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CGM FOR THE EARLY DETECTION AND MANAGEMENT OF HYPERGLYCEMIA IN PREGNANCY

Protocol Identifying Number: IMAGINE

Version Number: 1.2

January 21, 2025

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VERSION HISTORY

VERSION NUMBER	AUTHOR	APPROVER	EFFECTIVE DATE	REVISION DESCRIPTION
1.0	Judy Sibayan	Celeste Durnwald Roy Beck		Original
1.1*	Judy Sibayan Sarah Frey Shannon Peleg	Celeste Durnwald Roy Beck Judy Sibayan		1. Updated HbA1c eligibility criteria for RCT. 2. Updated the target glucose time in range. 3. Added nonparticipation in a separate intervention trial as eligibility criteria for RCT. 4. Clarified risk of glycemic management. 5. Added DSMB safety management information 6. Clarified statistical considerations

*Version in effect at study initiation

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LIST OF ABBREVIATIONS

Add any abbreviations used in the protocol document. The use of abbreviations should be minimized to only those that are commonly known.

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
APO	Adverse Pregnancy Outcomes
BMI	Body Mass Index
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CI	Confidence Interval
CRF	Case Report Form
DKA	Diabetic Ketoacidosis
DSMB	Data and Safety Monitoring Board
EHR	Electronic Health Record
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GDM	Gestational Diabetes Mellitus
HbA1c	Hemoglobin A1c
HDP	Maternal Hypertensive Disorder of Pregnancy
ICH	International Conference on Harmonization
IQR	Interquartile Range
IRB	Institutional Review Board
LGA	Large for Gestational Age
MD	Maternal Dysglycemia
NICU	Neonatal Intensive Care Unit
OGTT	Oral Glucose Tolerance Test
QA	Quality Assurance
QC	Quality Control
RCT	Randomized Clinical Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SGA	Small for Gestational Age
UADE	Unanticipated Adverse Device Effect

SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: CGM FOR THE EARLY DETECTION AND MANAGEMENT OF HYPERGLYCEMIA IN PREGNANCY

Protocol Version/Date: 1.0/21OCT2024

I have read the protocol specified above and agree to personally conduct or supervise the study in accordance with the current protocol. In my formal capacity as a Site Principal Investigator, my duties include ensuring the safety of the study participants enrolled under my supervision and providing the Jaeb Center for Health Research, which serves as the Coordinating Center for the protocol, with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. I agree to maintain accurate and current records and to make those records available for inspection in accordance with 21 CFR 812.40.

This trial will be carried out in accordance with ICH E6 (R2) Good Clinical Practice (GCP) and United States (US) Code of Federal Regulations (CFR) 45 CFR 46, 21 CFR 50, 21 CFR 56, and 21 CFR 812.

[For participating sites outside of the United States, the trial will be carried out in accordance with ICH E6 (R2) Good Clinical Practice (GCP), the Declaration of Helsinki, and specific regulations applicable to the countries in which the trial will be conducted.]

As the Principal Investigator, I will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Coordinating Center and documented approval from the Institutional Review Board (IRB), or other approved Ethics Committee, except where necessary to eliminate an immediate hazard(s) to the trial participants. I will ensure that an IRB will be responsible for the initial and continuing review and approval of the investigation. I also agree to promptly report to the IRB all unanticipated problems involving risks to human subjects or others.

I agree to inform all participants that the investigational product is being used for investigational purposes. I agree to report to the Coordinating Center adverse experiences that occur in the course of the investigation in accordance with 21 CFR 812 and the current protocol. I understand the potential risks and side effects of the investigational product.

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Good Clinical Practice Training. Further, I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Investigator's Signature _____ Date: _____ / _____ / _____
dd mmm yyyy

Investigator's Name: _____

Site Name/Number: _____

PROTOCOL SUMMARY

Title	**CGM FOR THE EARLY DETECTION AND MANAGEMENT OF HYPERGLYCEMIA IN PREGNANCY: "IMAGINE"**
Rationale	Recent findings suggest that maternal hyperglycemia and its correlated increased risk with adverse pregnancy outcomes (APOs) is best mitigated with early detection and intervention prior to the 24th week of gestation, particularly in the first trimester or the beginning of the second trimester.[1] This underscores a potential limitation in the current standard of care in which the OGTT is administered in the late second/early third trimester (24-28 weeks) when, as an increasing body of clinical research suggests, it may be too late to counteract the perinatal consequences of maternal hyperglycemia. There may be benefit in identification and initiating treatment of maternal hyperglycemia earlier in pregnancy (prior to 16 weeks 6 days of gestation). [1.] *Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes—2019. Diabetes Care. 2019;42(Supplement 1):S165-S172. doi:10.2337/dc19-S014*
Précis	• Pregnant individuals without diabetes and a singleton, uncomplicated (low-risk) pregnancy will be enrolled by 14 weeks 6 days of gestation. Initially, a blinded CGM sensor will be worn to screen for hyperglycemia. • Participants with HbA1c (<6.5% [48 mmol/mol]) and exceeding the study-defined continuous glucose monitoring (CGM) threshold for hyperglycemia (≥5.0% of values >140 mg/dL [7.8 mmol/L]) will be randomly assigned to initiation of glucose management (unblinded CGM and medical therapy as indicated to minimize glucose levels >140 mg/dL [7.8 mmol/L]) or to usual care with collection of blinded CGM data at intervals. • Participants will be followed through the end of pregnancy and pregnancy outcomes will be assessed, including select APOs. • Participants not meeting CGM hyperglycemia criteria on initial screen or who do not enter the randomized controlled trial (RCT) for another reason and who have HbA1c <6.5% (48 mmol/mol), will form an observational cohort and have results of their OGTT and pregnancy outcomes recorded.
Objectives	• To determine whether the identification of maternal hyperglycemia using CGM early in pregnancy with initiation of

	dietary management and intensive glucose management, including medications if needed, at this early timepoint (intervention group) results in fewer APOs in the infant and mother compared with usual care (control group). • To compare CGM-measured glycemic metrics during the second and third trimesters of pregnancy in the Glucose Lowering group versus the Usual Care group. • To identify factors that modify the effect of early glucose-lowering intervention compared with usual care on a reduction in the risk of APOs. • To determine the frequency of normal and abnormal OGTTs at 24-28 weeks and APOs in pregnant individuals with no or little hyperglycemia at the time of study screening (i.e., screening CGM had hyperglycemia below the amount required for RCT eligibility)
Study Design	1. RCT of pregnant individuals with HbA1c (<6.5% [48 mmol/mol]) and CGM-measured hyperglycemia (5% to <25% of values >140 mg/dL [(7.8 mmol/L)]) on initial CGM screening 2. Observational study of pregnant individuals who undergo CGM screening but do not enter the RCT (provided that HbA1c is <6.5% [48 mmol/mol])
Number of Sites	~10-12 sites in the United States or United Kingdom
RCT Endpoints	**Primary Efficacy Outcome** • Composite endpoint of (1) neonatal complications of large for gestational age (LGA), shoulder dystocia (including humeral or clavicular fracture), elevated bilirubin requiring phototherapy, or neonatal intensive care unit (NICU) admission; or (2) maternal hypertensive disorder of pregnancy (HDP) **Key Secondary Efficacy Outcomes** • Composite of neonatal complications • Individual maternal and neonatal complications • Neonatal death **Key Safety Outcomes for Treatment Group Comparison:** • Small for gestational age (<10^{th} percentile) • CGM-measured time <54 mg/dL [3.0 mmol/L] (during comparative periods where Usual Care group has blinded CGM)

