AT GOAL: Adopting Technology for Glucose Optimization and Lifestyle in Pregnancy

NCT05370612
Protocol Version date: 18 March 2024

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Protocol Number: [IRB /Other Protocol Number 2022-028]
Principal Investigator: Jacquelyn Adams

IND/IDE Sponsor: Dexcom

University of Wisconsin Department of Obstetrics and Gynecology Research and Development Internal Funding

Protocol Version History

Protocol Version	Version Date	Summary of Revisions Made
1.0	10/2021	Initial version
1.1	03Nov2021	Incorporated into ICTR template
1.2	24Nov2021	Qualitative analysis to include all participants, stats info added
1.5	27Oct2022	Update to study risks
1.6	19Dec2022	Update to study calendar
1.8	29Jan2023	Change to screening procedures
1.11	16Oct2023	Update to withdraw, exit interviewing, and delineating measures for early delivery
1.14	01Nov2023	1. clarification of study procedures when subjects self-withdraw or are withdrawn by the PI 2. patient noncompliance description 3. description of subject final visit 4. description of mixed method study format 5. inclusion of communication with patients who speak Spanish

Table of Contents

1.0 STATEMENT OF COMPLIANCE

I confirm that I have read this protocol. I will comply with the IRB-approved protocol, and applicable regulations, guidelines, laws, and institutional policies.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitment.

Name	**Signature**	**Date**
Jacquelyn Adams Principal investigator		
Sponsor		

2.0 LIST OF ABBREVIATIONS

AE	Adverse Event
CCC	Clinical Coordinating Center
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitor
CMP	Clinical Monitoring Plan
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management Software
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DMC	Data Monitoring Committee
DSMB	Data & Safety Monitoring Board
DSMC	Data & Safety Monitoring Committee
DSMP	Data & Safety Monitoring Plan
eCRF	Electronic Case Report Forms
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IDE	Investigational Device Exemption
ICTR	Institute for Clinical and Translational Research
IND	Investigational New Drug Application
IRB	Institutional Review Board
MOP	Manual of Procedures
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PHI	Protected Health Information
PI	Principal Investigator
POC	Point of Contact
PRC	Pharmaceutical Research Center
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sIRB	single IRB
SMART IRB	Streamlined, Multisite, Accelerated Resources for Trials IRB
SMC	Safety Monitoring Committee
UP	Unanticipated Problem

3.0 STUDY SUMMARY

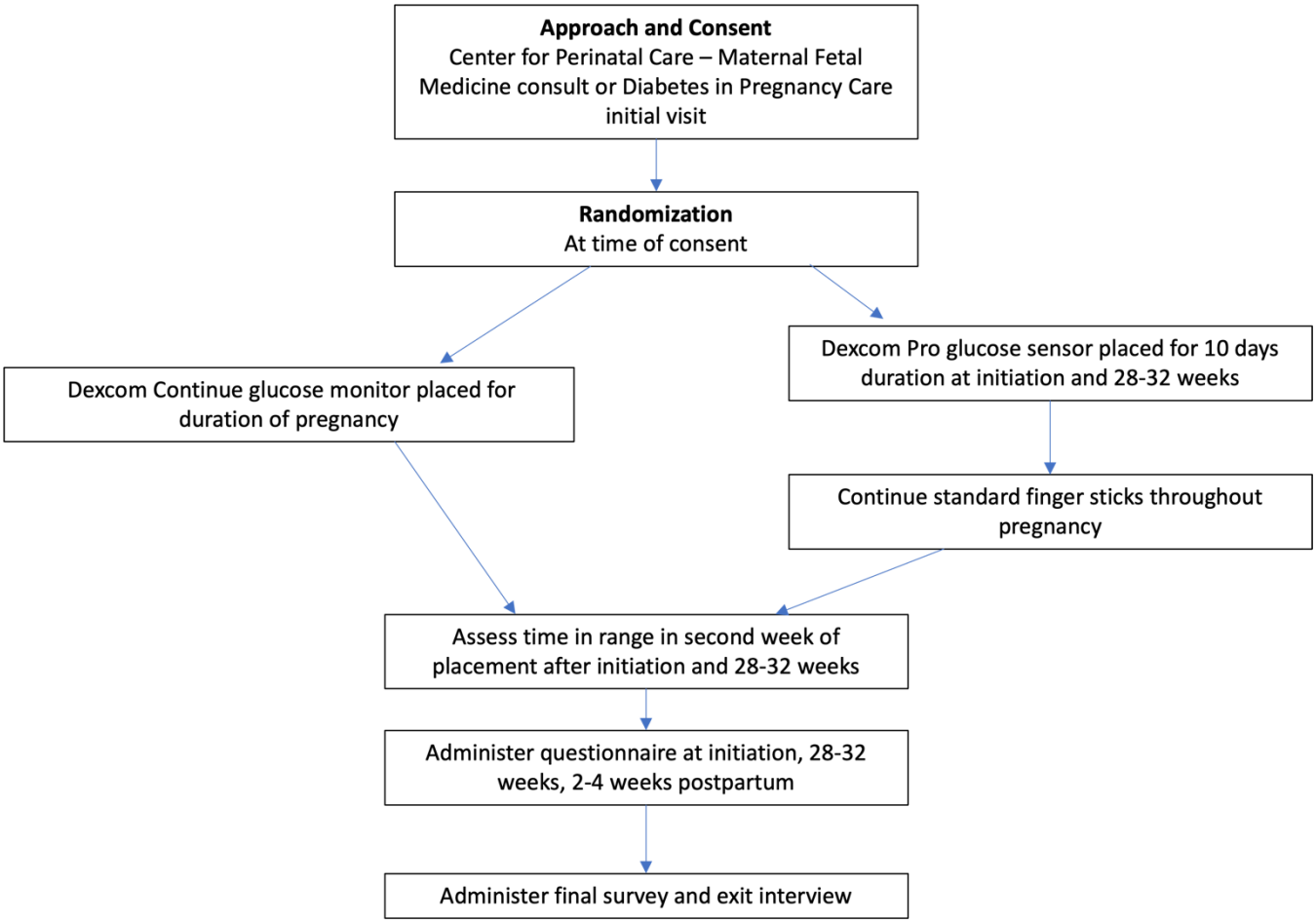
3.1 Synopsis

Full Title	Continuous glucose monitoring in pregnant patients with Type 2 Diabetes, a mixed methods approach
Short Title	CGM for T2DM
Protocol Number	UPH-Meriter IRB 2022-028
ClinicalTrials.gov Identifier & Summary	Clinicaltrials.gov identifier: NCT05370612 This is a randomized controlled, mixed methods pilot study on the use of continuous glucose monitors for the treatment of Type 2 diabetes in pregnant patients. Continuous glucose monitors (GGMs) will be compared to the standard of care point of care glucose testing (POCT). A qualitative component will consistent of patient surveys assessing satisfaction with treatment as well as semi-structured interviewing.
Number of Site(s)	Single site study – Center for Perinatal Health at Meriter Hospital
Main Inclusion Criteria	• Age ≥18 years of age at enrollment • Ability to consent in English or Spanish • Gestational age ≤ 19 weeks 6 days at enrollment • Appropriate dating by certain LMP or ultrasound performed ≤ 19 weeks 6 day • Diagnosis of Type 2 Diabetes ≤ 19 weeks 6 days • Singleton gestation
Main Exclusion Criteria	• Age <18 years of age at enrollment • Lack of appropriate dating • Multiple gestations • Use of concentrated insulin at enrollment (ie U500) • Preexisting CGM in place • Chronic use of medications known to cause hyperglycemia, such as HIV antiretrovirals and inhaled, injectable and oral corticosteroids • Be unwilling or unable to present to Center for Perinatal Care for visits
Objective(s)	<u>Primary Objective</u> To examine the feasibility of completing a study to assess for differences in patient preferences and glucose control between continuous glucose monitoring and standard glucose checks in pregnant patients with Type 2 Diabetes. <u>Secondary Objectives</u> • To estimate the effect of continuous glucose monitoring devices placed prior to 20 weeks in pregnancy in patients with Type 2 diabetes on time in range, as measured between 28-32 weeks of pregnancy. • To assess patient satisfaction to continuous glucose monitoring during pregnancy • To estimate the effect of continuous glucose monitoring on the incidence of neonatal morbidity and mortality.
Endpoints	<u>Primary Feasibility Endpoints</u>

