contingence tables is equal or less than 5 and the Cochran-Mantel-Haenszel method will be used as sensitivity analysis to adjust for possible centre specific effects. Continuous secondary outcome parameters (such as mean glucose, duration and amount of hyperglycaemia, glycaemic variability and other rt-CGM measures, postpartum OGTT data, HbA1c, glycosylated fibronectin or anthropometric data of the newborn) will be compared by student's t-test. Rank based inference (such as the Brunner-Munzel test[61]) will be used as an alternative in case of skewed distributed parameters. The association between HbA1c, rt-CGM measures and delivery and risk of LGA offspring will be assessed by binary logistic regression. There are many possible objectives for which further exploratory analysis could be performed in this study (e.g. functional principal components analysis for rt-CGM data). Hence, the present analysis plan represents only a selection of methods, which will be used for analysing the main objectives. Risk preferences will be analysed by non-parametric and parametric methods. In particular, we plan to classify study participants with respect to their risk tolerance (risk-aversion, risk-neutral, and risk-loving) and deriving CRRA (constant relative risk aversion) utility functions. Associations between risk preferences and behaviour (dietary patterns and physical activity) will be investigated. For the health economic evaluation, incremental cost-effectiveness ratios (ICER: Additional cost per additional LGA newborn avoided) and cost-utility ratios (ICUR: Additional cost per additional quality-adjusted life year gained) will be calculated. 95% confidence intervals will be analysed using bootstrap procedures[62]. To consider uncertainty, cost-acceptability curves will be calculated[63]. A two-sided p-value ≤0.05 is considered statistically significant. All analyses will be performed by using the statistic software R and contributing packages[64]. No further adjustment for multiplicity is planned for this study.

4. ETHICS AND DISSEMINATION

This study received ethical approval from the main ethic committee in Vienna (1863/2018). Ethics approval will be obtained by the local institutional review boards in Basel, Berlin,

Dusseldorf, and Orebro. It was registered under www.ClinicalTrials.gov (NCT03981328). Data will be presented at international conferences and published in peer-reviewed journals.

Author statement

EH, KW, JJ, AI, JS, AT, MM, CSG designed the study. MM, AT, AI, MV, GGG, JM, CSG, PR will perform statistical analysis and data interpretation. EH, TL, DE, KW, CK, KW, KS, GYS, IR, WH, KC, JS, CSG will be responsible for patient management. PH, WH, TL, IH, MR, PR, HF, MV, GGG, JM, BW, GYS, CK, KS will make important contributions and critically reviewed this study protocol.

Acknowledgements

Special thanks to all families who participate in this study.

Funding

This study is supported by Dexcom grant project number OUS-2018-027. The funding source is not involved in study design, the collection, analysis and interpretation of data, the writing of the manuscript; and in the decision to submit the article for publication.

Competing interest statement

The authors declare that there are no further financial or personal relationships with other people or organizations that could inappropriately influence the work reported or the conclusions, implications, or opinions stated.