	• Severe hypoglycemia events • Other serious adverse events
Glycemia Exposure Assessment	• CGM data obtained in the Glucose Lowering group will be compared with data obtained using blinded sensors in the Usual Care group. • CGM data will be assessed longitudinally within the Glucose Lowering group
Population	**Inclusion Criteria** 1) Maternal age of 18 years and older 2) Singleton pregnancy 3) Gestational age up to 14w 6d of pregnancy, determined on ultrasound, for initiation of screening • *Although it is preferable that ultrasound results be available prior to enrollment, if ultrasound results are not available at the time of enrollment, participant can have CGM initiated but will be dropped if not eligible after results are available* 4) HbA1c <6.5% (48 mmol/mol) since onset of pregnancy • *If HbA1c result not available at time of enrollment, participant can have blinded screening CGM initiated, but results will be needed prior to randomization to verify eligibility.* 5) No prior history of gestational diabetes mellitus (GDM) 6) Able to read English or Spanish **Exclusion Criteria** 1) Signs of abnormal fetal or placental development (suspected fetal anomaly or placenta accreta spectrum, low PAPPA) at first routine prenatal visit/ultrasound 2) Planned termination of pregnancy or any indications of miscarriage 3) Prior gastric bypass surgery 4) Pregravid diabetes (type 1 or type 2) 5) Unwillingness/inability to wear CGM sensor 6) Unwillingness to attend routine antenatal obstetric appointments 7) Use of corticosteroids by a route that can produce hyperglycemia (e.g., oral, intravenous, intramuscular, intra-articular) during the 7 days prior to initiating CGM screening or

	during the CGM screening • *Topical and inhaled corticosteroids are acceptable* 8) Use of insulin during the pregnancy prior to enrollment 9) Use of metformin within one week of the initiation of the blinded CGM sensor for screening or use of a GLP-1 or other weight-reduction medication that can affect glucose levels within 4 weeks of the initiation of the blinded CGM sensor for screening 10) Deemed unable to participate for medical reasons identified by their physician **<u>Additional Criteria for RCT Eligibility</u>** 1) Screening CGM meeting study criteria for hyperglycemia: 5% to <25% time >140 mg/dL 2) Randomization by 16 week 6 days of pregnancy 3) No participation in a separate intervention trial.
Sample Size	Screening sample size: ~6,000 RCT sample size: ~1,500
Treatment Groups	Random assignment (1:1) to • Glucose Lowering Group • Usual Care Group (with periodic blinded CGM)
Participant Duration	~26-30 weeks
Study Duration (planned)	~30 months from first enrollment until last participant delivery
Protocol Overview/Synopsis	<u>Clinics</u> Clinics will be selected to provide a broad representation of pregnant individuals, including a substantial number of underserved individuals. <u>CGM</u> Both the Dexcom G7 and Abbott FreeStyle Libre 3 sensors will be used in the study in both blinded and unblinded modes. Clinical sites will be randomly assigned to be either a Dexcom site or an Abbott site. All participants at a site will use the site-assigned type of sensor in both blinded and unblinded modes. • *In analyses comparing treatment groups, type of sensor will be a covariate* <u>Screening for Eligibility</u> After consent is signed and eligibility determined, participants will wear a blinded CGM sensor for up to 10-14 days to assess for the

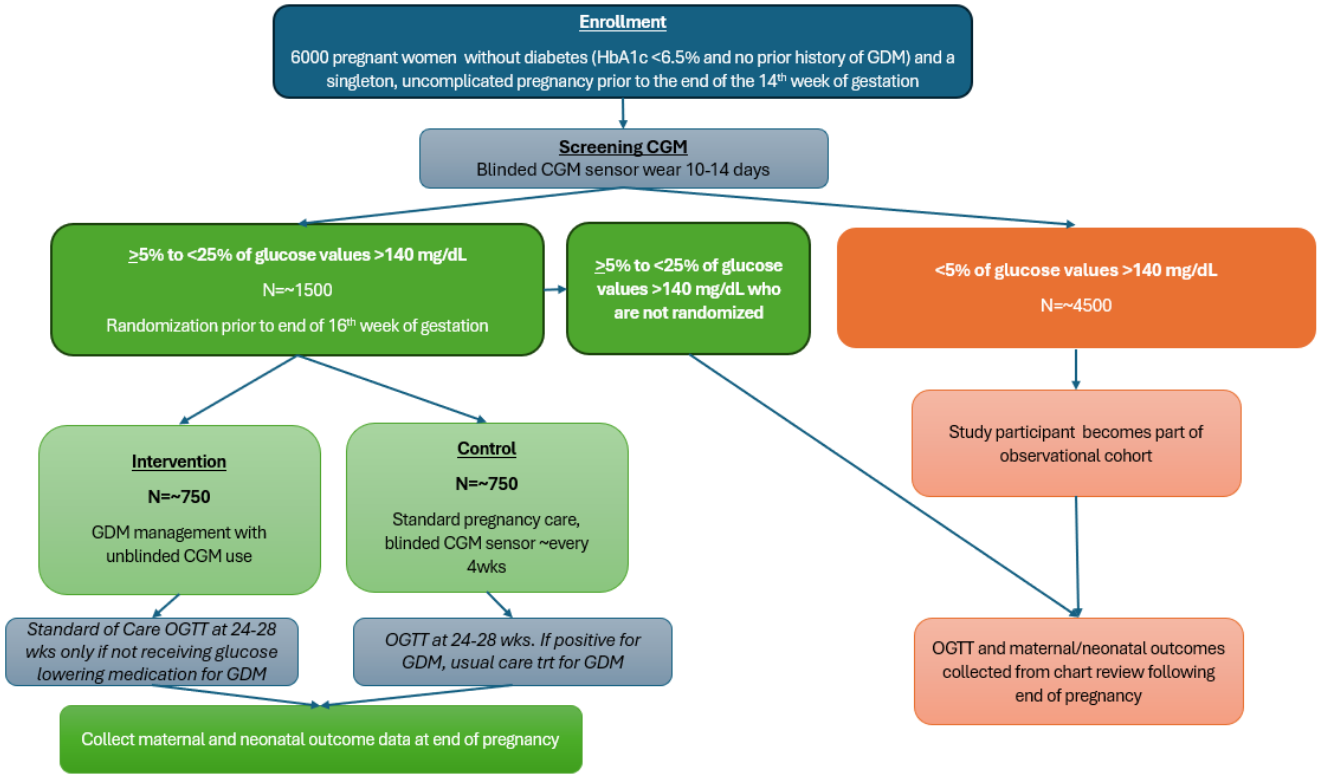
	presence of hyperglycemia. • As part of usual obstetric care, HbA1c will be measured and an ultrasound performed if not already done. <u>Determination of Eligibility for the RCT</u> The blinded CGM sensor data will be evaluated to determine if the following criterion is met: 5% to <25% of values >140 mg/dL • *An initial assessment will be made after 5 days and for those not meeting the criterion, again after 10 days* Participants meeting the CGM hyperglycemia criteria and the other study eligibility criteria will proceed to randomization, which must be performed by 16 weeks 6 days of gestation. Participants who do not meet the CGM hyperglycemia criteria will form an observational cohort, provided that HbA1c is <6.5% (48 mmol/mol) (see below) **Randomized Trial** Eligibility for the RCT will be reassessed in participants meeting the blinded CGM hyperglycemia criteria, including a determination that the participant is willing and able to follow the study protocol and will accept assignment to either treatment group. The Randomization Visit will be in clinic. All visits after randomization will be standard care visits. Eligible participants will be randomly assigned (1:1) to • Glucose Lowering Group: unblinded CGM plus glucose lowering management • Usual Care Group: usual care plus blinded CGM at intervals <u>Glucose Lowering Group</u> Management will include: • An unblinded CGM sensor worn 24/7 • GDM specific nutrition information • Training on using CGM in daily glucose management to achieve euglycemia (maximizing time 63-140 mg/dL [3.5-7.8 mmol/L]) • Guidelines for the clinician investigator on when and how to intervene pharmacologically with insulin or metformin o Insulin may be any commercially-available insulin by subcutaneous injection or inhalation in the U.S. or subcutaneous injection in the U.K., based on investigator and participant preference • Visits (which could be telehealth) per usual obstetrical care for glycemia management (expected to be about every 4

	weeks for most participants) • Weekly glycemic management with review of CGM data by site and by central CGM Resource Center for flagged cases • Participants not receiving glucose lowering medication by 24-28 weeks will undergo OGTT per usual obstetrical management o Participants with positive OGTT will be treated for GDM per usual clinic routine and continue to wear an unblinded CGM. <u>Usual Care Group</u> The control group will receive usual obstetrical care at the clinical center. • General pregnancy nutrition information handout will be provided to each participant. • A blinded CGM sensor will be placed at routine obstetrical care visits (no more often than once approximately every 4 weeks) and worn for 10-14 days each time throughout the pregnancy beginning between 18-22 weeks gestation (ideally to include 20, 28, 32 and 36 weeks if available). o If a routine visit is performed by telemedicine, then the participant may place the sensor at home • At 18-22 weeks, blinded CGM data will be reviewed to assess if participant has ≥25% time >140 mg/dL to determine if an early OGTT or glycemic management is required. Site clinicians will be unblinded to the masked CGM data for participants with CGM data ≥25% time >140 mg/dL and those participants may be treated as those with a positive OGTT. • An OGTT will be performed at ~24-28 weeks per the clinic's usual routine o Participants with positive OGTT will be treated for GDM per usual clinic routine ▪ Insulin, if prescribed, can be any commercially-available insulin by subcutaneous injection or inhalation in the U.S. or subcutaneous injection in the UK, based on investigator and participant preference ▪ If real-time CGM is to be used, then unblinded study CGM sensors can be used instead of blinded sensors for the duration of the study.