	• Completion of the study within the 26-month timeframe, including recruitment, randomization, retention, and completion of 36 out of 40 subjects Primary Clinical Endpoint • The primary endpoint or primary objective is the total time within range (blood glucose level 70-140, min). All CGM data will be extracted from the Dexcom server for analysis. Secondary Endpoints • Maternal End points 1. Cesarean delivery rate in each group. 2. Change in hemoglobin A1c (%) from initiation to third trimester. 3. Time spent in hyperglycemic range (>140 mg/dL) 4. Time spent in hypoglycemic range (<70 mg/dL) 5. Rates of gestational hypertension (systolic blood pressure 140 mm Hg or diastolic blood pressure 90 mg Hg on two occasions at least 4 hours apart) 6. Rates of preeclampsia (gestational hypertension plus either new-onset proteinuria [300 mg/24 hours, protein:creatinine 0.3 mg/dL], thrombocytopenia [platelet count<100,000/uL], elevated Aspartate transaminase or alanine transaminase [>2 upper limit of normal], renal insufficiency [serum creatinine>1.1 mg/dL or an unexplained doubling of creatinine], pulmonary edema, or cerebral or visual symptoms) 7. Rates of polyhydramnios • Neonatal Endpoints 1. Incidence of neonatal hypoglycemia 2. Rates of fetal macrosomia (actual birthweight >95% by Fenton growth curve for newborns) 3. Rates of NICU Admission 4. Rates of spontaneous preterm delivery (<37 weeks)
Study Design	This is a pilot prospective, randomized trial. Patients and investigators will not be blinded to assignment.
IND or IDE Number	IDE NSR
Study Intervention	Patients who are less than 20 weeks pregnant with Type 2 diabetes diagnosed prior to pregnancy will be randomized to receive a Dexcom G6 continuous glucose meter or standard point of care finger glucose monitoring with a Dexcom G6 Pro sensor placed for a ten day period at study enrollment and again at 28-32 weeks. Participants and investigators will be blinded to the Dexcom G6 Pro data throughout pregnancy. Questionnaires will be completed at study enrollment, 28-32 weeks gestation and postpartum or at the exit of the study if early withdrawal. Directed individual interviews will be conducted at the conclusion of the study.
Total Number of Subjects	A total of 40 subjects will be recruited from a single site.
Study Population	A total of 40 gravid patients (age 18-45) who are less than 20 weeks' gestation at time of consent with preexisting Type 2 diabetes who receive diabetes care from the Center for Perinatal Health at Meriter Hospital.
Statistical Methodology	Subjects will be randomized 1:1 into the treatment or control group based on a random block size randomization scheme. This will insure balance in both arms throughout the entirety of the study. Estimation of treatment effect size will be the focus of the statistical analyses. The primary clinical outcome will be time in range. The effect size of treatment on time in range

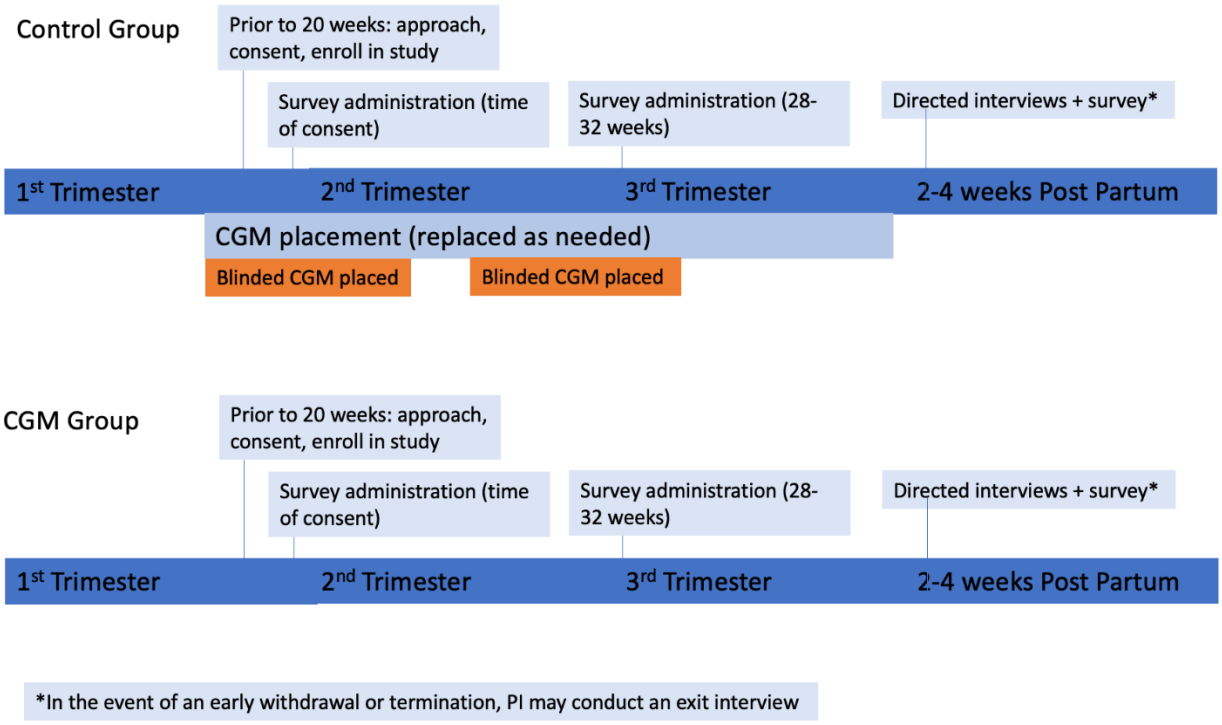
	will be estimated via longitudinal data analysis models with subject as a random effect. Effect size on secondary clinical outcomes will utilize similar models for continuous variables and mixed effects logistic regression for binary variables. Patients will be analyzed on the intention to treat principal. Additional per protocol analysis will also be performed.
Estimated Subject Duration	The duration of the study for each participant is expected to be approximately 26 weeks
Estimated Enrollment Period & Study Duration	Study enrollment and follow-up will occur over 20 months, from the date of first enrollment, with the total expected duration of the trial to be 26 months.

3.2 Schematic of Study Design



*In the event of early withdrawal by patient or PI, patient will be eligible for exit interview following withdrawal from the study.

Patient Anticipated Flow through Study



*In the event of early withdrawal by patient or PI, patient will be eligible for exit interview following withdrawal from the study.

4.0 KEY ROLES

The following is a list of all key personnel and roles:

Principal Investigator	Jacquelyn Adams, MD, Assistant Professor University of Wisconsin 202 S Park St. Madison, WI 53715 608-417-6667 Jhadams3@wisc.edu
Participating Site(s)	University of Wisconsin 202 S. Park St., Madison WI 53715
Data Monitoring Committee	ICTR Data Monitoring Committee UW Madison (608) 263-3804 asiedschlag@wisc.edu
Study Monitoring Contact	Kristen L. Mahaffey, MA, CCRP Central Monitoring Service Manager Central Monitoring Service FDA Regulated Research Oversight Program UW School of Medicine and Public Health 750 Highland Avenue Madison WI 53705 *klmahaffey@wisc.edu*
Funding Sponsor	UnityPoint Health - Meriter Foundation 202 S. Park Street Madison, WI 53715 Phone: (608) 417-5300 Fax: (608) 417-5325 Email: *msn_foundation@unitypoint.org*
Biostatistician	Scott Hetzel, MS UW ICTR Address Phone Number Email

5.0 INTRODUCTION

5.1 Type 2 Diabetes Background

Diabetes prevalence has been steadily increasing for the past several decades with increasing numbers of pregnant women affected by the disease. Estimates now suggest that up to 2% of all pregnancies are impacted by pregestational diabetes, with Type 2 significantly more common than Type 1.[1,2] As rates of obesity increase, as do rates of insulin resistant Type 2 diabetes in younger, reproductive age women.[3] The impacts on pregnancy are significant – both to mother and fetus. In the first trimester, elevated A1c is associated with increased rates of miscarriage and fetal anomalies, including complex cardiac defects. Later in pregnancy, rates of stillbirth, polyhydramnios, and macrosomia increase. After delivery, neonates of mothers with diabetes are more like to require neonatal intensive care admissions and prolonged hospital stays. In labor, rates of operative deliveries and cesarean sections are higher for mothers with diabetes. The maternal

impacts of diabetes in pregnancy are significant as well, and include increased rates of hypertensive disorders of pregnancy, diabetic retinopathy, diabetic nephropathy, as well as diabetic ketoacidosis.

Improved blood sugar control throughout pregnancy has been demonstrated to decrease these risks; however, blood glucose control is recommended to be tighter in pregnancy as well, which can be challenging to manage and maintain.

