HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2017-1)

Protocol Title: CAPO: Continuous glucose monitoring in A2 Gestational Diabetes and Pregnancy Outcomes

Principal Investigator: Audrey Merriam

Version Date: 10/5/2022

(*If applicable*) Clinicaltrials.gov Registration #: NCT04219085

INSTRUCTIONS
This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:** 1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library. 2. If a section or question does not apply to your research study, type "Not Applicable" underneath. 3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

APPROVED BY THE YALE UNIVERSITY IRB 11/23/2022

SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.
   This is a randomized controlled trial of pregnant women with A2 GDM to use continuous glucose monitoring to assess glycemic metrics from the time of diagnosis of A2 GDM in pregnancy until delivery.

   We hypothesize that women with A2 GDM who are randomized to continuous glucose monitoring will have a lower incidence of the composite primary outcome, which includes the following variables: perinatal death, shoulder dystocia, birth weight greater than 4,000 grams, NICU admission for treatment of hypoglycemia (blood glucose level <40mg/dL) and birth trauma, including fracture or nerve palsy.

   Secondary outcomes will include cesarean delivery for an arrest of labor disorder and hypertensive disorders of pregnancy.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.
   Approximately 525 women are diagnosed with gestational diabetes annually in our patient population. Assuming 50% of these will require medication and be diagnosed with A2 GDM that is around 140 patients annually eligible for recruitment and we anticipate being able to recruit these patients over the course of 1.5 years with 1 additional year for follow up and data analysis.

3. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.
   Diabetes complicates 6-7% of pregnancies annually and approximately 85% of these cases are women diagnosed with gestational diabetes (GDM).[1,2] The prevalence of GDM varies within populations based on obesity rates, maternal age and ethnicity. GDM is diagnosed during the third trimester through a two-step process of a 50-gram oral glucose challenge screen and a subsequent 100-gram oral glucose challenge test if the woman screens positive. Once the diagnosis is confirmed women are asked to monitor their glucose levels with finger sticks at least four times a day [upon waking up (fasting) and after each major meal (breakfast, lunch and dinner)] and medication is added when glucose target goals cannot be reached by diet and exercise alone. Approximately, 15% of women will not reach glucose target goals with diet and exercise alone and will require medication. These women are then diagnosed with class A2 GDM by the White classification of diabetes, which is the standard classification method used to categorize diabetics pregnancy and is standard practice for the Yale Maternal-Fetal Medicine Diabetes Clinic.

   Identification of women with GDM who require treatment is essential in optimizing pregnancy outcomes for these women. Treatment of GDM results in lower neonatal morbidity, reduced incidence of large for gestational age infants (LGA), reduced incidence of preeclampsia and shoulder dystocia and a reduced need for cesarean delivery.[3-5] Since LGA infants are at higher risk for hypoglycemia which may necessitate admission to the neonatal intensive care unit (NICU), treatment of GDM reduces the incidence of LGA infants resulting in less hypoglycemia and NICU admissions.

APPROVED BY THE YALE UNIVERSITY IRB 11/23/2022

Given that pregnancy outcomes are directly tied to blood glucose control, it is essential that women with GDM play an active role in the monitoring of their disease. The frequency of monitoring and frustration with diet can lead to issues with patient compliance and ultimately impact their pregnancy outcomes. One study found that just over half of women successfully tested their blood glucose via finger sticks ≥ 80% of the time. About 25% of the women in the same study had <90% of the values matching in their glucometer and their blood glucose log.[6] Given these issues with compliance the need for a better and more convenient monitoring system is evident. Continuous glucose monitors (CGM) are a relatively new device that have yet to be fully explored for their utility in pregnancy. The current generation of CGM has had exponential growth in the clinical care of diabetes, driven primarily by the improved accuracy of these devices, longer duration sensor life (ranging from 7-14 days in currently available models), and the ability to collect these data without performing calibration of the sensors with fingerstick glucose readings. Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial (CONCEPTT), demonstrated the utility of CGM data to decrease the frequency of adverse neonatal outcomes in a pregestational diabetes population.[7] A more recent trial of blinded CGM data in women with GDM showed mean sensor glucose was significantly higher in women who delivered LGA infants. The 24-hour mean glucose was different between groups in this study (112 mg/dL vs. 104 mg/dL, p=0.025), driven by higher overnight mean glucose levels (108 mg/dL vs. 99 mg/dL, p=0.005).[8] Given that this is not a time that women with GDM would normally be monitoring their blood sugar it is evident that CGM may be useful, not only in increasing patient compliance by eliminating the need for measuring serum glucose via finger sticks and a glucometer four times a day but by allowing for monitoring of blood glucose levels at times that are not normally convenient for testing.