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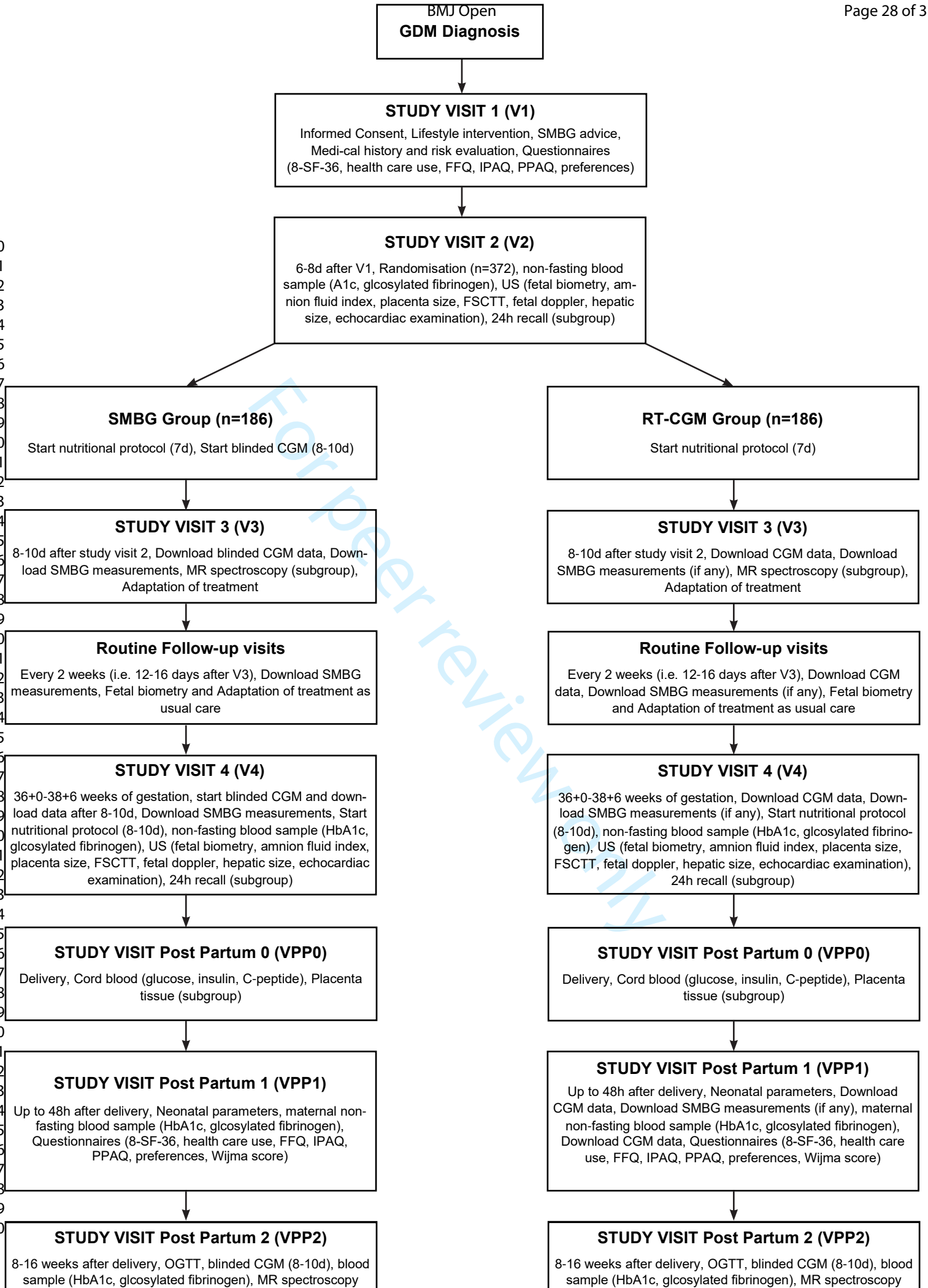
6 FIGURES

Figure 1: Patient flow diagram



SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym → title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry → page 3
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier → only in original protocol
Funding	4	Sources and types of financial, material, and other support → page18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors → page 2
	5b	Name and contact information for the trial sponsor → page 1/18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention → page 5-7 (Introduction)
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses → page 7 (Hypotheses)

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) → see Title
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained → page 8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) → page 8 (Eligibility criteria)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered → page 8/9 (Study procedure)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) → not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) → not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial → not applicable
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended → page 6 (Study outcomes)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) → page 8/9
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations →page 17/18 (Sample size justification)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
Methods: Assignment of interventions (for controlled trials) → page 9		

Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how –> not applicable
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial → not applicable
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol → page 13-15 (Study analysis plan)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) → page 15-19 (Other study measurements)

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct → see Reporting of adverse events, page 17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval → page 8 (Study settings/design)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial → page 9 (Data recording)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site → (page 3 (Conflict of interest)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions → page 18
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.