5.2 Current Standard of Care – Point of care glucose testing

Historically, pregnant patients with Type 2 diabetes have been asked to check blood sugar using a home point of care glucose meter at least 5 times per day, although sometimes more frequently: fasting, 1-2 hours postprandial and prior to bed. It is not uncommon to ask patients to check a 2am blood sugar as well. This is a more onerous regimen than most patients adhere to prior to pregnancy and can be a difficult and stressful adjustment.

Continuous glucose meters (CGM) are sensors that are placed on the body and test the interstitial glucose level every few minutes and transmit the data to a receiver where the output can either be uploaded to the cloud or a computer, or viewed in real time using a smart phone. Although CGMs are not approved for use in the pregnant population, several recent studies have demonstrated benefit in lowering blood glucose levels in Type 1 and gestational diabetic populations. To date, this research has not included patients with Type 2 diabetes. Furthermore, no data has been collected regarding patient perspective and satisfaction with CGMs, and therefore little is known about whether it actually improves patient quality of life and feelings of control and satisfaction with care during pregnancy.

This study will utilize the Dexcom G6 CGM in the experimental group. The CGM remains in place for 10 days. Patients will be provided with the same training and information that all patients receiving Dexcom CGMs receive. The protocol for wear will not differ compared to that of non-pregnant patients and will follow standard of care. Patients will be provided with sufficient quantity of CGM so that they will have one in place for the duration of pregnancy.

The control group will continue to utilize point of care finger sticks, using their preexisting glucometer. If a new glucometer is needed during the pregnancy, one will be prescribed in the same manner as a patient not involved in the study. At two time points during the study – enrollment and at 28-32 weeks, a Dexcom Pro G6 sensor will be placed and remain in place for 10 days. Neither patients nor providers will have access to this data until after delivery, with the purpose being that it not be used to guide clinical decision making.

Time in range is the primary outcome we are using for determine glucose levels. This is something that is only available through a CGM. Therefore to compare the control group to the experimental group, we need to have the control group wear a sensor that can provide time in range data. We are using two time points because the first time point is prior to starting the intervention and the second time point is after the experimental group will have worn the sensor for at least 8-12 weeks.

5.3 Continuous glucose monitors/glucose sensors

The device intervention to be used is a Dexcom 6 CGM, an FDA approved device. The device will be placed at time of enrollment and patients will be provided standardized instructional videos and information provided by Dexcom. Additionally, clinic staff will be available to ensure patients can

place sensors correctly. The patients will be instructed as to how to set up online accounts and user interfaces on their personal smart phones, as well as provided with instruction regarding viewing the data on their smartphone in real time. If a patient does not have a smart phone, she will be provided with one to use for the purpose of viewing glucose data for the duration of pregnancy. Additionally, patients will be instructed regarding timing and procedures for changing the CGM and transmitter.

Controls will be asked to wear a blinded sensor, Dexcom G6 Pro, for two ten-day periods throughout the study – once at enrollment and once between 28-32 weeks. The sensor will be placed for them and the data uploaded to the cloud, which will be stored on a password protected Redcap server, by the clinical team.

Several prior studies have examined similar sensors in pregnant women over the past 10 years.[4–7]

5.4 Rationale

Several recent studies have demonstrated benefit in lowering blood glucose levels in Type 1 and gestational diabetic populations.[5,6,8] To date, this research has not included patients with Type 2 diabetes. Furthermore, no data has been collected regarding patient perspective and satisfaction with CGMs, and therefore little is known about whether it actually improves patient quality of life and feelings of control and satisfaction with care during pregnancy.

Mixed methods is the optimal format for this study given the dearth of knowledge around management of Type 2 diabetes in pregnancy using CGM. This comprehensive approach will allow for direct comparison of quantitative outcomes, hypothesis generation, and protocol development for larger clinical trials. The qualitative arm will identify themes for further exploration in diabetes management in pregnancy, CGM use in pregnancy, management satisfaction as well as explore patients' experience with the protocol and study design. Interviewing patients that have been non-compliant with assigned group or who choose to leave the study will allow accurate assessment of potential changes for a larger trial as well as improve methodology and experience.

6.0 STUDY OBJECTIVES AND ENDPOINTS

Quantitative Outcomes	
Objectives	Endpoints
Primary	
To examine the feasibility of completing a study to assess for differences in patient preferences and glucose control between continuous glucose monitoring and standard glucose checks in pregnant patients with Type 2 diabetes.	• Completion of the study within the 26 month timeframe, including recruitment, randomization, retention, and completion of 36 out of 40 subjects.
Secondary	
• To estimate the effect of continuous glucose monitoring devices placed prior to 20 weeks in pregnancy in patients with Type 2 diabetes on time in range, as measured between 28-32 weeks of pregnancy.	• The primary clinical endpoint is the total time within range (blood glucose level 70-140, min)

• To estimate the effect of continuous glucose monitoring on the incidence of neonatal morbidity and mortality.	• Incidence of neonatal hypoglycemia. • Rate of fetal macrosomia (actual birthweight >95% by Fenton growth curve for newborns). • Rates of NICU admission • Rates of spontaneous preterm delivery (<37 weeks
• To estimate the effect of continuous glucose monitoring on the incidence of maternal morbidity	• Cesarean delivery rate in each group. • Change in hemoglobin A1c (%) from initiation to third trimester. • Time spent in hyperglycemic range (>140 mg/dL)d. Time spent in hypoglycemic range (<70 mg/dL) • Rates of gestational hypertension (systolic blood pressure 140 mm Hg or diastolic blood pressure 90 mg Hg on two occasions at least 4 hours apart) • Rates of preeclampsia ((gestational hypertension plus either new-onset proteinuria [300 mg/24 hours, protein:creatinine 0.3 mg/dL], thrombocytopenia [platelet count<100,000/uL], elevated Aspartate transaminase or alanine transaminase [>2 upper limit of normal], renal insufficiency [serum creatinine>1.1 mg/dL or an unexplained doubling of creatinine], pulmonary edema, or cerebral or visual symptoms) • Rates of polyhydramnios
• To assess patient satisfaction to continuous glucose monitoring during pregnancy	• Satisfaction scores from quality of life and satisfaction survey administered at 3 time points: initial study enrolment, 28-32 weeks, 2-4 weeks postpartum or at the conclusion of the study if the patient decides to withdraw or is withdrawn early.

Qualitative Outcomes	
Objectives	Endpoints
Primary	
Critically assess patients' perceptions of diabetes control in pregnancy using standard testing versus continuous glucose monitoring	Gather information about patients' thoughts and experiences in both arms of the trial about their ability to manage diabetes in pregnancy through surveys administered at study onset, 28 weeks and 32 weeks gestation, or at study completion
Secondary	

Explore how glucose monitoring affects patients' thoughts and feelings about pregnancy and health.	Directed/semi-structured interviewing of patients at the end of the study period during the postpartum period.
Explore if traditional management versus continuous glucose management has higher feelings of control over diabetes management.	Use of well validated tools in non-pregnant adults to discuss feelings about diabetes management with addition of pregnancy specific questions.

7.0 STUDY DESIGN

7.1 General Design

This pilot single site randomized control trial will compare the blood glucose control and patient satisfaction scores of continuous glucose monitoring vs standard glucose checks in pregnant women with a prior diagnosis of Type 2 diabetes.

The study population will consist of 40 women who are less than 20 weeks pregnant at time of enrollment who have a pre-pregnancy diagnosis of Type 2 diabetes. Subjects will be randomized to one of two treatment arms.

- Arm 1: Placement of Dexcom G6 continuous glucose monitor for glucose monitoring for duration of pregnancy
- Arm 2: Continuation of standard glucose finger sticks with placement of a blinded Dexcom Pro G6 continuous glucose sensor for two ten day periods (at enrollment and again at 28-32 weeks)

Subject accrual will occur over 20 months at 1 site. Subjects will complete 3 study visits, all of which will be in conjunction with previously scheduled prenatal or diabetes visits over the course of approximately 26 months. Surveys will be administered at each time point, as well as at the postpartum visit. At the final visit, patients will be asked for participate in a 10 minute semi structured interview.

7.2 End of Study Definition

The end of the study is defined as the date of completion of any final follow-up activity or data collection described in the protocol.

8.0 SUBJECT SELECTION

8.1 Inclusion & Exclusion Criteria

Inclusion Criteria
1. Willing to provide informed consent.
2. Willing to comply with all study procedures and be available for the duration of the study.