	▪ The usual target range will be standard of care targets and left to the discretion of the investigator. <u>Both Groups</u> • Serious adverse events will be reported during the pregnancy. Other reportable adverse events will be captured as part of the review of the Electronic Health Record (EHR) after completion of the pregnancy. • After completion of the pregnancy, data collected from the EHR will include: gestational week at time of delivery/end of pregnancy, maternal outcomes, fetal/neonatal outcomes, infant birth weight, adverse events, OGTT results, glycemic treatment **Observational Cohort** Participants who undergo CGM screening but do not enter the RCT (provided that HbA1c is <6.5% [48 mmol/mol]) will form an observational cohort. (There may be some with ≥5% time >140 mg/dL (7.8 mmol/L) who are not randomized.) • There will be no study-specific visits, procedures, or data collection. • At the end of the pregnancy, information collected as part of usual care will be obtained from the EHR: OGTT results, diagnosis of GDM, and maternal and infant outcomes.

SCHEMATIC OF STUDY DESIGN

Figure 1. Study Flow Diagram



SCHEDULE OF STUDY VISITS AND PROCEDURES

Table 1. Schedule of Enrollment/Screening

	SCREENING VISIT	PRIOR TO 16W 6D GESTATION	RANDOMIZATION VISIT
Informed Consent	**X**		
Eligibility Assessment*	**X**		**X**
Blinded CGM sensor insertion	**X**		
Review of CGM data centrally**		**X**	
Randomization of eligible participants			**X**

**Although it is preferable that ultrasound and HbA1c results be available prior to enrollment, if results are not available at the time of enrollment, participant can be enrolled and have CGM initiated but will be dropped if not eligible after results are available*

***CGM data will be assessed centrally after 5 days (and again at 10 days for those not meeting the initial criterion at 5 days) for eligibility. Site will be informed whether participant is eligible for randomization.*

Table 2. RCT Schedule of Procedures for Glucose-Lowering Group

	RANDOMIZATION VISIT	STANDARD CARE FOLLOW-UP	RESEARCH PROCEDURES	END OF PREGNANCY
Eligibility Assessment	**X**			
GDM Nutrition CGM Education, and Glucose Lowering Management	**X**		**X**	
Clinical review of unblinded CGM data reports*			**X**	
OGTT**		**X**		
Chart review at end of pregnancy				**X**

Follow-up visits per standard care.

**Weekly review of CGM data; feedback/treatment recommendations to participants as indicated.*

***May not be performed for participants receiving glucose lowering medications.*

Table 3. RCT Schedule of Procedures for Usual Care Group

	RANDOMIZATION VISIT	STANDARD CARE FOLLOW-UP	RESEARCH PROCEDURES	END OF PREGNANCY
Eligibility Assessment	**X**			
General Pregnancy Nutrition Education	**X**			
Blinded CGM use*			**X**	
OGTT		**X**		
Chart review at end of pregnancy				**X**

Follow-up visits per standard care

**Blinded CGM sensor inserted at standard care visits ~every 4 weeks beginning at 18-22 weeks. At about 20 week CGM data will be assessed to identify participants with ≥25% CGM time >140 mg/dL and the site will be unmasked to those identified participants CGM data.*

Chapter 1: Background Information

1.1 Background and Rationale

Recent findings suggest that maternal hyperglycemia and its correlated increased risk with many adverse pregnancy outcomes (APOs) is best mitigated with early detection and intervention prior to the 24th week of gestation, particularly in the first trimester or the beginning of the second trimester.[1] This underscores a potential weakness in the current standard of care in which the OGTT is administered towards the end of the second trimester when- as an increasing body of clinical research suggests- it may be too late to counteract the adverse effects of maternal hyperglycemia. There may be benefit in assessing and treating maternal hyperglycemia prior to the 16th week of pregnancy.

The GLAM observational study showed overall, CGM-derived mean glucose was slightly higher and percent time 63-120 mg/dL (3.5-6.7 mmol/L) was slightly lower in the first trimester, but both mean glucose and percent time 63-120 mg/dL (3.5-6.7 mmol/L) remained steady in the second and third trimesters for participants with uncomplicated pregnancies.[2] The median percent time 63-120 mg/dL (3.5-6.7 mmol/L) was 86% (interquartile range 82%-89%) suggesting this range is seen in a large percentage of uncomplicated pregnancies and may be an important metric to use when comparing CGM-derived metrics to perinatal outcomes in pregnancies complicated by gestational diabetes mellitus (GDM). The median percent time >140 mg/dL (>7.8 mmol/L) was 2.5% (IQR: 1.3% to 4.1%) indicating most uncomplicated pregnancies had approximately 30 minutes per day with glucose above 140 mg/dL (7.8 mmol/L) often occurring after lunch or dinner.

There is no standard CGM-based glucose range for euglycemic pregnancies; recommendations for glucose levels using CGM are mainly based off studies of participants with type 1 diabetes.[3] In one study of 58 normoglycemic pregnant individuals between gestational age 8-20 weeks, CGM data for up to 72 hours showed a percent time 63-140 mg/dL (3.5-7.8 mmol/L) of 98.2%.[4] In another study of individuals with gastric bypass that used a matched control group based on age, parity and BMI (no GDM), and found a percent time 63-140 mg/dL (3.5-7.8 mmol/L) of 96.1%, 95.9% and 93.5% in trimesters one, two and three, respectively among those without GDM.[5] The CGM-based glucose ranges observed in this study may be representative of glucose levels in all trimesters of uncomplicated pregnancies.

The post-prandial GLAM CGM data showed the peak glucose remained relatively stable throughout pregnancy. While there is no CGM-based consensus on a post-prandial glucose target in non-pregnant individuals, the post-prandial levels measured by CGM in this pregnant population are in the range of 100 to 120 mg/dL, which is similar to previously published post-prandial capillary glucose levels in participants with normoglycemic pregnancies.[6, 7] Additional analyses to confirm the observed time to peak glucose of approximately 60 minutes is similar in the GDM population of this cohort will help assess the optimal timing for basing postprandial glycemic targets in pregnancy, particularly when it comes to treatment with insulin.

In the current study, we propose use of blinded continuous glucose monitoring (CGM) as a tool to detect maternal hyperglycemia in early pregnancy prior to 16 weeks 6 days gestation and then randomly assign participants who meet a pre-specified threshold of hyperglycemia either to begin use of unblinded CGM and glucose lowering treatment or to standard care with interval

blinded CGM sensor wear and have a routine OGTT administered between the 24th and 28th week of gestation (and initiate GDM treatment thereafter if so diagnosed).

Towards the goal of assessing these hypotheses, we aim:

1) To determine whether the identification of hyperglycemia using continuous glucose monitoring (CGM) early in pregnancy with initiation of dietary and glucose management at this timepoint (intervention group) results in fewer adverse pregnancy outcomes (APOs) associated with hyperglycemia in the mother and infant compared with usual care (control group).
2) To compare CGM-measured glycemic metrics during the second and third trimesters of pregnancy in the intervention group versus the control group.
3) To identify factors that modify the effect of intensive intervention compared with usual care on a reduction in the risk of APOs.
4) To determine the frequency of normal and abnormal OGTTs at 24-28 weeks and APOs in pregnant individuals with no or little hyperglycemia at the time of study screening (i.e., screening blinded CGM had hyperglycemia below the amount required for RCT eligibility)

1.2 Potential Risks and Benefits

1.2.1 Known Potential Risks

The CGM sensor may briefly produce pain when it is inserted just underneath the skin. There is a low risk for developing a local skin infection at the site of the sensor placement. Itchiness, redness, bleeding, and bruising at the insertion site may occur as well as local tape reactions. On rare occasions, the sensor may break and leave a small portion of the sensor under the skin that may cause redness, swelling or pain at the insertion site.

In any study with transmission of data, there is always a risk of breach of confidentiality. However, all electronic data transfers will be encrypted, and data will be stored securely to prevent breaches.

1.2.1.1 Risks of Glycemic Management

The goal of treatment of GDM is to achieve glucose levels as close to normal as possible to reduce the risk of APOs. In the study, the treatment prescribed to participants will be at investigator discretion and may include the use of metformin and any commercially-available insulin administered in the U.S. by subcutaneous injection or inhalation and in the UK by subcutaneous injection. The risks associated with metformin and insulin are described in each drug's Prescribing Information (product label). The main risk of intensive glucose management is that it may lead to an increased risk of hypoglycemia.

GDM is a known risk factor for the birth of large for gestational age (LGA) newborns. Glucose management has been effective in reducing the incidence of LGA. However, these interventions may also increase the risk of small for gestational age (SGA) infants.

