IRB Minimal Risk Protocol Template

Note: If this study establishes a human specimen repository (biobank) for research purposes, do not use this template. Use the Mayo Clinic Human Specimen Repository Protocol Template found on the IRB home page under Forms and Procedures at http://intranet.mayo.edu/charlie/irb/

First-time Use: Use this template to describe your study for a new IRB submission.

1. Complete the questions that apply to your study.
2. Save an electronic copy of this protocol for future revisions.
3. When completing your IRBe application, you will be asked to upload this document to the protocol section.

Modification: To modify this document after your study has been approved:

1. Open your study in IRBe. Click on the study 'Documents' tab and select the most recent version of the protocol. Save it to your files.
2. Open the saved document and activate "Track Changes".
3. Revise the protocol template to reflect the modification points , save the template to your files
4. Create an IRBe Modification for the study and upload the revised protocol template.

General Study Information

Principal Investigators: Yogish Kudva – Mayo Clinic, Carol Levy – Mt. Sinai, Jordan Pinsker – Sansum Diabetes Research Institute, and Eyal Dassau – Harvard John A Paulson School of Engineering and Applied Sciences

Study Title: Observational study of patient important outcomes in pregnant patients with type 1 diabetes mellitus on Insulin pump

Protocol version number and date: V3, JUN 18, 2019.

Research Question and Aims

Hypothesis: We anticipate that when compared to subjects using an Artificial pancreas system(AP) as part of a future protocol, this comparator group of subjects undergoing usual care will exhibit less time in target Continuous glucose monitoring (CGM) glucose range defined as 63-140 mg/dL and an increased duration of hypoglycemia with CGM glucose <63 mg/dL.

Aims, purpose, or objectives: The overall goal of this study is to serve as a comparator group to a group of patients that will be managed with AP for varying periods of time during pregnancy. We will enroll this cohort and follow them prospectively throughout the pregnancy and into the post-partum period. Data collected will include records of continuous glucose monitoring (CGM) based glucose, insulin delivery, self-monitoring of blood glucose (SMBG), and maternal and fetal outcomes from pregnant women with type 1 diabetes. These data will be used to: (1) develop and refine algorithms for an AP system tailored to the needs of pregnant

women with type 1 diabetes, and (2) to serve as a comparator group for concurrent AP protocols (3) describe Dexcom G6 CGM data throughout the pregnancy and (4) describe insulin changes which occur in pregnancy.

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc*.):

Pregnancy in patients with type 1 diabetes (T1D) continues to be associated with mortality, preeclampsia, hypertension, and premature labor, all linked to hyperglycemia throughout gestation. Pregestational and gestational elevations of hemoglobin A1c (HbA1c) (a standard measure of glucose control in people with diabetes) and gestational time in target glucose range, time in hyperglycemia, and perhaps incidence of severe hypoglycemia have been associated with poorer outcomes. To reduce the risk of poor maternal and fetal outcomes, more stringent glucose targets for pregnant T1D women are recommended; however the quest to reduce hyperglycemia results in a significantly higher risk of hypoglycemia [1]. The greatest risk for both hyperglycemia and hypoglycemia often occurs overnight when patients are least able to make insulin dose adjustments. To optimize outcomes for women with T1D, more knowledge regarding CGM based glucose variability during the pregnancy and the changes in insulin requirements and sensitivity throughout pregnancy are needed. This information would facilitate the development of an automated insulin delivery system tailored to the specific needs of this population.

Pregnancy is characterized by complex hormonal and metabolic changes. The first trimester of pregnancy is a time when women are the most insulin sensitive and hypoglycemia can be problematic for women with diabetes [2, 3]; whereas by late pregnancy, insulin resistance develops and requires an increase of 200-250% in insulin secretion in women without diabetes [2, 4]. This increased insulin requirement in pregnant women with T1D makes it very challenging to maintain euglycemia, which is necessary to promote the health of both the mother and the developing fetus.