3. Must have a confirmed intrauterine pregnancy less than 20 weeks' gestational age at time of enrollment
4. Individuals at least 18 years of age.
5. Verified Type 2 Diabetes prior to pregnancy
6. Must have a singleton pregnancy
7. Ability to consent in English or Spanish

Exclusion Criteria
1. Age <18 years of age at enrollment
2. Lack of appropriate dating
3. Multiple gestations.
4. Use of concentrated insulin at time of enrollment (ie U500)
5. Preexisting CGM in place
6. Chronic use of medications known to cause hyperglycemia, such as HIV antiretrovirals and inhaled, injectable and oral corticosteroids
7. Unwilling or unable to present to Center for Perinatal Care for visits

8.2 Vulnerable Populations

This study will enroll pregnant women because the intervention being studied has the potential to improve maternal health during pregnancy which will therefore benefit fetuses. There is minimal to no risk to fetuses. In fact, glucose control in early pregnancy is of paramount importance to preventing maternal and neonatal morbidity.

8.3 Lifestyle Considerations

During this study, subjects are asked to: adhere to standard lifestyle pregnancy modifications, as well as those specific to any additional conditions they may have. No additional modifications will be asked of patients for the purpose of this study.

8.4 Subject Identification and Recruitment

Subjects will be identified at their referring provider's office, by the Diabetes in Pregnancy Program, or by maternal fetal medicine physician at the time of consultation.

Location or scenario where approached	Obtain permission to contact	Consent and study discussed	Consent form signed	Randomization
Provider's office at entry to prenatal care	YES	YES	NO – Will be done at referral	NO – Will be done at referral
Diabetes in Pregnancy Program –	YES	YES	YES	YES – Performed by study staff

Center for Perinatal Care				
Center for Perinatal Care – Maternal Fetal Medicine Consult	YES	YES	YES	YES – Performed by study staff
Phone Call	NO	YES	NO – Will be done at referral	NO – Will be done at referral

All subjects who are enrolled in this study should be recorded on Enrollment Log. Enrollment should take place just prior to sampling, but after the subject has signed the IRB-approved consent form, undergone the screening process, and met all of the inclusion and none of the exclusion criteria. Study staff will enter the subject's Study ID as designated into REDCap. The patients will be screened, and all criteria will be collected in REDCap when the patient is given a study ID before they can be randomized.

Patient Phone Call

Study staff will be phoning subjects prior to their appointments at the Perinatal Clinic to introduce the study. Study staff will be getting consent and HIPAA authorization at either the clinic appointment or at another time. Enrollment of the patient is a time consuming process. This extra step is necessary to limit the amount of time that the patient spends in clinic, reviewing the research study with staff. If the patient feels inconvenienced, this may lead to reduced enrollment. This will be done once patient is identified as an appropriate candidate by the research team.

Inclusion of Patients who speak Spanish
The study will enroll subjects who speak and read either English or Spanish. All documents, including the consent and HIPPA authorization form are translated into Spanish by a certified medical interpreter in the UW Hospital Interpreter Services Department.

An interpretation service, LanguageLine, will be used during the informed consent process. Interviews with patients who speak Spanish will be conducted by Dr. Iruretagoyena, who is a native Spanish speaker and a provider in the department of Ob/Gyn. The interviews will be transcribed into English.

First Approach
The coordinator may use LanguageLine or a certified hospital translator for first approach. The coordinator will call LanguageLine to go over the consent form with the patient. If there is no interpreter present, permission to approach will be delayed. The patient needs to be able to understand and communicate with the coordinator. Every effort will be made to approach Spanish-speaking subjects at the same locations/circumstances as non-Spanish speaking patients.

8.5 Remuneration and Retention Strategies

Strategies for retention include:

- Phone call reminders from clinic staff regarding upcoming appointments
- Email reminders with surveys before and after each time point with email surveys for patients to complete
- Paper copies of surveys available in clinic appointments to complete if unable to do so electronically
- Flexible study visit windows to accommodate subject schedules.
- Subjects will receive reimbursement for each completed study visit, a total of three payments for $50 each ($150 total). They will receive $10 dollars for completing a phone interview. If they complete all study visits and the interview, they will receive $160 for participation in the study.

8.6 Early Termination and Withdrawal

Subjects are free to withdraw from participation in the study at any time upon request.
The Principal Investigator (PI) may discontinue or withdraw a subject from the study for the following reasons at his/her discretion:

- Subject non-compliance with study requirements (e.g., study intervention non-compliance)
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject
- If the subject is no longer an appropriate candidate for participation
- There is evidence of progressive disease or unacceptable toxicity
- Subject unable to receive study intervention for 10 days

Subjects who sign the informed consent form and are randomized but do not receive the study intervention will be replaced. Subjects who sign the informed consent form, are randomized and receive the study intervention, then subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

The following actions must be taken if a subject withdraws, or fails to return for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit within the next 2 weeks and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
    - If a subject withdraws, study staff will clarify with the patient what they are withdrawing from
    - all study procedures and contact
    - participation with their randomized group
    - personal information/delivery outcome collection
    - study conclusion interview
    - survey materials (if applicable)
    - research access and collection of data from their medical record
- Study team will document in the electronic medical record the above findings

Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent method>. These contact attempts shall be documented in the subject's study file.

If the subject continues to be unreachable, they will be considered to have withdrawn from the study with a primary reason of lost to follow-up. The withdrawn date is the last day of attempted contact.

9.0 STUDY AGENT (STUDY DRUG, DEVICE, BIOLOGIC, VACCINE, ETC.) AND/OR PROCEDURAL INTERVENTION AND/OR BEHAVIORAL OR SOCIAL INTERVENTION

9.1 Study Agent and Control Description

Dexcom G6 Continuous Glucose Monitor

This device qualifies for an abbreviated IDE as it poses no significant risk.

Active Control

Standard glucose finger sticks with blinded Dexcom G6 Pro sensors will be used at two time points

Source

All study devices will be provided free of charge by Dexcom during the treatment phase.

Packaging and Labeling

- The G6 Dexcom system box contains the applicator and transmitter. The device will be packaged in its standard packaging provided by Dexcom.

Preparation

Dexcom Sensor

See user guide Chapter 6 – Start your Sensor – page 71 for Commercial, and Page 10 – Inserting the Sensor, for the Pro products, included in the Addendum

Storage and Stability

Sensor
• Keep in its sterile packaging until you're ready to use it.
• Store at temperatures between 36° F and 77° F.
• Storing outside this range may cause inaccurate G6 readings.
• May store sensor in refrigerator if it's within temperature range.
• Store sensors in a cool, dry place. Don't store in parked car on a hot day or in freezer.

Transmitter
• Keep protected when not in use
• Store at temperatures between 32° F and 113° F
• Store between 10% and 95% relative humidity

Receiver
• Keep protected when not in use
• Fully charge the battery before storing for over 3 months
• Store at temperatures between 32° F and 104° F
• Store between 10% and 95% relative humidity

Accountability

Order forms will be provided by Dexcom to request products. Product will be shipped via FedEx. Products will be ordered in 3-month increments.

Dosing and Administration

- Sensors are to be placed on the abdomen according to package instructions.

9.2 Method for Assigning to Treatment Groups

Patients will be randomized at time of enrollment using random block randomization. There are no blinding procedures. The randomization table will be developed by the statistician and loaded into REDCap. Once the patient is entered into the REDCap system and informed consent is obtained, they can then be assigned to their study group through the randomize function.

A separate paper and envelope randomization will be available in the event the REDCap server is unavailable. The instruments needed for enrollment and randomization will also be available on paper. These will be utilized until the REDCap server is available and then the patient will be entered into REDCap by the study team.

9.3 Study Intervention Compliance

Compliance will be assessed by reviewing CGM glucose output or point of care glucose checks at each follow up visit, which is standardly performed by clinical staff. Unblinded participants will be able to upload their data to the study staff and Diabetes in Pregnancy program from their app at any point.

If the patient utilizes management methods outside their assigned group, they will continue to be analyzed in the assigned group based on intention to treat basis and a protocol deviation will be entered. This will allow for unbiased analysis and conclusions regarding the effectiveness of the study intervention. Non compliance to study protocol and understanding patient motivation is a critical component of mixed methods research and key to future study design. In addition, the intention to treat analysis preserves the benefits of randomization and efficacy based on adherence to the protocol.

Patients non-compliant with treatment will be noted in the electronic medical record and field notes. The patient will be asked to participate in surveys and a study completion interview to better understand their experience with the study and interventions.