Glucose-lowering medications that are being prescribed are considered usual care for treatment of GDM. Although there is no study drug or protocol specifying what drug or dose should be

prescribed, the informed consent form nevertheless will describe the risks of insulin and metformin.

All insulins have similar information regarding use in pregnancy, indicating that an association with fetal abnormalities has not been demonstrated but data are lacking, and that it is clear that treatment to limit hyperglycemia is important to minimize risks to the fetus.

1.2.2 Known Potential Benefits

Participants in the intensive group may have a reduced risk of pregnancy complications and adverse pregnancy outcomes in their infant.

The individual participant may not benefit from study participation.

1.2.3 Risk Assessment

The study is considered *greater than minimal risk with prospect of benefit* as defined in 45CFR46.102.

1.3 General Considerations

The study is being conducted in compliance with ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice (GCP).

Chapter 2: Study Enrollment and Screening

2.1 Participant Recruitment and Enrollment

Enrollment will proceed with the goal of screening at least 6,000 participants (maximum 9,000) to identify approximately 1,500 who meet the study defined threshold of CGM hyperglycemia to be included in the randomized trial. Screening will continue until the target for the randomized trial is reached (unless changed as part of interim sample size reestimation as described in section 7.10).

- Participants who have signed consent and don't meet the CGM screening minimum hyperglycemia criteria for eligibility for the RCT, or who meet the criteria but do not enter the RCT, will have OGTT and maternal and neonatal outcome data collected from medical record at the end of the pregnancy.

Study participants will be recruited from ~10 clinical centers in the United States and ~2 clinical centers in the United Kingdom. Participants will be included without regard to gender/sex, race, or ethnicity. There is no restriction on the number of participants to be enrolled by each site toward the overall recruitment goal. Clinics will be selected to provide a broad representation of pregnant individuals, including a substantial number of underserved individuals. A recruitment target will be to have at least 25% of the cohort be from a minoritized race or ethnicity.

Individuals generally will be recruited from each site's existing patient population or from a list of individuals who contact the site. Study recruitment methods may consist of one or more of the following:

- Culling of pre-existing databases at the clinical sites to identify patients who may be eligible. Those identified will be contacted via IRB-approved mailing sent through post, email, or via phone and will be provided information about the study and how to proceed if potentially interested;
- IRB-approved press release announcing study and study fact sheet;
- IRB-approved information about the study distributed through support groups, other internet groups, patient education classes, not-for-profit organizations;
- IRB-approved paper and digital advertisements;
- IRB-approved digital advertisements posted on social media sites like LinkedIn, Twitter, YouTube, Instagram, Facebook, and other public forums;
- In-person recruitment of patients seen in the clinic; and
- An IRB-approved website dedicated to clinical trial recruitment.

All recruitment methods and specific advertising materials will be approved by the Central and/or local IRB prior to their implementation.

Individuals from all methods of recruitment who express an interest in participation will be contacted by members of the research team by phone or in-person to discuss the study details and responsibilities and evaluate whether they are likely to be eligible if they are formally screened for the study. No study data will be recorded prior to consent being signed.

2.1.1 Informed Consent and Authorization Procedures

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Informed consent will be obtained by a method approved by the IRB (either written or electronic).

The study protocol will be discussed with the potential study participant by study staff. The potential study participant will be given the Informed Consent Form to read. Potential study participants will be encouraged to discuss the study with family members and their personal physicians(s) before deciding whether to participate in the study.

If a potential participant is unable to read and understand English, then the consent form(s) must be translated to that person's primary language before consent occurs and a qualified interpreter must be available for the consent process and all subsequent study interactions.

As part of the informed consent process, each participant will be asked to sign an authorization for release of personal information. The investigator, or his or her designee, will review the study-specific information that will be collected and to whom that information will be disclosed. After speaking with the participant, questions will be answered about the details regarding authorization.

A participant is considered enrolled when the informed consent form has been signed.

2.2 Participant Inclusion Criteria

Individuals must meet all of the following inclusion criteria in order to be eligible to participate in the study.

1) Maternal age of 18 years and older
2) Singleton pregnancy
3) Gestational age up to 14w 6d of pregnancy, determined on ultrasound, for initiating of screening
    - *Although it is preferable that ultrasound results be available prior to enrollment, if ultrasound results are not available at the time of enrollment, participant can be enrolled and have CGM initiated but will be dropped if not eligible after results are available*
4) HbA1c <6.5% (48 mmol/mol) since onset of pregnancy
    - *If HbA1c is not available at time of consent, blinded screening CGM sensor wear can proceed but HbA1c value must be available prior to randomization*
5) No prior history of GDM
6) Able to read English or Spanish.

2.3 Participant Exclusion Criteria

1) Signs of abnormal fetal or placental development (suspected fetal anomaly or placenta accreta spectrum, low Pregnancy Associated Plasma Protein-A (PAPPA)) at first routine prenatal visit/ultrasound
2) Planned termination of pregnancy or any indications of miscarriage

3) Prior gastric bypass surgery
4) Pregravid diabetes (type 1 or type 2)
5) Unwillingness/inability to wear CGM sensor
6) Unwillingness to attend routine antenatal obstetric appointments
7) Use of corticosteroids by a route that can produce hyperglycemia (e.g., oral, intravenous, intramuscular, intra-articular) during the 7 days prior to initiating CGM screening or during the CGM screening
    - *Topical and inhaled corticosteroids are acceptable*
8) Use of insulin during the pregnancy prior to enrollment
9) Use of metformin within one week of the initiation of the blinded CGM sensor for screening or use of a GLP-1 or other weight-reduction medication that can affect glucose levels within 4 weeks of the initiation of the blinded CGM sensor for screening
10) Deemed unable to participate for medical reasons identified by their physician

Additional Criteria for RCT Eligibility

1. Screening CGM meeting study criteria for hyperglycemia: 5% to <25% time >140 mg/dL
2. Randomization by 16 weeks 6 days of pregnancy
3. No participation in a separate interventional trial.

2.4 Screening Procedures

After informed consent has been signed, a potential participant will be evaluated for study eligibility. Except for the 10-14 days of blinded CGM data collection, no procedures will be performed that are not part of usual care and generally data to assess eligibility will be available in the electronic medical record.

These data may include patient health history, prior pregnancies, demographics, height/weight, HbA1c, and relevant ultrasound abnormalities.

A blinded CGM sensor will be placed, and replaced as needed, no later than 15 weeks 2 days of gestation (so that there will be 10 days of sensor wear prior to the maximum time to randomization). Participants will be instructed on care of the sensor.

2.4.1 Determination of Eligibility for RCT

The blinded CGM sensor data will be evaluated at ~5 days of blinded CGM wear to determine if the following criteria are met:

- 5% to <25% of values >140 mg/dL

If eligibility is not met after ~5 days of blinded CGM wear, then the CGM data may be re-evaluated at ~10 days or at the end of the CGM wear. If the participant has ≥ 25% of CGM readings >140 mg/dL, then the participant will be placed into the observational cohort. Eligible participants meeting the CGM hyperglycemia criteria will proceed to randomization, which must be performed by 16 weeks 6 days of gestation.

2.5 Randomization

Eligibility for the RCT will be reassessed in participants meeting the screening blinded CGM hyperglycemia criteria, including a determination that the participant is willing and able to follow the study protocol and will accept assignment to either treatment group.

Eligible participants will be randomly assigned (1:1) to one of the following:

- Glucose Lowering Group: unblinded CGM plus glucose-lowering management
- Usual Care Group: usual care plus blinded CGM at intervals

Randomization will be stratified by site and use a permuted block design within each site.

Once a study participant is randomized, that participant will be counted regardless of whether the assigned treatment is received. Thus, the investigator must not proceed to randomize an individual until he/she is convinced that the individual is eligible and will accept whichever treatment group is assigned through randomization.

Participants who are eligible but don't proceed into the RCT will become part of the observational cohort as described in section 2.7.

2.6 Screen Failures

Individuals who do not initially meet study eligibility requirements will not be randomized and will not be eligible to be rescreened.

2.7 Observational Cohort

Participants screened with CGM who do not meet the CGM hyperglycemia criteria or who meet the criteria but do not enter the RCT will form an observational cohort. There will be no study-specific visits, procedures, or data collection. At the end of the pregnancy, information collected as part of usual care will be obtained from the EHR, including results of the usual care OGTT (generally at 24-28 weeks), diagnosis and treatment of GDM, and maternal and infant outcomes.

Chapter 3: Randomized Trial Procedures

3.1 Office Visits

All visits after randomization will follow a standard care schedule, which for most participants will be about every 4 weeks per usual care. (Some of these visits may be done via telemedicine.)