This study will utilize the Dexcom G6 continuous glucose monitoring device from Abbott Pharmaceuticals. Dexcom recently complete a trial in pregnancy utilizing this device but results are not yet available. This device is approved by the Food and Drug Administration (FDA) but has not yet been evaluated thoroughly for use in pregnancy and is not approved, at this time, for use in pregnant women; however, as demonstrated by CONCEPTT and other studies it has been studied for use in pregnant women with improvement in pregnancy outcomes.[7,8]

Bibliography

1. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK, Drake P. Births: Final Data for 2017. Natl. Vital Stat.Rep. 2018;67(8):1-50.
2. The American College of Obstetricians and Gynecologists Practice Bulletin Number 190. Gestational Diabetes Mellitus. February 2018.
3. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS. Effect of Treatment of Gestational Diabetes Mellitus on Pregnancy Outcomes. Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. N Engl J Med 2005;352:2477–86.
4. Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. N Engl J Med 2009;361:1339–48.
5. Hartling L, Dryden DM, Guthrie A, Muise M, Vandermeer B, Donovan L. Benefits and harms of treating gestational diabetes mellitus: a systematic review and meta-analysis for the U.S.

APPROVED BY THE YALE UNIVERSITY IRB 11/23/2022

Preventive Services Task Force and the National Institutes of Health Office of Medical Applications of Research. Ann Intern Med 2013;159:123–9.
6. Cosson E, Baz B, Pharisien I, Nguyen MT, Sandre-Banon D, Jaber Y, Cussac-Pillegand C, Banu I, Carbillon L, Valensi P. Poor reliability and poor adherence to self-monitoring of blood glucose are common in women with gestational diabetes mellitus and may be associated with poor pregnancy outcomes. Diabetes are 2017;40:1181-1186.
7. Feig DS, Donovan LE, Corcoy R, Murphy KE, Amiel SA, Hunt KF, Asztalos E, Barrett JFR, Sanchez JJ, deLeiva A, Hod M, Jovanovic L, Keely E, McManus R, Hutton EK, Meek CL, Stewart ZA, Wysocki T, O'Brien R, Ruedy K, Kollman C, Tomlinson G, Murphy HR, Group CC. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet. 2017;390(10110):2347-2359.
8. Law GR, Alnaji A, Alrefaii L, Endersby D, Cartland SJ, Gilbey SG, Jennings PE, Murphy HR, Scott EM. Suboptimal Nocturnal Glucose Control Is Associated With Large for Gestational Age in Treated Gestational Diabetes Mellitus. Diabetes Care. 2019.

4. Research Plan: Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths. Describe the setting in which the research will take place.

This will be a randomized clinical trial assessing the use of a continuous glucose monitor on glycemic control for gestational diabetics requiring medication management during pregnancy. Women who are diagnosed as having gestational diabetes will be identified through consultative or new patient visits to the Yale Diabetes in Pregnancy Program through the Maternal-Fetal Medicine Division in the Department of Obstetrics, Gynecology and Reproductive Sciences. Women will be followed to see if they ultimately require medication for management of their gestational diabetes. All pregnant women who receive the diagnosis of gestational diabetes requiring medication (A2 GDM) are managed in this clinic.

During pregnancy all women are screened for gestational diabetes.. Women may be screened prior to this time based on certain risk factors (i.e. age, history of gestational diabetes, ethnicity, BMI) and if they pass this initial, earlier screening they will be rescreened in the third trimester. Women diagnosed with gestational diabetes at any time during pregnancy are potentially eligible for this study.

Screening for gestational diabetes is done by a standard 2-step process. The first test is a 50-gram oral glucose challenge (GCT). If the subject fails this test (≥130mg/dL or ≥140mg/dL depending on the laboratory used) then they will require a 100-gram fasting glucose tolerance test (GTT). Alternatively, if the patient has a value of ≥200mg/dL on the 50-gram glucose challenge she would be diagnosed with gestational diabetes at that time. For the 100-gram GTT the standard at for Yale Maternal-Fetal Medicine is to use the Carpenter-Coustan criteria to make the diagnosis of gestational diabetes, with the following blood sugar cutoffs at the stated time points: fasting – 95m/dL, 1 hour – 180nmg/dL, 2 hours – 155mg/dL, 3 hours – 140mg/dL If the patient has 2 or more values above the cutoffs she would be diagnosed with gestational diabetes. Subjects who test positive for gestational

APPROVED BY THE YALE UNIVERSITY IRB 11/23/2022

diabetes by either the 50-gram GCT of ≥200mg/dL or by having 2 or more elevated values on the 100-gram GTT are notified by their primary Ob-Gyn provider and referred to the Yale Diabetes in Pregnancy Program for education on their diagnosis, blood sugar monitoring, diet, and exercise. This is standard practice for all pregnant patients receiving this diagnosis and would not be considered an extra visit for study purposes.