9.4 Preterm Delivery

In the event of a preterm delivery prior to data collection at visits 1, 2, or 3, patients will have data collected and completed for all clinical outcomes. If delivery occurs before the 2nd survey administration and data collection point, the survey will be sent to the patient and notation made in the medical record and field notes. The postpartum survey instrument will be dispatched at the normal time frame. Data from surveys will be accepted up to 8 weeks post partum. Control patients will not be asked to wear the blinded sensor for the second time point. The patient will be offered an exit interview with study staff.

9.5 Concomitant Therapy

Permitted Concomitant Therapy

All additional medications and supplements, except those as listed below, will be reviewed and documented at each clinic visit.

Prohibited Concomitant Therapy

Prohibited medications include those that are known to cause hyperglycemia, including HIV antiretrovirals, inhaled, oral and injectable corticosteroids when taken for chronic use.

10.0 STUDY VISITS AND PROCEDURES

10.1 Study Calendar

The procedures performed at each study visit are listed in the table below.

Procedure	Baseline	Visit 1	Visit 2	Visit 3	Early Termination*	Postpartum
Visit Window	**<20 weeks' gestation**	**2-3 weeks after enrollment**	**28-32 week's gestation**	**2-3 weeks after visit 2**		**2-4 weeks postpartum (up to 8 weeks postpartum)**
Informed Consent	X					
Demographics	X					
Review Concomitant Medications	X	X	X		X	X
Obtain Medical History	X					
Randomization	X					
Administer Study Intervention	X		X			
Adverse Event Review and Evaluation	X	X	X	X	X	X
Survey administration	X		X		X	X
Review glucometer data		X		X	X	
Directed individualized interview					X	X

* "If early termination is before Visit 2, the Visit 2 survey will be sent out at early termination. The exit interview will be conducted post the early termination. A postpartum survey will also be sent out 2-4 weeks post participant's original due date."

10.2 Screening and Enrollment

The Screening and Enrollment visits and procedures are described in detail below.

Pre-screening

Pre-screening consists of examining a subject's medical records by research staff who have completed HIPAA and human subjects training. All patients presenting for consults with at the Center for Perinatal Care at Meriter Hospital will be screened. In addition, physicians at outlying facilities can screen potential patients and offer patient facing brochures to assess interest. If the patient is willing to speak with study staff, the outlying facility may contact study staff by phone, email, or message in the electronic medical record.

Informed Consent

Study staff will be phoning subjects prior to their appointments at the Perinatal Clinic to introduce the study. Study staff will be getting consent and HIPAA authorization either at the clinic appointment or at another time.

Preliminarily eligible subjects will be approached at initial appointment at Meriter Center for Perinatal Care for informed consent and formal screening. The informed consent process will be conducted following all federal and institutional regulations relating to informed consent. Informed consent will be obtained prior to conducting any study-related activities.

The informed consent process will be performed as follows:

- Research coordinators or study staff will review the informed consent form and discuss the study in detail with the potential research subject.
- Research coordinators or study staff will explain the study, its risks and benefits, what would be required of the research subject, and alternatives to participation.
- The research subject will be given the opportunity to take the informed consent form home so that they may discuss it with family members, friends, clergy, or others when possible.
- The subject will have the opportunity to ask questions and have all questions answered by the Research coordinators or study staff and/or PI.
- The informed consent document must be signed and dated by the research subject.
- Research coordinators or study staff will review the informed consent document to ensure that all fields that require a response are complete (i.e., checkbox marked yes or no, etc.) as applicable.
- The research subject will be given a copy of the signed and dated informed consent form. The original signed informed consent form is kept in a secure, locked cabinet in the OB/Gyn clinical research office. A copy will also be taken to patient registration to be scanned into the patient's chart.

Baseline

The baseline visit will be in conjunction with the patient's first antenatal visit to the Center for Perinatal Care at Meriter Hospital. For some of these patients, it may be a consultation with maternal fetal medicine, an initial obstetrics visit, or an appointment with the diabetes in pregnancy program. At the time of the visit, the pre-screened patient will be approached regarding participation in the study. If interested, informed consent, enrolment, randomization, and a brief survey will be administered at that time. If randomized to the control group, a Dexcom G6 Pro sensor will be placed and participant will be scheduled to return to clinic in 10-14 days to obtain data from the sensor. If randomized to the CGM placement, device education and placement will be performed at that time. Follow up on sensor data will be performed either remotely or in person, as guided by clinical necessity.

Enrollment

Enrollment will be defined as the time of consent. The subject will not count toward the total "n" until they are consented and successfully randomized by the research staff.

Screen Failure and Re-enrollment

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a misdiagnosis of Type 2 Diabetes or previously placed CGM may be rescreened. Rescreened subjects should be assigned a new subject ID number when they are re-screened.

10.3 On-Study/Follow-up Visits

After subjects have been enrolled, the On-Study/Follow-up visit and the procedures performed at each visit are described in detail below.

Visit 1

All controls will be scheduled for a visit 10-14 days after the baseline visit to collect the sensor data. Decision as to whether to collect CGM data from the experimental group in person or virtually will be at the discretion of the provider.

Visit 2

Patients in the control group will have a second sensor placed at 28-32 weeks. This visit will be performed in conjunction with an already scheduled prenatal or diabetes visit. A survey will be administered at this visit. For experimental group participants, a survey will be administered at a previously scheduled prenatal or diabetes visit between 28-32 weeks.

Visit 3

All controls will be scheduled for a visit 10-14 days after the baseline visit to collect the sensor data. Decision as to whether to collect CGM data from the experimental group in person or virtually will be at the discretion of the provider.

Final Study Visit

The final study visit will be defined as the final interaction with the study team. Patients may return unused materials if they desire for study team to dispose, however, returning unused equipment is not necessary given study supplies cannot be reused nor returned.

All patients will be asked to participate in a 10-minute semi structured interview regarding their perceptions and thoughts regarding study participation. This visit may take place over the phone or in person per patient's preference. Patients may decline interviewing with study staff and this will be documented in the medical record and placed as a protocol deviation.

10.4 Unscheduled Visits

Unscheduled visits will not routinely occur for this study. Study procedures will be combined with clinically necessary visits to avoid undue burden on the patient. Exceptions may be made with patient's permission if:

- The patient misses a scheduled appointment
- A new appointment is necessary to collect time-sensitive patient data such as professional sensor for control subjects
- The patient prefers a separate appointment with study staff due to commute or schedule

10.5 Early Termination/Withdrawal Visit

In the event of early withdrawal by a patient, patients will be asked their reason for early withdrawal from the study, and this will be documented in the electronic medical record as well as field notes in REDCap. The patient will be asked if they agree to participate in a semi-structured interview so that qualitative data can be collected. This will be scheduled following patients' withdrawal from the study rather than postpartum to allow for adequate assessment. Patients will be considered withdrawn from the study following this final interaction with the study team, if agreeable.

10.6 Long-Term Follow-up | Re-contacting Subjects

Not Applicable. Study subjects will not be contacted following their final interview.

11.0 DATA HANDLING AND RECORD KEEPING

11.1 Data Collection

Data Collection Forms

Standardized data collection forms (e.g., source documents, case report forms, standardized assessment forms, etc.) are used to ensure data collected are consistent and compliant with the protocol and IRB application.

Data collection is the responsibility of study team members under the supervision of the Principal Investigator (PI). The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the recorded and reported data.

All data collection forms must be completed in a legible manner; any missing data will be explained. Data entry errors will be corrected with a single line through the incorrect entry and the correct data is entered above/near the correction. All changes will be initialed and dated.

All interviews will be recorded using a recording device. The file will be stored in REDCap, as discussed below in section 11.1.2. Additionally, interviews will be transcribed using NVivo 12, text files from which will also be stored in REDCap.

Data collection forms are maintained in the subject files and retained as described in Section 11.3: Records Retention.

Data Management Software System(s)

Clinical data (including AEs, concomitant medications, and solicited events data) and clinical laboratory data will be entered into the following data management software system(s) to ensure consistent data entry and data quality. Clinical data will be entered directly from the source documents.

REDCap

The Obstetrics and Gynecology Research Electronic Data Capture (REDCap) system is used to manage the data for this study.

REDCap is a largely self-service, secure, web-based application for building and managing data collection forms. REDCap provides data management functionality by allowing the development of instrument and surveys to support data capture for research studies.

11.2 Confidentiality and Privacy

Subject confidentiality and privacy are strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. 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 sponsor.

All research activities will be conducted in as private a setting as possible.

All study staff engaged in the conduct of this project have completed training on the protection of human subjects and the Health Insurance Portability and Accountability (HIPAA) Privacy Rule. In addition, all key personnel (i.e., Principal Investigator, individuals involved in identifying/recruiting subjects, obtaining informed consent, or interacting and intervening with subjects) have undergone Good Clinical Practice (GCP) training.