3.2 Glucose Lowering Group

Glycemic management will include the following:

- GDM-specific nutrition information handout will be provided to each participant in addition to counseling by the clinical care team.
- An unblinded CGM sensor will be worn continuously 24/7 if possible
- Training will be provided on using CGM in daily glucose management to achieve normoglycemia
    - Participants may be trained to use the CGM app to indicate meals and exercise when possible to aid glucose management.

The clinician investigator will perform the following:

- Weekly review of CGM data
- Intervene pharmacologically with insulin and/or metformin as determined by the investigator

3.2.1 Glycemic Management Guidelines

Investigators will prescribe treatment in accordance with their standard care. Glycemic management, including the type and dose of insulin to prescribe, will be at investigator discretion. Guidelines will be provided for utilizing CGM data in the determination of optimal therapy. Metformin may be used based on usual prescribing practices of the clinical site.

3.3 Usual Care Group

The Usual Care group will receive usual pregnancy care at the site.

- At each routine clinic visit (expected to be about every 4 weeks through pregnancy), a blinded CGM sensor will be placed and worn for 10-14 days.
- Blinded CGM data collection will begin around the 18-22 week routine clinic visit.
- At ~20-weeks, blinded CGM data will be reviewed to assess if participant has ≥25% time >140 mg/dL and if an OGTT should be performed earlier or glycemic management needed.
- Participants with positive usual care OGTT will be treated for GDM per usual clinic routine.

3.4 Oral Glucose Tolerance Test

3.4.1 Glucose Lowering Group

An OGTT is not part of the study protocol. Per usual care, it is not expected that an OGTT will be performed for Glucose Lowering group participants who are receiving insulin or other

glucose-lowering medications. An OGTT may be performed according to institutional guidelines for participants not receiving glucose-lowering medications.

3.4.2 Usual Care Group

An OGTT, which may involve more than one test, is expected to be performed as part of usual care for the Usual Care group, according to the sites' institutional guidelines, generally between 24 and 28 weeks. Results will be recorded in the study database.

- A blinded CGM sensor may be worn during the OGTT unless this is not feasible (e.g., timing related to new sensor placement).

Participants with positive OGTT will be treated for GDM per usual clinic routine. Insulin, if prescribed, can be any commercially-available insulin by subcutaneous injection or inhalation in the U.S. or by subcutaneous injection in the UK, based on investigator and participant preference. If real-time CGM is to be used, then unblinded study CGM sensors can be used instead of blinded sensors for the duration of the study. The participant may use an unblinded sensor or can opt to use a personal CGM that is not provided by the site; however, in the instance of utilizing a personal CGM, that participant must continue to use the study blinded CGM sensor per protocol for their Randomization group (see section 3.3). The usual target range will be standard of care targets and left to the discretion of the investigator.

3.5 Data Collected at End of Pregnancy

After completion of the pregnancy, data to be entered into the study database will include glucose-lowering treatments, maternal weight, reportable adverse events during the study, gestation week at time of delivery/end of pregnancy, maternal outcomes, OGTT results, fetal/neonatal outcomes, infant birth weight and height.

Chapter 4: Study Devices

4.1 CGM

Commercially-available Dexcom and Abbott CGM sensors will be used in the study in both blinded and unblinded modes.

Clinical sites will be assigned to the brand of CGM used. All participants at a site will use the site-assigned type of sensor in both blinded and unblinded modes.

At the enrollment visit, a CGM sensor will be inserted, and the participant will be instructed on its use and care. The device will be blinded so that the participant is not able to see the sensor readings. A study mobile phone may be provided if necessary for running the app used for CGM blinding.

Participants randomly assigned to the Glucose Lowering group will be supplied with sensors for the duration of pregnancy and be instructed on sensor placement and use of CGM data in managing glycemia.

Participants in the Usual Care group will have blinded sensors inserted during routine prenatal care visits about every 4 weeks (or could be inserted remotely). Sensors may be replaced if necessary. Usual Care participants diagnosed with GDM may be given an unblinded study sensor as part of GDM management per investigator discretion.

CGM may continue through labor and delivery for the Glucose Lowering group.

4.2 Blood Glucose Meter and Strips

The Glucose Lowering group will be provided with a commercially-available blood glucose meter that may be used to calibrate the sensor and to check the blood glucose level as recommended by CGM manufacturers' labeling.

4.3 Study Device Accountability Procedures

Device accountability procedures will be detailed in the site procedures manual.

Chapter 5: Adverse Event and Device Issue Reporting

5.1 Adverse Events

5.1.1 Definitions

Adverse Event (AE): Any untoward medical occurrence (including laboratory findings) associated with study procedures, the use of a device, biologic, or drug in humans, including any comparator used, whether or not the event is considered related (i.e., irrespective of the relationship between the adverse event and the device(s) under investigation).

- To further clarify, an adverse event is any unintended disease or injury, or untoward clinically significant clinical sign (including abnormal laboratory findings) in a research participant that manifests while in the study if it was not present before enrolling in the study, or if it was present before enrolling, it has increased in severity, frequency or type since enrolling in the study. For this purpose, a participant is considered enrolled once the participant has signed the consent form. Reportable AEs for this protocol are defined in section 5.2.
- Medical interventions such as surgeries, diagnostic procedures, and therapeutic procedures are not AEs but the action taken to treat a particular medical condition. If the medical intervention relates to a pre-existing medical condition that has not worsened since enrollment, the intervention does not need to be reported unless an AE occurs as a result of the procedure or study drug/device needs to be temporarily discontinued due to the procedure. Also, if the intervention is done in the absence of a condition meeting the definition of an AE, such as for prevention (e.g. colonoscopy) or cosmetic surgery, the intervention should not need to be reported as an AE. If a pre-existing medical condition worsens after enrollment, this will be reported as an AE and the medical intervention will be recorded on the AE form as treatment of the AE.

Serious Adverse Event (SAE): Any untoward medical occurrence that results in any of the following outcomes:

- Maternal death
- A life-threatening adverse event; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.

An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical and

surgical intervention to prevent one of the outcomes listed in this definition. Note: If either the Medical Monitor or investigator believes that the event is serious, the event must be considered serious and evaluated by the Coordinating Center for expedited reporting. See 21 CFR 312 for more information.

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a study device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants (21 CFR 812.3(s)).

Adverse Device Effect (ADE): An adverse event related to the use of a study investigational medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. This includes comparator if the comparator is a medical device. (Note that an Adverse Event CRF is to be completed in addition to a Device Deficiency or Issue CRF, unless excluded from reporting as defined in section 5.8).

Comparator: Medical device, therapy (e.g., active treatment, normal clinical practice), placebo or no treatment, used in the control group in a clinical investigation. (ISO 14155:2020)

Device Complaints and Malfunctions: A device complication or complaint is something that happens to a study device or related to study device performance, whereas an adverse event happens to a participant. A device complaint may occur independently from an AE, or along with an AE. An AE may occur without a device complaint or there may be an AE related to a device complaint. A device malfunction is any failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. For cleared devices, the intended performance of a device refers to the intended use for which the device is labeled or marketed (21 CFR 803.3). Note: for reporting purposes, sites will not be asked to distinguish between device complaints and malfunctions.

User Error: User action or lack of user action while using the medical device that leads to a different result than that intended by the manufacturer or expected by the user. Includes the inability of the user to complete a task. Use errors can result from a mismatch between the characteristics of the user, user interface, task or use environment. Users might be aware or unaware that a use error has occurred. An unexpected physiological response of the patient is not by itself considered a use error. A malfunction of a medical device that causes an unexpected result is not considered a use error. (ISO 14155:2020)

5.2 Reportable Adverse Events

For this protocol, a reportable adverse event includes treatment related events that meets one of the following criteria:

1. An SAE as defined in section 5.1.1, that is considered related to the study intervention in the Glucose Lowering Group or a maternal death in both groups

2. Severe hypoglycemia meeting the following criteria: Hypoglycemia producing altered consciousness, which required the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the participant was impaired cognitively to the point that he/she was unable to treat himself/herself, was unable to verbalize his/her needs, was incoherent, disoriented, and/or combative, or experienced seizure or loss of consciousness. These episodes may be associated with sufficient neuroglycopenia to induce seizure or loss of consciousness. If glucose measurements are not available during such an event, neurological recovery attributable to the restoration of glucose to normal is considered sufficient evidence that the event was induced by a low glucose concentration.
3. Diabetic ketoacidosis (DKA) meeting the following criteria:
    - Symptoms such as polyuria, polydipsia, nausea, or vomiting;
    - Serum ketones >1.5 mmol/L or large/moderate urine ketones;
    - Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate (or CO2) <15; and
    - Treatment provided in a health care facility
4. Severe skin reaction from CGM sensor that requires medical treatment

All reportable AEs in the Glucose Lowering Group will be reported on an AE CRF online. Each AE CRF is reviewed by the Medical Monitor to assess safety and to verify the coding and the reporting that is required. Reportable skin reactions in the Usual Care Group will be captured on an AE CRF; other reportable AEs in the Usual Care Group will be recorded at the time of EMR review at the end of pregnancy.