They will be introduced to the study at their first visit with the diabetes nurse educator after failing their 3-hour GTT. Patients will then be followed, as is routine practice in the clinic, for a minimum of 1 week to see if their blood sugar values for fasting (<95mg/dL) and 1-hour after meals (<140mg/dL) are mostly (>75%) at goal for all time-points tested. Women will use the MyChart Diabetes in Pregnancy log that is standard practice for patients in the Yale Diabetes in Pregnancy clinic. Those women who do not have reliable access to this technology will be allowed to use paper logs. Both types of logs, electronic and paper, are reviewed routinely by the diabetes nurse educator and/or physician in the Yale Maternal-Fetal Medicine clinic.

Women who do not have at least 75% of their blood sugar values at or below the previously stated goals require medication for management of their gestational diabetes and will be diagnosed as A2GDM. When these women return to the Yale Diabetes in Pregnancy Clinic at Yale Maternal-Fetal Medicine for initiation of medication therapy for gestational diabetes they will again be approached about participating in the study and given time to consider their participation at that visit. Should they require more time and wish to discuss with others outside the clinic visit we will contact the patient again in 1 week to inquire about participation in the study. Women who consent to participation will be randomized to the control group (checking blood glucose as previously done with fasting and 1-hour post meal finger sticks) or to receive the Dexcom G6 CGM device, which is a device to monitor blood glucose continuously for 10 days placed on the upper arm or abdomen. The device will stay in place for the duration of the pregnancy and the sensors will be changes every 10 days, as is standard for this device. This device has been used off-label in pregnant women in previous studies. It complies with the standard of care for monitoring blood sugar values for women with gestational diabetes requiring medication but is a novel approach that does not require multiple finger sticks to monitor blood glucose values. It is FDA approved for use in non-pregnant patients. The device is compatible for use with smartphones. Women who do not have smartphones will receive a receiver if needed.

We have practice using this device in the Yale Diabetes in Pregnancy Clinic in our patients with pre-gestational diabetes (Type 1 and Type 2 diabetes) who present to pregnancy with a CGM already in place and those women with pregestational diabetes who we initiate CGM for monitoring of their blood glucose during pregnancy. As with the women in this population, women in the study who are randomized to receive the CGM device to monitor their blood sugar we will instruct them how to place the device, use the device, change the sensor and monitor their blood sugars with the device website and smartphone application. The CGM has a mechanism that alerts the patient when their blood sugar is low, in pregnancy this is set at a blood glucose value of 60 mg/dL. The women in the trial will be informed that if their CGM alerts them to this blood sugar value that they should have a snack that is a mix of carbohydrate and protein, as we instruct all our patients with diabetes who have a blood glucose value of this level. Additionally, women in both arms of the trial will be instructed that if they are experiencing symptoms of hypoglycemia (diaphoresis, shakiness, weakness, confusion, visual disturbances, dizziness, nervousness or lightheadedness) they should

APPROVED BY THE YALE UNIVERSITY IRB 11/23/2022

check their blood glucose value and have a snack that is a mix of carbohydrate and protein. Women who have hypoglycemia are then instructed to call the office after they treat their hypoglycemia to discuss next steps in management with either the triage nurse (Monday-Friday 8am -5pm) or the physician on call (Friday 5pm-Monday8am and Monday-Thursday nights 5pm-8am).

In addition to approaching women who meet criteria, flyers and posters will be placed in the exam rooms in the office location of 1 Long Wharf Maternal-Fetal Medicine office. Women will also be notified of their eligibility through a MyChart message. Information on the study will also be available through the YCCI website, the Ob-Gyn Department website and the Clinical Research at Yale Facebook Page.

Women in the control group will continue to check their blood sugar levels as previously stated (fasting and 1 hour after eating) and use the MyChart Diabetes in Pregnancy log or paper log as they were using prior to requiring medication for the treatment of their diabetes. They will continue to be followed by the diabetes nurse educator and physicians in the Yale Maternal-Fetal Medicine clinic. Women who are randomized to the CGM group will also have their CGM data followed by the diabetes nurse educator and physicians in the Yale Maternal-Fetal Medicine clinic.

At the initial visit where the CGM is placed the reading on the device will be checked against a fingerstick value on a glucometer in clinic. This practice is then repeated at every clinic visit to ensure the device is calibrated correctly. If the blood glucose value between the CGM device and the glucometer differs by more that 10mg/dL the blood glucose will be rechecked with the glucometer using a different fingerstick. At this time if the blood glucose reading is still more than 10mg/dL different between the glucometer and the CGM the CGM sensor will be changed. If the sensor cannot reliably be confirmed with the glucometer at any clinic visit after following these steps the patient will be instructed to use her glucometer to monitor her blood glucose, as in the placebo group, and return to clinic in 1 week for attempted placement of the CGM again.