Information about study subjects will be kept confidential and managed according to HIPAA requirements. All subjects will sign an informed consent document and a HIPAA authorization form or. Study data will be maintained per federal, state, and institutional data policies.

The investigator(s) will ensure that the identities of subjects are protected by using coded subject information. The log of subject identifying information that links subjects to their study-specific identification number will be maintained by the investigator. The log and all study records will be maintained in locked rooms and access will be limited to essential study personnel. Electronic study records/files will be stored on a department server and accessed via networked computers that are password-protected with access provided only to authorized study personnel.

Authorized representatives of the following groups may need to review this research as part of their responsibilities to protect research subjects: the study monitor, other authorized representatives of the sponsor, representatives of the IRB, DSMB/DMC, DCC staff, regulatory agencies or pharmaceutical company supplying study product, and federal oversight agencies, such as the Food and Drug Administration (FDA). The clinical study site will permit access to such records.

Study staff may use e-mail to communicate with research subjects, if the subject has agreed to using email in the Informed Consent form. The information contained in emails will be limited to study visit time and date information, general questions, etc. All emails to subjects will be sent from UW/wisc.edu accounts; personal, home or Gmail email accounts will not be used.

11.3 Records Retention

It is the investigator’s responsibility to retain study essential documents for a minimum period of 7 years following completion of the study per UW-Madison institutional policy, or at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product, whichever comes last.

11.4 Retention for Future Research: Data, Image, Audio- or Video-Recording & Biospecimen Banking

Purpose of Storage

Not applicable

11.5 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or investigational plan requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the Principal Investigator/site investigator/study staff to use continuous vigilance to identify and report deviations. The Principal Investigator is responsible for assessing whether the deviation constitutes noncompliance as defined by the reviewing IRB and if so, reporting it within the required time frames. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

11.6 Publication and Data Sharing Policies

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/) upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

12.0 STUDY ANALYSIS

12.1 Statistical Hypotheses

- **Primary Efficacy Endpoint(s):**
  As this is a pilot study we do not have a primary hypothesis test for efficacy. Our main goal of the study is to demonstrate the ability to recruit, randomize, and retain at least 36 out of 40 subjects throughout the 26 month duration of this pilot study. In doing this we will learn barriers to recruitment and entry into the study. We will also learn reasons why subjects drop-out from a study of this design. This pilot study will also allow us to estimate the effect size (95% CI) of the continuous glucose monitoring on time in range. All of this information will strengthen the design of a future fully powered efficacy study.

- **Secondary Efficacy Endpoint(s):**

There are no secondary efficacy hypothesis tests. Effect size (95% CI) of continuous glucose monitoring will be estimated for secondary endpoints.

12.2 Sample Size Justification

Sample size justification is based on the precision of the 95% CI of the effect size of continuous glucose monitoring on time in range. In this longitudinal randomized design the effect size will be the mean difference in change in time in range from baseline to 28-32 weeks of pregnancy. With 18 subjects in both groups our expected 95% CI around the effect size will be +/- 0.66*SD. This would equate roughly to a Cohen's D medium effect size, which will give us a good precision to make subsequent study sample size justification. To account for planned 10% attrition rate we will recruit 20 subjects in both groups for a total of 40 subjects.

12.3 Subject Population(s) for Analysis

Estimation of effect sizes will be based on Intention-to-Treat.

12.4 Statistical Methods

Subjects will be randomized 1:1 into the treatment or control group based on a random block size randomization scheme. This will insure balance in both arms throughout the entirety of the study. Estimation of treatment effect size will be the focus of the statistical analyses. The primary clinical outcome will be time in range. The effect size of treatment on time in range will be estimated via longitudinal data analysis models with subject as a random effect. Effect size on secondary clinical outcomes will utilize similar models for continuous variables and mixed effects logistic regression for binary variables. Patients will be analyzed in assigned groups in concordance with intention to treat analysis. Per protocol analysis will also be performed.

12.5 Planned Interim Analysis

There are no planned interim analyses for this pilot study.

12.6 Handling of Missing Data

All missing data will be considered missing at random for this pilot study. To account for a possible 10% attrition we have increased our needed sample size accordingly.

13.0 RISK/BENEFIT ASSESSMENT

13.1 Known Potential Benefits to the Subjects

The potential benefits to research subjects associated with this study include the possible improvement of blood glucose control as well as improved quality of life in pregnancy.

If this study is able to show a therapeutic benefit of CGM in pregnant patients with Type 2 diabetes, the community at large would benefit by the availability of a superior treatment option.

13.2 Known Potential Risks

Known Interventional Risks

Detailed information on risks can be found in the IB
Dexcom G6 and G6 Pro

The sensor used in this study is composed of medical grade plastic and unlikely to cause a reaction. Upon insertion of the device, there is a slight risk of bleeding at the insertion site. The integrity of the sensor may be impacted by bug spray, sunscreen and MRI machines, so glucometer should be used in the event that there is concern the sensor is no long accurate, until a replacement may be obtained. There are no obvious or foreseeable risks associated with the sensor itself.

Survey
The survey, although brief, poses a theoretical risk of consuming additional participant time. No significant harm is expected to occur from this intervention.

13.3 Risk/Benefit Analysis

There is no significant harm anticipated from either CGM placement or from survey or interview participation. Patients have the opportunity to potentially avoid glucometer finger sticks, which could be a significant advantage. Participants will also be compensated for all aspects of the study in which they participate.

14.0 DATA AND SAFETY MONITORING

14.1 Adverse Event (AE) Definition

An adverse event is defined as any untoward or unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

14.2 Serious Adverse Event (SAE) Definition

An adverse event is considered "serious" if, in the view of either the investigator or sponsor, it meets any of the following outcomes:

- Death.
- A life-threatening adverse event.
- Inpatient hospitalization or prolongation of existing hospitalization for $\geq$ 24 hours.
    - Does NOT include usual post-partum hospitalization of 2-4 days post-operative stay
    - Does NOT include antepartum admissions related solely to blood pressure monitoring or hypertensive disease of pregnancy
    - DOES include post-op stay >4 days
    - DOES include re-admissions after the usual postpartum hospitalization for indications other than blood pressure monitoring or hypertensive disease of pregnancy
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important Medical Events (IME) that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

14.3 Classification of an Adverse Event

Severity of Event

All AEs will be assessed by the clinician using CTCAE v5.0, each event searchable using the Safety Profiler website (https://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx). For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity. Specifically, hypo- and hyperglycemic events will only be an adverse event if additional medical treatment is sought for that event.

Mild (Grade 1)	Events require minimal or no treatment and do not interfere with the subject's daily activities.
Moderate (Grade 2)	Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
Severe (Grade 3)	Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.
Life Threatening (Grade 4)	The subject was at risk of death at the time of the event.
Fatal (Grade 5)	The event caused death.

Relationship to Study, Study Procedure and/or Study Intervention

For all collected AEs, the clinician who examines and evaluates the subject will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

Definitely Related	Clearly related to the study procedures/intervention and other possible contributing factors can be ruled out.
Probably Related	Likely related to the study procedures/intervention and the influence of other factors is unlikely.
Possibly Related	Possibly related to the study procedures/intervention and there are other factors that could be equally likely.
Unlikely to be related	Doubtfully related to the study procedures/intervention and there is another likely cause.
Unrelated	Clearly not related to the study procedures/intervention and/or evidence exists that the event is definitely related to another cause.

Expectedness for Study, Study Procedure and/or Study Intervention

The PI will be responsible for determining whether an AE is expected or unexpected in relation to the study procedures and intervention (as applicable).

For investigational drug and device studies: An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in the clinical protocol, device manual, investigator's brochure, the package insert(s),

the IRB application, or the informed consent document. Expectedness is recorded for both study procedures and interventions.

14.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after the administration of the study drug and for up to 30 days after the date of the last dose of study drug. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution, stabilization, or completion of study participation.

14.5 Reporting AEs and SAEs

Reporting AEs

The research coordinator and clinical research team will perform chart review during the patient's hospitalization as well as following discharge. This information will be used to investigate our three specific aims and one developmental aim. Additional data will be obtained from patients via postpartum survey evaluations at two and six weeks postpartum. This will be collected and analyzed using REDCap.