Hospitalizations, emergency room visits, and intercurrent events or treatments that could affect glucose levels will be captured from the medical record review at the end of the pregnancy for both groups.

5.3 Relationship of Adverse Event to Study Intervention

The site investigator will assess the relationship of any reportable adverse event to be related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by the study device or intervention. The Medical Monitor also will make this assessment, which may or may not agree with that of the site investigator. Reporting requirements will be based on the Medical Monitor's assessment.

To ensure consistency of adverse event causality assessments, investigators should apply the following general guideline when determining whether an adverse event is related:

- **Unrelated:** The AE is clearly not related to a study drug/device/procedure and a likely alternative etiology exists such as an underlying disease, environmental or toxic factors or other therapy.
- **Unlikely Related:** The AE does not follow a reasonable temporal sequence during or after use of study drug/device/procedure and a more likely alternative etiology exists such as an underlying disease, environmental or toxic factors, or other therapy.

- **Possibly Related:** The AE occurred in a reasonable time during or after use of study drug/device or a study procedure; but could be related to another factor such as an underlying disease, environmental or toxic factors, or other therapy; and there is a possible, though weak, scientific basis for establishing a causal association between the AE and the study drug/device.
- **Probably Related:** The AE occurred in a reasonable time during or after use of study drug/device or a study procedure; is unlikely to be related to another factor such as an underlying disease, environmental or toxic factors, or other therapy; and there is a plausible, though not strong, scientific basis for establishing a causal association between the AE and the study drug/device.
- **Definitely Related:** The AE occurred in a reasonable time during or after use of study drug/device or a study procedure; cannot be explained by another factor such as an underlying disease, environmental or toxic factors, or therapy; and there is a strong scientific basis for establishing a causal association between the AE and the study drug/device.

Events determined to be *Possibly Related, Probably Related,* or *Definitely Related* will be considered to meet the *reasonable possibility* causality standard for relatedness and necessitate reporting as required (see 21 CFR 312.32 for more information).

5.4 Severity (Intensity) of Adverse Events

The severity (intensity) of a reportable adverse event will be rated on a three-point scale by the site investigator and the Medical Monitor: (1) mild, (2) moderate, or (3) severe. A severity assessment is a clinical determination of the intensity of an event. Thus, a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

- MILD: Usually transient, requires no special treatment, and does not interfere with the participant's daily activities.
- MODERATE: Usually causes a low level of inconvenience, discomfort or concern to the participant and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures and participant is able to continue in study.
- SEVERE: Interrupts a participant's usual daily activities, causes severe discomfort, may cause discontinuation of study device, and generally requires systemic drug therapy or other treatment.

5.5 Expectedness

For a serious adverse event that is considered possibly related to study device/procedure, the Medical Monitor will classify the event as unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described CGM device labeling.

5.6 Coding of Adverse Events

To facilitate coding, the site will enter a preliminary event code which the Medical Monitor may accept or change (the Medical Monitor's event description code will be used for all reporting and site's preliminary coding will not be updated or used in reporting). The Medical Monitor will review the investigator's assessment of causality and severity and may agree or disagree. Both

the investigator's and Medical Monitor's assessments will be recorded for causality and severity. The Medical Monitor will make the final determination with respect to causality as well as whether an event is classified as a serious adverse event and/or an unanticipated adverse device effect.

5.7 Outcome of Adverse Events

The outcome of each reportable adverse event will be classified by the investigator as follows:

- RECOVERED/RESOLVED (COMPLETE RECOVERY) – The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
- RECOVERED/RESOLVED WITH SEQUELAE – AE/SAE where the subject recuperated but retained pathological conditions resulting from the prior disease or injury.. Record the AE/SAE stop date.
- FATAL – A fatal outcome is defined as the SAE that resulted in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the time of death; however, were not the cause of death, will be recorded as "resolved" at the time of death.
- ONGOING (NOT RECOVERED/NOT RESOLVED) – An ongoing AE/SAE is defined as an ongoing event with an undetermined outcome.
    - An ongoing outcome will require follow-up by the site in order to determine the final outcome of the AE/SAE.
    - The outcome of an ongoing event at the time of death that was not the cause of death, will be updated and recorded as "resolved" with the date of death recorded as the stop date.
- ONGOING (MEDICALLY STABLE) – AE/SAE is ongoing, but medically stable. For example, a chronic condition where no further change is expected.

If any reported adverse events are ongoing when a participant completes the study (or withdraws), adverse events classified as [SUSARs or] UADEs or related SAEs will be followed until they are either resolved, or have no prospect of improvement or change, even after the participant has completed all applicable study visits/contacts. For all other adverse events, data collection will end at the time the participant completes the study unless further follow up is requested by the Medical Monitor. Note: participants should continue to receive appropriate medical care for an adverse event after their participation in the study ends.

If a participant is lost to follow up and participant outcome cannot be determined, outcome classification will be the last known outcome.

5.8 Reportable Study Device Issues

CGM is the only study device. Device issues associated with a reportable AE will be reported in a Device Issue CRF in addition to the AE CRF.

Study device complaints and device malfunctions related to CGM will only be reported if the issue affected the CGM glucose measurements or data capture.

The following occurrences will not be reported:

- CGM sensor or transmitter needing replacement prior to labelled maximum use duration
  CGM tape adherence issues
- Battery lifespan deficiency
- Intermittent communication failures
- Device issues addressed in the user guide manual that do not require additional troubleshooting
- Skin reaction that is not severe or does not require treatment

5.9 Timing of Event Reporting

Reportable SAEs possibly related to a study intervention and UADEs must be reported by the investigator to the Coordinating Center within twenty-four (24) hours of the site becoming aware of the event. This can occur via phone or email, or by completion of the AE CRF and Device Issue CRF if applicable. If the AE CRF is not initially completed, it should be completed as soon as possible after there is sufficient information to evaluate the event. All other reportable ADEs and other reportable AEs should be submitted by completion on the respective CRF within seven (7) days of the site becoming aware of the event.

The Coordinating Center will notify all participating investigators of any adverse event that is serious, related, and unexpected. Notification will be made within ten (10) working days after the Coordinating Center becomes aware of the event.

Each site principal investigator is responsible for reporting serious study-related adverse events and abiding by any other reporting requirements specific to his/her Institutional Review Board or Ethics Committee.

Upon receipt of a qualifying event, the Coordinating Center will investigate the event to determine if a UADE has occurred, and if indicated, report the results of the investigation to all overseeing IRBs, and the FDA within ten (10) working days of the Coordinating Center becoming aware of the UADE per 21CFR 812.46(b) (2). The Coordinating Center in conjunction with the Medical Monitor must determine if the UADE presents an unreasonable risk to participants. If so, the Coordinating Center must ensure that all investigations, or parts of investigations presenting that risk, are terminated as soon as possible but no later than five (5) working days after the Coordinating Center makes this determination and no later than fifteen (15) working days after first receipt notice of the UADE. The investigator(s) may then be required to provide approval or acknowledgment of receipt of that notification and must submit to their overseeing IRB as required.

The investigators are also required to report, without unjustified delay, all reportable device deficiencies that could have led to a UADE, including device deficiencies, irrespective of whether an adverse event occurred.

5.10 Safety Oversight

The study Medical Monitor will review all reported adverse events and device issues that are reported during the study. SAEs typically will be reviewed within twenty-four (24) hours of reporting. Other AEs typically will be reviewed on a weekly basis. Additionally, the Medical Monitor will review compiled safety data at periodic intervals.

The Clinical Study Director will be informed of all cases of severe hypoglycemia and DKA and the Medical Monitor's assessment of relationship to the study intervention.

A Data and Safety Monitoring Board (DSMB) will be informed of all cases of severe hypoglycemia, diabetic ketoacidosis, and intervention-related SAEs that occur in the Glucose Lowering Group at the time that they occur during the study and will review compiled safety data annually. The DSMB can request modifications to the study protocol or suspension or outright stoppage of the study if deemed necessary based on the totality of safety data available. Details regarding DSMB review will be documented in a separate DSMB document.

5.11 Stopping Criteria

5.11.1 Participant Discontinuation of Study Intervention

The study intervention will be discontinued if any of the following occur:

- The investigator believes it is unsafe for the participant to continue on the intervention. *This could be due to the development of a new medical condition or worsening of an existing condition; or participant behavior contrary to the indications for use of the device that imposes on the participant's safety*
- The participant requests that the treatment be stopped

Even if the study intervention is discontinued, the participant will be encouraged to remain in the study through the end of pregnancy, unless the participant formally withdraws. Medical record information collected up to the time of formal withdrawal will still be captured.