Visits to the Yale Maternal-Fetal Medicine clinic will then occur every 1-4 weeks depending on blood glucose control and the gestational age of the pregnancy, as is standard for all women being managed by Yale Maternal-Fetal Medicine for diabetes in pregnancy. At each visit blood sugars will be reviewed as well as diet and current medication dose. A fingerstick blood glucose value will be obtained at every clinic visit for all women in the study, as is standard practice for women being seen in the Yale Diabetes in Pregnancy Clinic. Medication adjustments will be made at the visits, over the phone or through MyChart messages (as is currently standard practice for all women in the Yale Diabetes in Pregnancy Clinic) when blood sugar values are reviewed for both the control and study group. Blood glucose values will be assessed at least weekly for all patients in the study, as is standard practice for all women in the Yale Diabetes in Pregnancy Clinic. The CGM data will not be monitored in real time. This is the standard we currently follow for our patients with pregestational diabetes who use a CGM during pregnancy. After review of their blood glucose values patients will be called or notified at their clinic visit if adjustments need to be made to their medication management. Women who do not have any data logged for a week will be contacted and reminded to log their glucometer readings in MyChart or to reconnect to their sensor depending on which

APPROVED BY THE YALE UNIVERSITY IRB 11/23/2022

group they are in. If they are having difficulty with either method, they will be scheduled for an urgent visit with our diabetes nurse educator. If erratic values are noted on the CGM device or in the standard monitoring group, the patient will be brought in for an urgent visit with our diabetes nurse educator. No additional steps or care will be required at these visits if women participate in the study. Medication adjustments will be made at the same interval and using the same protocol for women in the study (both the CGM and control arm) and those who do not participate in the study.

At a visit between 32-34 weeks women in the fingerstick group will be given a CGM and instructed to wear it for 10 days. The data from the CGM will be blinded and used to assess nocturnal glucose control between the CGM group and the fingerstick group. During this time the group will continue to check fingersticks four times a day and this will be used to make medication changes as needed.

Women will be followed from the time of enrollment through the rest of their antenatal course with delivery occurring no later than 40 weeks' gestation as per recommended for all women with A2 GDM per the American College of Obstetricians and Gynecologists. Delivery outcomes will be assessed through MyChart. There will be no special follow-up required postpartum for women who participate in the study. Following delivery, the CGM group will be asked to return their study devices. Additionally, both groups will be provided with a short survey regarding their perceptions of their blood glucose monitoring modality focusing on their preference for fingerstick monitoring versus CGM use and the ease of usability of the device during their pregnancy. Once the survey is completed, participation in the study will be over.

We hypothesize that women with A2GDM who are randomized to continuous glucose monitoring will have a lower incidence of the composite primary outcome, due largely in part to the ability to better track overnight glycemic control and adjust medications as needed to decrease the possibility of hyperglycemia overnight, as shown in the previous study using CGM in pregnancy, which will then decrease the incidence of adverse outcomes that are part of the composite primary outcome.

5. Genetic Testing N/A ☒

A. Describe

i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned *Write here*

ii. the plan for the collection of material or the conditions under which material will be received *Write here*

iii. the types of information about the donor/individual contributors that will be entered into a database *Write here*

iv. the methods to uphold confidentiality *Write here*

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects? *Write here*

C. Is widespread sharing of materials planned? *Write here*

D. When and under what conditions will materials be stripped of all identifiers? *Write here*

E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials? *Write here*

APPROVED BY THE YALE UNIVERSITY IRB 11/23/2022

i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)? *Write here*

F. Describe the provisions for protection of participant privacy *Write here*

G. Describe the methods for the security of storage and sharing of materials *Write here*

6. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

Women with no history of pregestational diabetes, other than GDM during previous pregnancies, who are >18 years of age will be recruited for participation at the time of diagnosis of A2 GDM. As all women are screened for gestational diabetes in pregnancy there will be adequate representation across all ethnic groups who receive care at Yale-New Haven Hospital. All women will be approached for participation in the study regardless of ethnicity. As certain ethnic groups are at increased risk for gestational diabetes (i.e. Asian, African-American, Hispanic) this will be represented in the study population; however, this should not affect the study outcome as we are looking to assess the use of a device to monitor gestational diabetes and will not change any intervention based on the group women are randomized to. Women will be randomized to receive a continuous glucose monitor or to monitor their diabetes in the standard fashion with finger sticks and glucometer measurement of plasma glucose four times daily (fasting and 1 hour postprandial).

7. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐Children	☐ Healthy	☐Fetal material, placenta, or dead fetus
☐Non-English Speaking	☐ Prisoners	☐Economically disadvantaged persons
☐Decisionally Impaired	☐ Employees	☒Pregnant women and/or fetuses
☐Yale Students	☐ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?
Yes ☐ No ☒

8. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

Inclusion Criteria: women between 18-50 years old, pregnant, diagnosed with gestational diabetes requiring medication (A2) during pregnancy
Exclusion Criteria: pregestational diabetes, diagnosis with gestational diabetes > 33 weeks gestation (too late in pregnancy for study enrollment due to proximity to delivery), anomalous fetus, fetal growth restriction during current pregnancy diagnosed prior to enrollment, , abnormal diagnostic genetic testing or screening for the fetus, twin or higher order multiple gestation, non-compliance with prenatal visits (missing ≥3 visits prior to enrollment), maternal medical comorbidities (lupus, chronic hypertension, cancer, ischemic cardiovascular disease).

9. How will **eligibility** be determined, and by whom?
Eligibility will be determined by the PI and the study coordinator through chart review. The PI is the director of the Diabetes in Pregnancy clinic and oversees all patients that attend this clinic.

APPROVED BY THE YALE UNIVERSITY IRB 11/23/2022

10. Risks: Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.
    Risks to participating in the research include any risk associated with wearing the continuous glucose monitor. The sensor wires for the CGM go under the skin and the device is placed by the patient after instruction from one of our diabetes nurse educators. The device has been deemed safe for use by the FDA.
    The standard of care is fingersticks and the CGM device is deemed to be as safe as fingersticks, which the patients will have been doing up until the point of enrollment.
    Patients will be de-identified for data analysis.
    There is no anticipated increased risk to the woman or her fetus for women in the CGM group compared to the standard monitoring group (with the glucometer and four times a day fingersticks) based on the use of the CGM alone. The risks to the pregnancy are related to the risks of developing gestational diabetes and are the same for women in the CGM arm and the control arm.

11. Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.
    The patient will be properly instructed in how to wear the device and will have received previous training on how to take fingersticks for glucose monitoring. All information collected for the study will be stored on a Yale University Laptop and in the Yale University Secure Box system, both of which are password protected. Once enrolled, patients will also receive a study ID number and the data will be de-identified when analyzed.

12. Data and Safety Monitoring Plan: Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? There is minimal risk to the subject for participating. CGMs are FDA approved for use in humans.
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? n/a
    c. Data safety and Monitoring Plan:

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency monthly. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment.

The principal investigator or the Institutional Review Board (IRB) have the authority to stop or suspend the study or require modifications.

This protocol presents minimal risks to the subjects and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, are not anticipated. In the unlikely event that such events occur, Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or Unanticipated Problems Involving Risks to Subjects or Others that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project through regular

APPROVED BY THE YALE UNIVERSITY IRB 11/23/2022

study meetings and via emails as events occur after the events are reviewed by the primary investigator. The DSMB and IRB will be informed of the following adverse events within 5 days of the event becoming known to the principal investigator: intrauterine fetal demise, neonatal injury at birth due to large for gestational age, neonatal intensive care unit admission due to hypoglycemia or other complication from gestational diabetes, and maternal admission for hyperglycemia or hypoglycemia for other reason. The previously stated risks are not related to the use of CGM but are known risks of gestational diabetes. Risks related to the use of the CGM include the following: CGM device breaking causing need for professional assistance with removal, CGM malfunctioning resulting in admission for hypoglycemia or hyperglycemia.

13. **Statistical Considerations:** Describe the statistical analyses that support the study design.
    Assuming an incidence in the standard monitoring group of 60% and an effect size of 40% with a power of 80% and an alpha of 0.05 we would need to recruit 134 women (67 per arm). Approximately 140 women are diagnosed with gestational diabetes annually in our patient population. Around 50% of these will require medication and be diagnosed with A2 GDM that is around 60 patients annually eligible for recruitment.

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

1. Name of the radiotracer: *Write here*

2. Is the radiotracer FDA approved? ☐YES ☐NO

If NO, an FDA issued IND is required for the investigational use unless RDRC assumes oversight.

3. Check one: ☐IND# *Write here* or ☐RDRC oversight (RDRC approval will be required prior to use)

4. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this radiotracer is being administered to humans, include relevant data on animal models.
Write here

4. **Source:** Identify the source of the radiotracer to be used. *Write here*

5. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, method of sterilization and method of testing sterility and pyrogenicity.
Write here

APPROVED BY THE YALE UNIVERSITY IRB 11/23/2022

B. DRUGS/BIOLOGICS ☒N/A

1. If an **exemption from IND filing requirements is** sought for a clinical investigation of a drug product that is lawfully marketed in the United States, review the following categories and complete the category that applies (*and delete the inapplicable categories)*:

Exempt Category 1: The clinical investigation of a drug product that is lawfully marketed in the United States can be exempt from IND regulations if all of the following are yes:	
1. The intention of the investigation is NOT to report to the FDA as a well-controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug.	☐
2. The drug that is undergoing investigation is lawfully marketed as a prescription drug product, and the intention of the investigation is NOT to support a significant change in the advertising for the product.	☐
3. The investigation does NOT involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product	☐
4. The investigation will be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56).	☐
5. The investigation will be conducted in compliance with the requirements regarding promotion and charging for investigational drugs.	☐

Exempt Category 2 (all items i, ii, and iii must be checked to grant a category 2 exemption)

☐i. The clinical investigation is for an *in vitro* diagnostic biological product that involves one or more of the following (check all that apply):

- ☐ Blood grouping serum
- ☐ Reagent red blood cells
- ☐ Anti-human globulin

☐ii. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and

☐iii. The diagnostic test is shipped in compliance with 21 CFR §312.160.