We plan to utilize the UW ICTR Data Monitoring Committee (DMC) to oversee the study. The UW ICTR DMC is comprised of experienced members (core plus ad hoc) with expertise required to oversee this study. The DMC members will review protocol-specific reports created by statisticians using data pulled from the Research Electronic Data Capture (REDCap) data management tool. These standard reports will include an overview of study objectives, a review of actual and projected accrual rates, an evaluation of patient demographics for balance of randomization, and a summary of the number and seriousness of adverse events. An interim analysis of study results may be performed and source documents may be reviewed to allow the DMC to independently judge whether the overall integrity and conduct of the protocol remain acceptable based on data provided and reported by the Principal Investigator. The DMC will make recommendations to the Principal Investigator that could include actions of continuation, modification, suspension, or termination.

In providing oversight for the conduct of this study, the ICTR DMC will meet twice during the study to review all adverse events. Additional meetings may be scheduled as determined by the DMC or as requested by the PI. The predefined stopping points for this study will include excess rates of infection or reaction to the glucose monitors or uncontrolled blood glucoses in one arm requiring excess admissions. We will submit all reportable events to the DMC and the UnityPoint Health-Meriter IRB in accordance with their reporting guidelines.

Adverse events will be identified by review of the EMR on week days while the subjects are admitted for delivery and for six weeks postpartum. Any adverse events will be discussed at weekly research team meetings and will be reviewed to determine whether a change in protocol is necessary.

AE/SAEs that meet the definition of an unanticipated problem will be reported to the IRB within 14 business days. Events that are immediately life threatening, severely debilitating to other current subjects or resulted in a death will be reported to the IRB Chair or IRB Director via telephone or email within 24 hours (1 business day) of site awareness.

All AEs will also be reported to the ICTR DMC by completing the AE/SAE forms in REDCap and will be reported within the same timeframe as required by the IRB. Once entered, an automatic notification of an SAE will be sent to the ICTR DMC. The DMC co-chairs will review the SAE and if needed, schedule an ad hoc meeting of the full committee.

Reporting SAEs

The investigator will immediately report to the sponsor any SAE, whether or not considered study intervention-related, including those listed in the protocol or investigator's brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are SAEs (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the subject is stable. Other supporting documentation of the event may be requested by the Data Coordinating Center (DCC)/study sponsor and should be provided as soon as possible.

All AEs will also be reported to the ICTR DMC by completing the AE/SAE forms in REDCap and will be reported within the same timeframe as required by the IRB. The DMC co-chairs will review any reported SAE and if needed, schedule an ad hoc meeting of the full committee.

14.6 Unanticipated Problems

An unanticipated problem (UP), as defined by the DHHS Office for Human Research Protection (OHRP), is any incident, experience, or outcome that meets all of the following criteria:

- The incidence, experience, or outcome is unexpected given the research procedures described in protocol-related documents (e.g., the study protocol, the informed consent documents, the Investigator's Drug Brochure) and the characteristics of the subject population being studied. An event may be considered unexpected if it exceeds the nature, severity, or frequency described in the study-related documents, Investigator's Drug Brochure, product labeling, or package insert.

- The incidence, experience, or outcome is related or probably related to participation in the research study. “Probably related” means the incidence, experience, or outcome is more likely than not to be caused by the research study procedures.
- The occurrence of the incidence, experience, or outcome suggests that the research places subjects or others at a greater risk of harm (physical, psychological, economic, or social) than was previously known or recognized.

The investigator will report UPs to the reviewing IRB and to the Data Coordinating Center (DCC)/lead Principal Investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI’s name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol, informed consent documents, or other corrective actions that have been taken or are proposed in response to the UP.

Report UPs within the timeframe(s) specified by the IRB(s) of record.

14.7 Unanticipated Adverse Device Effect

An unanticipated adverse device effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a 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 subjects (21 CFR 812.3(s)).

An investigator shall submit to the sponsor and to the reviewing Institutional Review Board (IRB) a report of any UADE occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (21 CFR 812.150(a)(1)).

A sponsor who conducts an evaluation of an UADE shall report the results of such evaluation to the FDA and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests (21 CFR 812.150(b)(1).

14.8 Incidental Findings

There are no anticipated incidental findings that will be discovered

14.9 Safety Oversight

Safety oversight will be performed under the DMS and DMC as described above.
We plan to utilize the UW ICTR Data Monitoring Committee (DMC) to oversee the study. The UW ICTR DMC is comprised of experienced members (core plus ad hoc) with expertise required to oversee this study. The DMC members will review protocol-specific reports created by statisticians using data pulled from the Research Electronic Data Capture (REDCap) data management tool. These standard reports will include an overview of study objectives, a review of actual and projected accrual rates, an evaluation of patient demographics for balance of randomization, and a summary of the number and seriousness of adverse events. An interim analysis of study results

may be performed and source documents may be reviewed to allow the DMC to independently judge whether the overall integrity and conduct of the protocol remain acceptable based on data provided and reported by the Principal Investigator. The DMC will make recommendations to the Principal Investigator that could include actions of continuation, modification, suspension, or termination

14.10 Study Monitoring

While many institutions involved in clinical research conduct various types of quality assurance reviews and audits, UW is one of the few institutions to offer independent Centralized Monitoring Services (CMS), a robust academic equivalent to the Industry Contract Research Organization (CRO) standards for ongoing study monitoring.

The Centralized Monitoring Services have been contracted for in the study and include the conduct and follow-up of monitoring visits throughout the life cycle of the study (e.g., Study Initiation Visit, Interim Monitoring Visits, and Close-Out Visit). Study monitoring visits occur off-site (remotely) and/or on-site at a frequency necessitated by the protocol risk and complexity. For this study, UW CMS personnel will conduct a Study Initiation Visit (SIV) with the University of Wisconsin's research personnel in person after IRB approval was confirmed and before enrollment of any subjects into the study. The SIV will included a detailed review of the protocol, good clinical practice guidelines, and data management expectations of the research team at the study site and CMS personnel.

Following the Study Initiation Visit (SIV), CMS personnel will routinely conduct ongoing Interim Monitoring Visit (IMVs) for all data collection sites, either on-site, remotely or a combination of both, following enrollment of the first subject(s) and throughout the duration of the study. During the IMVs, the monitor will review study materials, including but not limited to: regulatory files, consent forms, case report forms, and drug accountability logs. CMS personnel will review compare the electronic data to that of the primary source documents and case report forms (described above). UW CMS personnel will conduct a Close-Out Visit (COV) upon completion of the study at the study site.

Monitoring consists of full or partial review of study records, depending on the risk level and observed compliance. As such, during their monitoring activities, UW CMS personnel plan to review all (100%) of the study-related subject records for at least 25% of the enrolled subjects. CMS personnel could increase the percentage of study or subject records to be reviewed if warranted by the ongoing monitoring findings. The study monitor(s) work with the ICTR DMC statistician to conduct periodic central data reviews, with follow-up conducted by the study monitors for any data discrepancies identified.

The CMS conducts interim-monitoring visits (IMV) to ensure compliance and safety. The first IMV will be scheduled following the enrollment of the first 1-2 subjects. Subsequent IMVs will be scheduled to occur approximately quarterly or after the enrollment of the next 8-10 subjects. The schedule may vary based on study enrollment rate. Unscheduled visits may be conducted based on reports or evidence of potential noncompliance, significant increases in subject enrollment rates, or changes in protocol/personnel and training activities.

14.11 Study Stopping Rules

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be

provided by the suspending or terminating party to investigator, funding agency, the IND/IDE sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality is addressed and satisfy the applicable federal and institutional regulatory authorities.

15.0 STUDY FEASIBILITY

15.1 Economic Burden to Subjects

Subjects will not have to pay for study devices, such as CGMs. Subjects who are randomized to receive a CGM will be provided with sufficient quantity of sensors and transmitters for the duration of pregnancy. Phones will be provided to those who do not have access to a smart phone as well. The subject will not be billed by the healthcare system or their health insurance company for any costs related to a study procedure.

Subjects will be responsible for any costs related to their diabetes follow-up as directed by their healthcare team, such as clinic visits and diabetes medication, including all out-of-pocket costs.

15.2 Facilities and Locations

Center for Perinatal Health at Meriter Hospital in Madison, WI.

15.3 Feasibility of Recruiting the Required Number of Subjects

On review of previous records, our goal will be to recruit 40 subjects in 20 months. For the past 3 years, our diabetes in pregnancy program has cared for 67, 84, and 87 patients with Type 2 diabetes, respectively. With our numbers increasing each year and our hope to reach out to clinics such as Access Community Health and GHC, this timeline should be within reason.

15.4 Principal Investigator Considerations

Time Devoted to Conducting the Research

The Principal Investigator time devoted to conducting the research. Dr. Erin Bailey will serve as co-investigator. She has 12 months dedicated research time in her fellowship. April Eddy works full time in the Diabetes in Pregnancy program and will serve as an important member of the study staff. In addition, we have the benefit of a research coordinator with 20% dedicated time over the next 20 months.