5.11.2 Criteria for Suspending or Stopping Overall Study

Study activities could be suspended if the Medical Monitor deems suspension of study activities or stoppage of the study necessary based on the totality of safety data available or if the CGM manufacturer requires stoppage of device use for safety reasons (e.g., product recall). The affected study activities may resume if the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension.

Chapter 6: Miscellaneous Considerations

6.1 Collection of Medical Conditions and Medications in Randomized Study Participants

At the end of the pregnancy, information will be retrieved from the medical record for relevant medical conditions that developed during the study and the use of medications that could affect glucose levels or maternal or fetal health.

6.2 Participant Compensation

Participant compensation will be specified in the informed consent form.

6.3 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. The reason for withdrawal will be recorded. For participants who discontinue the study but don't formally withdraw consent for further data collection, data will be extracted from the EMR after the end of pregnancy similar to the Observational cohort. For participants who withdraw consent for further data collection, their data collected for the study and available in the EMR will be used up until the time of withdrawal.

6.4 Unanticipated Problems

Site investigators will promptly report all suspected unanticipated problems meeting the criteria below to the Coordinating Center. Sites must also report Unanticipated Problems to the IRB of record within the timeline specified by the IRB. For this protocol, an unanticipated problem is any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given the information provided in research-related documents and the characteristics of the subject population being studied
- Related or possibly related to participation in the research
- Suggests that the research places participants or others at a greater risk of harm than was previously known or recognized

6.5 Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the coordinating center, the Jaeb Center for Health Research in Tampa, FL. De-identified participant information may also be provided to research sites involved in the study.

Chapter 7: Statistical Considerations

7.1 Statistical and Analytical Plans

The approach to sample size and statistical analyses are summarized below.

A detailed statistical analysis plan (SAP) will be finalized before the first database lock. Any deviations from the analyses described below will be described in the SAP.

The statistical plan below refers to the RCT. The statistical plan for the observational study is described in section 7.15.

7.2 Statistical Hypotheses

The primary endpoint is a test for superiority in the incidence of the primary composite endpoint comparing the two treatment groups (the Glucose Lowering group and the Usual Care group). The statistical hypotheses for the primary endpoint is as follows:

Null Hypothesis: There is no difference in the incidence of the composite endpoint between the Glucose Lowering and Usual Care groups.

Alternative Hypothesis: There is a nonzero difference in the incidence of the composite endpoint between the Glucose Lowering and Usual Care groups.

7.3 Sample Size

Sample size has been computed for the primary composite endpoint. We expect ~25% of screened participants to meet the eligibility requirement of 5 to <25% time >140 mg/dL at prior to 17 weeks' gestation. To achieve 90% power in detecting a difference in composite endpoint prevalence between the Glucose Lowering and Usual Care groups, assuming an estimated 41% of participants with the composite endpoint in the Usual Care group, an expected relative risk reduction of the composite endpoint of 25% in the Glucose Lowering group, a two-sided test, and a type I error rate of 5%, the calculated sample size is 900 participants randomized. The sample size has been increased to 1,500 randomized (~6,000 screened) to account for dropouts and additional exposure time. Screening will continue until 1,500 have been randomized (or expected to be randomized), unless this number is changed following an interim sample size re-estimation.

7.4 Outcome Measures

7.4.1 Primary Efficacy Endpoint

The primary endpoint is:

- A composite that includes the following:
    - Large for gestational age (LGA)
    - Shoulder dystocia (including humeral or clavicular fracture)
    - Elevated bilirubin requiring phototherapy
    - Neonatal intensive care unit (NICU) admission
    - Maternal hypertensive disorder of pregnancy (HDP)

7.4.2 Secondary Efficacy Endpoints

- Composite consisting of neonatal complications of LGA, shoulder dystocia (including humoral or clavicular fracture), elevated bilirubin requiring phototherapy, NICU admission
- Maternal HDP
- LGA
- Shoulder dystocia
- Elevated bilirubin requiring phototherapy
- Neonatal death
- NICU admission

7.4.3 Safety Endpoints

- Small for gestational age (SGA, <10th percentile)
- CGM-measured time <54 mg/dL (during comparative periods where Usual Care group has blinded CGM)
- Severe hypoglycemia events
- Other serious adverse events

7.5 Analysis Datasets and Per-Protocol Analyses

All efficacy and safety analyses comparing the treatment groups will follow the intention-to-treat approach, which means participants will be analyzed in the treatment arm assigned by randomization regardless of actual treatment received. All randomized participants will be included in the efficacy and safety analyses unless otherwise specified.

A per-protocol analyses will be performed for the primary endpoint only if >5% of participants will be excluded due to not adhering to the protocol as defined in the SAP.

7.6 Analysis of the Primary Efficacy Endpoint

The primary composite endpoint at delivery will be compared between the Glucose Lowering and Usual Care groups using a logistic regression model with a compound symmetry covariance structure to handle the correlation within site. In the event that the primary composite endpoint at delivery is missing, multiple imputation with treatment group in the model will be used to handle missing values. Imbalances between groups in important covariates are not expected to be of sufficient magnitude to produce confounding. However, the presence of confounding will be evaluated in the sensitivity analyses by including factors potentially associated with the outcome for which there is an imbalance between groups (section 7.7).

A 95% confidence interval (CI) will be constructed on the treatment group risk difference (Glucose Lowering minus Usual Care).

7.7 Sensitivity Analyses

Confounding

A sensitivity analysis will be conducted if potential confounding factors collected at baseline are imbalanced between treatment groups. The imbalance will be assessed based on clinical judgment reviewing the distributions in the two treatment arms, not on a p-value. The person making this judgement will be unaware of whether there is an association between baseline variables and study outcome. All variables obtained on a continuous scale will be entered into the models as continuous variables, unless it is determined that a variable does not have a linear relationship with the log odds of the outcome. In such a case, categorization and/or transformation will be explored.

Missing Data

Missing data will be handled using multiple imputation using treatment group in the imputation model assuming the outcome is missing at random. It is worth noting that all statistical methods for handling missing data rely on untestable assumptions and there is no one correct way to handle missing data. The goal is to minimize the amount of missing data so that the results will not be sensitive to which statistical method is used.

To that end, sensitivity analyses will be performed to explore whether results are similar for the primary analysis when using different methods. Sensitivity analyses will only be performed if >5% of the primary composite outcome is missing. The following methods will be applied:

- Multiple imputation with a pattern mixture model assuming the dropout trajectory of the Glucose Lowering group is that of the Usual Care group
- Available cases only
- Two-way tipping point analysis

7.8 Analysis of Secondary Efficacy Endpoints

7.8.1 Binary Outcomes

Binary outcomes will be compared between the Glucose Lowering and Usual Care groups using models similar to that of the primary composite endpoint (section 7.6). Endpoints are only tested if there are enough events (at least 5 events combined between the two treatment groups).

7.8.2 Additional Exploratory Analyses

Weight gain from randomization to end of pregnancy will be compared between groups.

Within each group, the association of hyperglycemia and other CGM metrics with maternal and fetal/neonatal outcomes will be explored.

Additional exploratory analyses will be detailed in the SAP.

7.9 Safety Analyses

All randomized participants will be included in the safety analyses. All reportable adverse events will be tabulated by treatment group. Safety analyses for the RCT will include events occurring on or after randomization until hospital discharge following the delivery.

For the following outcomes, the number of participants with ≥1 event and number of events will be tabulated by treatment group:

- SGA (<10th percentile)
- Severe hypoglycemia events
- Other serious adverse events

If enough events occur (at least 5 events combined between the two treatment groups), the prevalence of SGA will be summarized and a formal statistical comparison between treatment groups will be performed using a model similar to that used for the primary composite endpoint (section 7.6).

CGM-measured time <54 mg/dL will be calculated and compared between treatment groups using a linear mixed effects regression model adjusting for the baseline time <54 mg/dL, sensor type, and site (random effect). A separate variance will be modelled for each treatment group. Residual values will be examined for an approximate normal distribution. If residuals are highly skewed, then a generalized linear mixed effects regression model with the t-distribution for the error terms will be used instead. Missing data will be handled using direct likelihood.

7.10 Planned Interim Analyses

Re-estimation of the sample size will be undertaken as specified in the Statistical Analysis Plan or a separate Sample Size Re-estimation Plan. The analysis will determine if the eligibility criterion based on the blinded CGM screening and the planned RCT sample size meets the desired power. The sample size may be modified or eligibility criteria revised based on the analysis.