APPROVED BY THE YALE UNIVERSITY IRB 11/23/2022

Exempt Category 3

☐ The drug is intended solely for tests in vitro or in laboratory research animals if shipped in accordance with 21 CFR 312.60

Exempt Category 4

☐ A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.
Write here

3. **Source:** Identify the source of the drug or biologic to be used. *Write here*

a) Is the drug provided free of charge to subjects? ☐YES ☐NO
If yes, by whom? *Write here*

4. **Storage, Preparation and Use:** Describe the method of storage, preparation, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.
Write here

Check applicable Investigational Drug Service utilized:

☐ YNHH IDS ☐ CMHC Pharmacy ☐ West Haven VA
☐ PET Center ☐ None
☐ Other:

Note: *If the YNHH IDS (or comparable service at CMHC or WHVA) will not be utilized, explain in detail how the PI will oversee these aspects of drug accountability, storage, and preparation.*

5. Use of Placebo: ☐Not applicable to this research project

If use of a placebo is planned, provide a justification which addresses the following:

a) Describe the safety and efficacy of other available therapies. If there are no other available therapies, state this. *Write here*

b) State the maximum total length of time a participant may receive placebo while on the study.
Write here
c) Address the greatest potential harm that may come to a participant as a result of receiving placebo.
Write here
d) Describe the procedures that are in place to safeguard participants receiving placebo.
Write here

6. Continuation of Drug Therapy After Study Closure ☐Not applicable to this project

APPROVED BY THE YALE UNIVERSITY IRB 11/23/2022

Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended?

☐ Yes If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access. *Write here*

☐ NO If no, explain why this is acceptable. *Write here*

B. DEVICES ☐N/A

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☒No

If Yes, please be aware of the following requirements:

A YNHH New Product/Trial Request Form must be completed via EPIC: Pull down the Tools tab in the EPIC Banner, Click on Lawson, Click on "Add new" under the New Technology Request Summary and fill out the forms requested including the "Initial Request Form," "Clinical Evidence Summary", and attach any other pertinent documents. Then select "save and submit" to submit your request; AND

Your request must be reviewed and approved in writing by the appropriate YNHH committee before patients/subjects may be scheduled to receive the investigational device or investigational procedure.

2. Background Information: Provide a description of previous human use, known risks, and any other factors that might influence risks. If this is the first time this device is being used in humans, include relevant data on animal models.
   The Dexcom G6 CGM device is FDA approved for use in monitoring blood glucose levels in patients 18 years and older with diabetes. The sensor must be changed every 10 days. Studies exist in pregnant women, but it is currently not FDA approved for use in this population.
   Risks of the device include breaking off of the sensor needle requiring medical removal with a simple office procedure. The sensor should be checked for the presence of the needle when it is changed. If the wearer is experiencing symptoms of hypoglycemia or hyperglycemia the reading on the sensor should be double checked with a fingerstick and a blood glucose meter. There may be pain, which would be temporary, similar to a needle stick, with sensor placement. Infection can occur at the site of sensor needle placement and patients will need to monitor the area for redness, warmth, swelling, increased pain and drainage. Some individuals may have a reaction to the adhesive of the device, which would manifest as skin irritation.
   The device should be removed prior to CT or MRI imaging. Subjects will carry a wallet card to alert medical personal that a CGM device is in place and will need to be removed before MRI or CT imaging.
3. Source:
   a) Identify the source of the device to be used: Dexcom's Dexcom G6 continuous glucose monitoring device
   b) Is the device provided free of charge to subjects? ☒Yes ☐No

4. Investigational device accountability: State how the PI, or named designee, ensures that an investigational device is used only in accordance with the research protocol approved by the HIC, and maintains control of the investigational device as follows:

APPROVED BY THE YALE UNIVERSITY IRB 11/23/2022

a) Maintains appropriate records, including receipt of shipment, inventory at the site, dispensation or use by each participant, and final disposition and/or the return of the investigational device (or other disposal if applicable): The device will be shipped to the research room at 1 Long Wharf from the company and given to each participant that is randomized to the study group upon enrollment in the study. They will be given one sensor and enough sensors to change the device every 10 days from the time of enrollment to delivery (maximum 8 replacement sensors). The sensor may be discarded after delivery and does not need to be returned. Sharps should be disposed of in a biohazard container, which the patients will be provided with. The sensor, without the needle, can be discarded with routine waste.