Process for Informing Study Teams

The process for informing study teams of their respective roles will be recorded in the training log for this study. The PI will sign off on the training of all study staff.

15.5 Availability of Medical or Psychological Resources

Not applicable.

16.0 REFERENCES

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17.0 APPENDICES

17.1 Patient Surveys

Patient Survey on Entry into Trial

First, a few background questions

What year were you diagnosed with diabetes?

Where do you live the majority of the year:

- Home or condo that you own
- House or condo that you rent
- A home or condo of a friend/family
- Shelter
- Other (please write in)

How many people live with you (drop down of number)?

How much schooling have you had?

- 8 grades or less
- Some high school
- Completed high school or GED
- Some college or technical school
- College graduate (bachelors degree)
- Graduate degree

Which of the following describes your current employment status:

- Full time (>35 hours per week)
- Part time (<35 hours per week)
- Unemployed or laid off and looking for work
- Unemployed and not looking for work
- Homemaker
- In school
- Disabled
- Other (please write in)

Family History

This question pertains to your immediate family: mom, dad, siblings and children. Do you have any immediate family members with diabetes?

- Yes or No
- If yes,
    - Biological Mom
    - Biological Dad
    - Sibling
        - If yes, how many?
    - Children
        - If yes, how many?

Do you have extended family members with diabetes (aunts, uncles, grandparents, first cousins)?

- Yes or No
- If yes,
    - Aunt
        - If yes, how many?
    - Uncle
        - If yes, how many?
    - Cousin
        - If yes, how many?

Previous Pregnancy History

Now we will ask a few questions about your prior pregnancy history
Have you been pregnant before? (yes/no)

IF yes:
Did you have diabetes in your previous pregnancy or pregnancies?

- Yes or No
    - If yes, how many?
        - Gestational (y/n)
        - Type 2 Diabetes (y/n)
        - Type 1 Diabetes (y/n)
        - Prediabetes (y/n)

For the following questions, please answer regarding your experience outside of pregnancy:

How many times did you check your blood sugar per day? (drop down)

Were you on medication (y/n)?

If yes, what type:

- Injectable insulin (y/n)
- Oral medication (excluding metformin) (y/n)
- Metformin only (y/n)
- Diet/exercise (y/n)

Have you ever worn a continuous glucose meter in the past? (y/n)

Patient Survey to be Completed on entry and 28 – 32 weeks:
Now we're going to ask you a few questions about diabetes in this pregnancy.

<u>Reaction/Motivation questions</u>

How comfortable were you in managing your diabetes prior to pregnancy?

- Extremely
- Very comfortable
- Somewhat comfortable
- Not comfortable or uncomfortable
- Uncomfortable
- Very uncomfortable
- Extremely uncomfortable

For the next questions, consider how you've felt over the previous 4 weeks.

How comfortable do you feel managing your diabetes now that you are pregnant?

- Extremely comfortable
- Very comfortable
- Somewhat comfortable
- Not comfortable or uncomfortable
- Uncomfortable
- Very uncomfortable
- Extremely uncomfortable

How often do you feel overwhelmed managing your care in pregnancy?

- Extremely comfortable
- Very comfortable
- Somewhat comfortable
- Not comfortable or uncomfortable
- Uncomfortable
- Very uncomfortable
- Extremely uncomfortable

Social Support Questions

Do you have a main support person for this pregnancy? A support person can be your partner, spouse, friend, or family member that is helping you during your pregnancy

- Yes or No
- If yes -
    - Who?
        - Write in

Does your support person encourage you or care for you by helping with each of the following? (Each question y/n)

- Helps with meal planning or prep
- Assists with grocery shopping
- Has switched diet to mimic mine
- Makes an attempt to exercise with me
- Reminds me to check my blood sugars
- Attends appointments with me
- Other
    - Please write in

- How much are each of the following of concern to you?
- Changing my diet
    - Extremely concerning
    - Very concerning
    - Moderately concerning
    - Slightly concerning
    - Not at all concerning
- Counting carbs
    - Extremely concerning
    - Very concerning
    - Moderately concerning
    - Slightly concerning
    - Not at all concerning
- Taking medications (by mouth)
    - Extremely concerning
    - Very concerning
    - Moderately concerning
    - Slightly concerning

    - Not at all concerning
- Giving myself injections
    - Extremely concerning
    - Very concerning
    - Moderately concerning
    - Slightly concerning
    - Not at all concerning
- Whether medications are safe for baby
    - Extremely concerning
    - Very concerning
    - Moderately concerning
    - Slightly concerning
    - Not at all concerning
- Whether diagnosis will affect my baby
    - Extremely concerning
    - Very concerning
    - Moderately concerning
    - Slightly concerning
    - Not at all concerning
- Will this affect my future health
    - Extremely concerning
    - Very concerning
    - Moderately concerning
    - Slightly concerning
    - Not at all concerning
- Other
    - Please write in

How often do you worry about diabetes affecting your pregnancy?

- Never
- Very seldom
- Sometimes
- Often
- All the time

How much do you think diabetes has affected your general pregnancy care?

- Extremely affected
- Very affected
- Moderately affected
- Slightly affected
- Not at all affected

How satisfied are you with the additional burden pregnancy has placed on your diabetes management?

- Extremely satisfied
- Very satisfied

- Moderately Satisfied
- Neither
- Moderately dissatisfied
- Very dissatisfied
- Extremely dissatisfied

Standardized Diabetes QOL Questions:

How satisfied are you with your current diabetes treatment?

- Extremely satisfied
- Very satisfied
- Moderately Satisfied
- Neither satisfied nor dissatisfied
- Moderately dissatisfied
- Very dissatisfied
- Extremely dissatisfied

How satisfied are you currently with the amount of time it takes to manage your diabetes?

- Extremely satisfied
- Very satisfied
- Moderately Satisfied
- Neither satisfied nor dissatisfied
- Moderately dissatisfied
- Very dissatisfied
- Extremely dissatisfied

How satisfied are you with the time it takes to determine your sugar level?

- Extremely satisfied
- Very satisfied
- Moderately Satisfied
- Neither satisfied nor dissatisfied
- Moderately dissatisfied
- Very dissatisfied
- Extremely dissatisfied

How satisfied are you with the total time it has taken to manage your diabetes over the last 2 weeks?

- Extremely satisfied
- Very satisfied
- Moderately Satisfied
- Neither satisfied nor dissatisfied
- Moderately dissatisfied
- Very dissatisfied
- Extremely dissatisfied

How satisfied are you with the time you spend exercising in pregnancy?

- Extremely satisfied
- Very satisfied
- Moderately Satisfied
- Neither satisfied nor dissatisfied
- Moderately dissatisfied
- Very dissatisfied
- Extremely dissatisfied

How satisfied are you with your sex life?

- Extremely satisfied
- Very satisfied
- Moderately Satisfied
- Neither satisfied nor dissatisfied
- Moderately dissatisfied
- Very dissatisfied
- Extremely dissatisfied

How satisfied are you with time spent getting checkups for your diabetes?

- Extremely satisfied
- Very satisfied
- Moderately Satisfied
- Neither satisfied nor dissatisfied
- Moderately dissatisfied
- Very dissatisfied
- Extremely dissatisfied

How often do you have a bad night's sleep because of diabetes?

- Never
- Very seldom
- Sometimes
- Often
- All the time

How often do you find that you eat something you shouldn't rather than tell someone that you have diabetes?

- Never
- Very seldom
- Sometimes
- Often
- All the time

Do you work outside the home? (y/n)

If yes:

How often do you worry about whether you will miss work?

- Never
- Very seldom
- Sometimes
- Often
- All the time

How often do you feel diabetes limits your career?

- Never
- Very seldom
- Sometimes
- Often
- All the time

How often do you have pain because of the treatment for your diabetes?

- Never
- Very seldom
- Sometimes
- Often
- All the time

How often do you feel your diabetes is a burden on your family?

- Never
- Very seldom
- Sometimes
- Often
- All the time

How often do you feel physically ill?

- Never
- Very seldom
- Sometimes
- Often
- All the time

How often do you worry about whether you will pass out?

- Never
- Very seldom
- Sometimes
- Often
- All the time

How knowledgeable do you feel you are about your diabetes?

- Extremely knowledgeable
- Very knowledgeable

- Moderately knowledgeable
- Neither knowledgeable or unknowledgeable
- Moderately unknowledgeable
- Very unknowledgeable