7.11 Subgroup Analyses

In exploratory analyses, the primary composite endpoint, LGA, and HDP will be compared in baseline subgroups. Treatment group by subgroup factor interaction terms will be added to the models described in sections 7.6 and 7.8.1.

- Formal statistical testing for interaction will be done only if the overall result is statistically significant. Results will be tabulated by subgroups regardless of statistical significance. For continuous variables, results will be displayed in subgroups based on the distribution of the data although the analysis will utilize the variable as continuous. Cut point selection for display purposes will be made masked to the outcome data.
- Subgroups will be analyzed according to the following baseline factors:
    - Baseline HbA1c

- Baseline % time >140 mg/dL
- Age
- Race/Ethnicity
- BMI
- Additional subgroups to be defined in the SAP

7.12 Glucose Exposure Assessment

Glucose exposure will be assessed using CGM which will be unblinded in the Glucose Lowering group and blinded in the Usual Care group. CGM data collected during screening will be used to calculate the baseline values for each CGM metric. CGM data collected after randomization up until the day before the delivery date will be used to calculate the CGM metrics for the follow-up period. During the follow-up period, time periods of CGM data in the Glucose Lowering group will be matched to the blinded CGM wear periods in the Usual Care group (the matching process will be described in the SAP).

CGM Metrics

- Mean glucose
- Glucose standard deviation
- Glucose coefficient of variation
- % Time 63-120 mg/dL
- % Time 63-140 mg/dL
- % Time <63 mg/dL
- % Time >120 mg/dL
- % Time >140 mg/dL
- Glucose level at 5 AM

Summary statistics (mean ± SD or median [interquartile range]) will be reported for the CGM metrics at baseline and follow-up for each treatment group. CGM metrics will also be summarized by daytime and nighttime, by trimester, and by 4-week time periods. Daytime is defined as 6:00am to 11:59pm and nighttime from 12:00mn to 5:59am.

CGM metric differences between treatment groups will be compared using a linear mixed effects regression model adjusting for the baseline value of the metric, type of sensor, and site (random effect). A separate variance will be modelled for each treatment group. Residual values will be examined for an approximate normal distribution. If residuals are highly skewed, then a generalized linear mixed effects regression model with the t-distribution for the error terms will be used instead. Missing data will be handled using direct likelihood.

Within the Glucose Lowering group, additional tabulations of CGM metrics will be done by gestational week.

7.13 Multiple Comparison/Multiplicity

The primary statistical analysis will be conducted using a p value threshold for significance of 0.05. For the secondary and exploratory efficacy analyses, the false discovery rate will be controlled using the adaptive Benjamini-Hochberg procedure.

P-values from the safety analyses, sensitivity analyses, and per-protocol analyses will not be adjusted for multiple comparisons.

7.14 Additional Tabulations and Analyses

The following tabulations will be performed according to treatment group:

- Baseline demographic and clinical characteristics, including maternal weight, gestational week at time of delivery/end of pregnancy, infant birth weight and height
- Flow chart accounting for all participants
- Protocol deviations
- Usual Care group: diagnosis of GDM
- Glucose Lowering group: glucose-lowering treatment received

7.15 Observational Study

All participants who complete the screening blinded CGM data collection, except for participants with HbA1c ≥6.5%, are enrolled into the Observational cohort.

Data will be extracted from the EHR after the end of pregnancy. Tabulations will include

- Baseline demographic and clinical characteristics
- OGTT results/GDM diagnosis
- Fetal and maternal outcomes as described in sections 7.4.1 and 7.4.2.

Exploratory analyses will compare the screening CGM metrics to the OGTT and fetal/maternal outcomes.

Chapter 8: Data Collection and Monitoring

8.1 Case Report Forms and Other Data Collection

The main study data are collected on electronic case report forms (CRFs) from EHR review and from CGM data downloads. When data are directly collected in electronic case report forms, this will be considered the source data. For any data points for which the eCRF is not considered source (e.g., lab results that are transcribed from a printed report into the eCRF), the original source documentation must be maintained in the participant's study chart or medical record and be able for verification as needed per the monitoring plan. This source must be readily verifiable against the values entered into eCRF. Even where all study data are directly entered into the eCRFs at office visits, evidence of interaction with a live subject must be recorded (e.g., office note, visit record, etc.).

Electronic device data files are obtained from the study software and individual hardware components. These electronic device files are considered the primary source documentation.

8.2 Study Records Retention

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

Study documents should be retained for a minimum of 2 years after the date that the investigation is terminated or completed. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Coordinating Center. It is the responsibility of the Coordinating Center to inform the investigator when these documents no longer need to be retained.

8.3 Quality Assurance and Monitoring

Designated JCHR personnel will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the trial is conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements, as well as to ensure that the rights and wellbeing of trial participants are protected and that the reported trial data are accurate, complete, and verifiable. Adverse events will be prioritized for monitoring.

A risk-based monitoring plan will be developed and revised as needed during the study, consistent with FDA's risk-based monitoring guidance, "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013). Study conduct and monitoring will conform with 21 Code of Federal Regulations (CFR) 812. The monitoring plan details who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

The data of most importance for monitoring at the site are participant eligibility and adverse events. Therefore, the monitoring plan will focus on these areas. As much as possible, remote monitoring will be performed in real-time with on-site monitoring performed to evaluate the verity and completeness of critical data and processes. Elements of the monitoring plan may include:

- Qualification assessment, training, and certification for sites and site personnel
- Oversight of Institutional Review Board (IRB) coverage and informed consent procedures
- Central (remote) data monitoring: validation of data entry, data edits/audit trail, protocol review of entered data and edits, statistical monitoring, study closeout
- On-site monitoring (site visits): source data verification, site visit report
- Investigational Product accountability
- Communications with site staff
- Patient retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

JCHR representatives or their designees may visit the study facilities at any time to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study. Clinical sites will provide direct access to all trial-related facilities/equipment, source data/documents, and reports for the purpose of monitoring and auditing by the Coordinating Center, and inspection by local and regulatory authorities.

8.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or procedure requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. A significant (or major) deviation is any deviation that departs from the established materials in such a way that it poses an increase in the risk to subjects, adversely affects the welfare, rights, or safety of the research subjects, or negatively influences the scientific study integrity. As a result of a significant deviation, a corrective and preventive action plan shall be developed by the site and implemented promptly.

The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the monitoring plan.

Chapter 9: Ethics/Protection of Human Participants

9.1 Ethical Standards

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

9.2 Institutional Review Boards

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the JCHR IRB for review and approval as the IRB of Record for the US sites. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be approved by the IRB, which will determine whether previously consented participants need to be re-consented.

9.3 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the Coordinating Center and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Coordinating Center.

The study monitor, other authorized representatives of the Coordinating Center, representatives of the IRB, regulatory agencies or company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or Coordinating Center requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Jaeb Center for Health Research. This will not include the participant's contact or identifying information, unless otherwise specified in the informed consent form. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the Jaeb Center for Health Research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Jaeb Center for Health Research.

9.4 Future Use of Stored Data

Data collected for this study will be analyzed and stored at the Jaeb Center for Health Research. No specimens will be stored from the study.

Chapter 10: References

1. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes—2019. *Diabetes Care*. 2019;42(Supplement 1):S165-S172. doi:10.2337/dc19-S014
2. Carlson, A.L., Beck, R.W., Li, Z., et al. Glucose levels measured with continuous glucose monitoring in uncomplicated pregnancies. *BMJ Open Diabetes Res Care* 2024; 12:(3). doi:10.1136/bmjdrc-2023-003989.PMID:38729771. PMC11097821.
3. Feig DS, Donovan LE, Corcoy R, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. *Lancet* 2017;390:2347-2359
4. Gupta Y, Singh C, Goyal A, et al. Continuous glucose monitoring system profile of women diagnosed as gestational diabetes mellitus by International Association of Diabetes and Pregnancy Study Groups criteria and labeled as normoglycemic by alternate criteria in early pregnancy. *J Diabetes Investig* 2022;13:1753-1760
5. Stentebjerg LL, Madsen LR, Støving RK, et al. Roux-en-Y Gastric Bypass Increases Glycemic Excursions During Pregnancy and Postpartum: A Prospective Cohort Study. *Diabetes Care* 2023;46:502-510
6. Harmon KA, Gerard L, Jensen DR, et al. Continuous glucose profiles in obese and normal-weight pregnant women on a controlled diet: metabolic determinants of fetal growth. *Diabetes Care* 2011;34:2198-2204
7. Hernandez TL, Friedman JE, Van Pelt RE, et al. Patterns of glycemia in normal pregnancy: should the current therapeutic targets be challenged? *Diabetes Care* 2011;34:1660-1668