b) Documents pertinent information assigned to the investigational device (e.g., date, quantity, batch or serial number, expiration date if applicable, and unique code number): Documentation of the device lot numbers and expiration dates, date given to the study participant, number of sensors given and information for the participant on how to apply, change and troubleshoot the device will be kept in the research binder in the research room at 1 Long Wharf in the Yale Maternal-Fetal Medicine office.

c) Stores the investigational device according to the manufacturer's recommendations with respect to temperature, humidity, lighting, and other environmental considerations: The devices will be stored in the research room in a locked storage area in the Yale Maternal-Fetal Medicine office at 1 Long Wharf Drive New Haven, CT 06511. Per the manufacturer this device and sensor kits need to be stored at 39-77^{o}F and between 10-90% humidity. The research room at the Yale Maternal-Fetal Medicine office meets these specifications for storage from the manufacturer.

d) Ensures that the device is stored in a secure area with limited access in accordance with applicable regulatory requirements: The device and sensor kits will be stored in the research room in a locked storage area in the Yale Maternal-Fetal Medicine office at 1 Long Wharf Drive New Haven, CT 06511. The people with access to the devices in this area will be research coordinators and the PI.

e) Distributes the investigational device to subjects enrolled in the IRB-approved protocol: The Dexcom G6 continuous glucose monitor will be distributed to study participants at the time of randomization to women in the study group and will be applied in the Yale Maternal-Fetal Medicine office with the assistance of the diabetes nurse educator, study coordinator and/or physician in the clinic that day. Additional sensor kits will be distributed to patients at future office visits at the same location. Randomization will take place through an online enrollment randomizer (https://studyrandomizer.com).

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. **Targeted Enrollment: Give the number of subjects:**
   a. Targeted for enrollment at Yale for this protocol: 134
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: n/a

2. **Indicate recruitment methods below.** Attach copies of any recruitment materials that will be used.

☒ Flyers	☐ Internet/web postings	☐ Radio
☐ Posters	☐ Mass email solicitation	☐ Telephone
☒ Letter	☒ Departmental/Center website	☐ Television
☒ Medical record review*	☐ Departmental/Center research boards	☐ Newspaper
☐ Departmental/Center newsletters	☐ Web-based clinical trial registries	☒ Clinicaltrails.gov
☒ YCCI Recruitment database	☒ Social Media (Twitter/Facebook):	
☐ Other:		

APPROVED BY THE YALE UNIVERSITY IRB 11/23/2022

* Requests for medical records should be made through JDAT as described at
http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

a. Describe how potential subjects will be identified. Eligibility will be determined by the PI and the study coordinator through chart review. The PI is the director of the Diabetes in Pregnancy clinic and oversees all patients that attend this clinic.

b. Describe how potential subjects are contacted. Potential subjects will be contacted while they are in the Diabetes in Pregnancy clinic either during their antenatal testing, diabetes nurse educator visit, ultrasound or clinic visit.

c. Who is recruiting potential subjects? The PI, study coordinator and other members of the study team will recruit subjects.

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☒Yes, all subjects

☐Yes, some of the subjects

☐No

If yes, describe the nature of this relationship.

Members of the research team also provide clinical care for the patients for management of their diabetes, prenatal care and delivery care.

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☐ For entire study

☒ For recruitment/screening purposes only

☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data: Patients will need to be screened prior to enrollment to determine eligibility

ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data: *Write here*

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

APPROVED BY THE YALE UNIVERSITY IRB 11/23/2022

6. Process of Consent/Assent: Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.
   Consent will be obtained by a member of the study team during the time of a prenatal visit, ultrasound appointment, antenatal testing appointment or diabetes nurse educator visit. Subjects will be approached and informed of the study. Their care in the Diabetes in Pregnancy Clinic will not be altered if they choose not to participate. Their pregnancy care will continue as scheduled whether they consent to enroll in the study or not.

7. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.
   The personnel obtaining study consent will review the patient's chart to ensure the patient has appropriate decision making capacity and ability to consent to the study. The personnel will also employ the teach-back method to ensure the potential study subject understands the study and what it entails.

8. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.
   Spanish speaking subjects are unable to be enrolled at this time as we no longer have a Spanish speaking research coordinator to aid with consent of subjects.