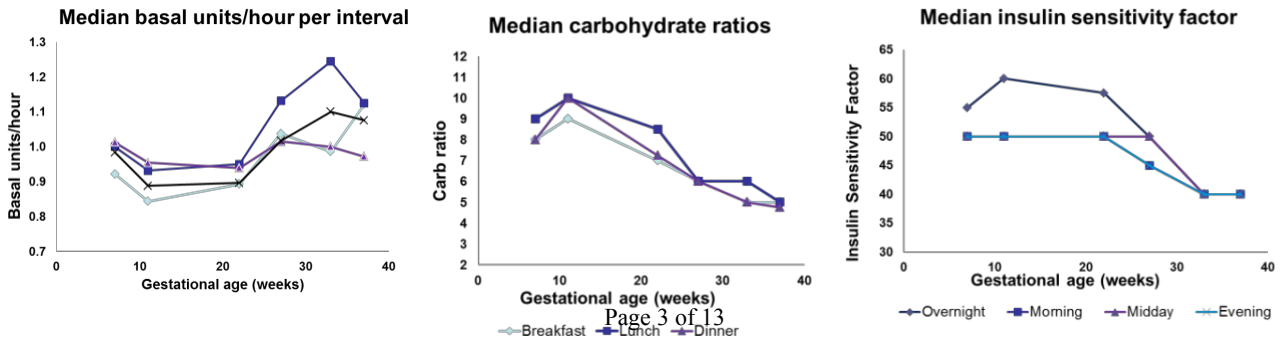
Sansum Diabetes Research Institute (SDRI) was the only US clinical site for the recent landmark CONCEPTT trial which revealed the benefit of CGM use on pregnancy outcomes and modest improvement in HbA1c. The CONCEPTT study revealed benefits of CGM use in pregnant women with T1D, demonstrating that in the setting of comparable overall good glucose control reflected by HbA1c level (mean HbA1c 6.35% in CGM group vs 6.53% in non-CGM group; p=0.0207), pregnant CGM users spent more time in target (68% vs 61%; p=0.0034) and less time hyperglycemic (27% vs 32%; p=0.0279) than did pregnant control participants, with comparable severe hypoglycemia episodes (18 CGM and 21 control) and time spent hypoglycemic (3% vs 4%; p=0.10) [6]. Fewer fetal adverse outcomes were reported for subjects wearing CGM [6]. CGM wear in this study was reported at 70% using the Medtronic Guardian sensor which requires calibration 2-4 times each day, is inaccurate in the setting of acetaminophen use, and must be replaced every 6 days. The Dexcom G6 CGM which provides high accuracy, mean absolute relative difference (MARD) <10 %, factory calibration, ten-day wear, and no acetaminophen interference should be particularly advantageous in the pregnant population.

There have been three hybrid AP studies published from European investigators showing safety and efficacy in pregnant women with T1D. The first study by Murphy et al. in 2011 conducted closed loop studies for 24 hours in an inpatient clinical research center in 10 pregnant women with T1D at 14.8 and 28 weeks of pregnancy [7]. The system required data entry by an RN every 15 minutes into a laptop computer that stored the algorithm. Overnight time in range was 84% and 100% (63-140 mg/dL) in the early and late gestation groups, respectively, with no hypoglycemia. Two follow up studies [8, 9] utilized a Sooil insulin pump and freestyle Navigator II