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☒ NO ☐

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐Not Requesting any consent waivers

☒Requesting a waiver of signed consent:

☒ Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

APPROVED BY THE YALE UNIVERSITY IRB 11/23/2022

☐ Entire Study (Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☐ NO ☒
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☐ NO ☒

OR

- Does the research pose greater than minimal risk? YES ☐ NO☒
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☒

☒ Requesting a waiver of consent:

☒ Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study

For a full waiver of consent, please address all of the following:

- Does the research pose greater than minimal risk to subjects?
  ☐ Yes *If you answered yes, stop. A waiver cannot be granted.*
  ☒ No
- Will the waiver adversely affect subjects' rights and welfare? YES ☐ NO☒
- Why would the research be impracticable to conduct without the waiver? Need to perform chart review to determine eligibility prior to consenting patients and the PI has an existing relationship with the patients eligible for participation in the study as she is the head of the Diabetes in Pregnancy Clinic at the Yale Maternal-Fetal Medicine office.
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? *Not applicable, requesting waiver for screening purposes only*

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?
   We will look at additional variables within the subjects' protected health information including the patients': age, prior pregnancy and delivery history, BMI, medications during pregnancy, gestational age, antenatal admissions, ultrasound findings, maternal weight at delivery, maternal blood glucose values and neonatal weight at birth, APGAR scores and admission to the NICU.

2. How will the research data be collected, recorded and stored?

APPROVED BY THE YALE UNIVERSITY IRB 11/23/2022

Patients' data within the Epic will be reviewed by only the researchers involved in this project. All data extracted from the electronic medical record will be stored with de-identified subject ID number-codes for later analysis. The data will be collected and stored in Yale Box on a Yale University password protected laptop.

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☒ Laptop Computer ☐Desktop Computer ☐Other

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study? Data extracted from the electronic medical records will be de-identified. Coding for participants will be a password-protected document that will stored on the Yale Box Drive, a secured server.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.
   The data will be de-identified and stored on the researchers' laptops and Yale Box Drive. The information will be stored for future research and potentially shared with other researchers, but names and other identifiers will not be shared. Additional permission will not be sought from study participants.

6. If appropriate, has a Certificate of Confidentiality been obtained? *Not applicable*

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)
This study may help to provide evidence that CGM is an acceptable alternative to 4 times daily fingersticks for the management of A2 gestational diabetes, which is the current standard of care. Many women find this level of monitoring difficult to complete and painful, leading to fewer fingersticks and less data for clinicians attempting to manage their medication and their pregnancies to help ensure a good outcome for both mothers and infants and reduce the potential complications of poorly controlled A2 GDM (intrauterine fetal demise, macrosomia, polyhydramnios, postpartum hemorrhage, 3rd and 4th degree lacerations, NICU admissions, neonatal hypoglycemia and respiratory distress). The use of a device that would allow for glucose monitoring without fingersticks is an attractive alternative for both patients and providers and could improve compliance with and management of A2GDM, therefore, improving patient outcomes.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?
   The alternative to the study is to continue routine care with 4 times daily fingersticks for blood glucose monitoring, which half of the study population will continue to do to compare routine practice to CGM for the

APPROVED BY THE YALE UNIVERSITY IRB 11/23/2022

management of A2GDM. All patients will continue routine care (including visits, ultrasounds and antenatal testing, as require for A2GDM).

2. Payments for Participation (Economic Considerations): Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.
   No compensation will be provided. Study devices will be provided at no cost to the participants.

3. Costs for Participation (Economic Considerations): Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.
   There will be no cost to the subjects. The CGM will be covered by the study investigators and the patient's insurance will cover all routine blood glucose monitoring devices, supplies and medications needed for management of gestational diabetes. There will be no additional clinic visits outside what is already required for routine prenatal care for patients with A2 gestational diabetes.

4. In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

    a. Will medical treatment be available if research-related injury occurs? Standard measures offered to pregnant patients will be available and patient's will be treated as needed in the clinic or on Labor and Birth at YNHH

    b. Where and from whom may treatment be obtained? The subject would receive these standard measures through their health care provider team (i.e. physician and nurse)
    c. Are there any limits to the treatment being provided? No
    d. Who will pay for this treatment? Insurance will be billed for any potential complications from the device use and the participants will be responsible for any co-pays required by the insurance company for standard treatment.
    e. How will the medical treatment be accessed by subjects? The subject would be treated immediately with appropriate means available in our hospital and clinic system, as is routine care

IMPORTANT REMINDERS

Will this study have a billable service? Yes ☐ No☒

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

APPROVED BY THE YALE UNIVERSITY IRB 11/23/2022

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities?
Yes ☒ No ☐

If Yes, please answer questions a through c and note instructions below.
All involved personnel (physicians, diabetes nurse educators, study coordinators) are familiar with the use of the device and have received training on it previously.

a. Does your YNHH privilege delineation currently include the specific procedure that you will perform?
Yes ☒ No ☐

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? Yes ☐ No ☒

c. Will a novel approach using existing equipment be applied? Yes ☐ No ☒

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.

APPROVED BY THE YALE UNIVERSITY IRB 11/23/2022