CGM. Neither of these off the shelf devices is available in the United States. Subjects (16 in each study) were studied in a randomized crossover fashion and served as their own controls. Subjects wore the system for 4 weeks overnight (Stewart et al., 2016) or wore the system day and night (Stewart et al., 2018). Results of these studies revealed the safety of the system in the home setting with fewer episodes of hypoglycemia and increased overnight time in the target glucose range of 63-140 mg/dL. In the overnight study, time in range (74.7 vs. 59.5% [95% CI 6.1 to 24.2]; P = 0.002) and mean glucose (119 vs. 133 mg/dL, P = 0.009) were significantly better. Time above goal was significantly reduced (>140 mg/dL: 24% vs 38.6%, P= 0.005; >180 mg/dL 7.4% vs 15.7%, P=0.004). In the day and night study, there were significantly fewer hypoglycemic episodes (median [range] 8 [1–17] vs. 12.5 [1–53] over 28 days; P =0.04) and time below goal was less (<63 mg/dL: 1.6 vs. 2.7%; P = 0.02; <50-mg/dL: 0.24 vs. 0.47%; P = 0.03). The time in range overall for the latter study was comparable between groups, but there was a trend toward higher overnight time in target (67.7 vs. 60.6%; P = 0.06). Maternal glycemia, however, was variable. Five (31%) of the study participants spent less time in target range and had higher mean glucose levels during AP therapy. These data support the importance of studying AP systems further in pregnant women with T1D. We will study several outcomes prospectively in this study including insulin delivery, CGM glucose specifically Dexcom G6 based glucose and maternal/fetal outcomes We will also evaluate the accuracy of the G6 based system with glucose meter testing at specific time points throughout the pregnancy.

Preliminary Data:

At the Mayo Clinic, Rochester during the years 2009-2013, 52 pregnant patients with T1D were seen with 32 (62%) using insulin pumps and none using sensor augmented insulin pumps (unpublished data). More recently, from 2013-2018, 60 pregnant patients with T1D were seen at Mount Sinai Hospital with 48 (80%) using insulin pumps and 34 (57%) using sensors. SDRI regularly provides care for 10 pregnant women with T1D per year who use these devices and was the only US clinical site for the recent landmark CONCEPTT trial.
The research teams at Barbara Davis Center and Joslin Clinic have studied CGM use in T1D pregnancies [10, 11].
Twenty-five pregnancies occurring between 2012-2017 in 22 patients seen at Mount Sinai Hospital and Mayo Clinic have been retrospectively reviewed (see figures). Pump settings at the initial visit and at designated 2-week intervals each trimester were analyzed. Compared to the initial visit, basal infusion rates overnight and in the morning decreased during the 1st trimester and rose in the 2nd and 3rd trimesters. Midday and evening infusion rates peaked during the late 2nd trimester to early 3rd trimester before plateauing during the last month of pregnancy. Carbohydrate ratios became more aggressive after week 12 with the earliest change in settings seen at breakfast. By the end of pregnancy, carbohydrate ratios had decreased by an average of 45%. Insulin sensitivity factors became more aggressive starting in the late 2nd trimester resulting in a 20% change from baseline by the end of pregnancy [5].



Summary: Understanding the hormonal and metabolic complexity as well as the subsequent requirements of adaptive insulin management over the entire gestation period in T1D will enable us to develop mathematical models that will describe the fluctuating glucose-insulin interactions during pregnancy. A multicenter database including CGM and insulin settings/bolus information from pregnant women during the gestation period will be collected to: 1) to serve as a comparator group for analysis of future AP studies data, 2) to further examine the glycemic variability and insulin management requirements throughout pregnancy to refine our AP algorithms, 3) to provide additional information on CGM use in pregnant women in comparison to fingerstick data utility, patient acceptance, and pregnancy outcomes.

Study Design and Methods

Methods: *Describe, in detail, the research activities that will be conducted under this protocol*:
All pregnant women with T1D at up to five sites on insulin pumps (CSII/SAP/PLGS) will be offered enrollment in a prospective study that will capture: 1) Dexcom G6 CGM data, 2) self-monitoring of blood glucose (SMBG), 3) insulin pump settings, 4) insulin delivery records, and 5) maternal and fetal outcomes.

Outpatient Screening and Enrollment:
Participants will be offered enrollment any time from pregnancy confirmation to 16 weeks and 6 days of gestational age. Participants will provide informed consent and will sign IRB-approved consent forms after eligibility has been confirmed based on pre-consent screening inclusion and exclusion criteria.

The study physician will perform a detailed history and physical with special emphasis on diabetes history. We will record participants' body weight, height, body mass index (BMI), average total daily insulin use (calculated over 1 week), insulin: carbohydrate ratio, correction factor (insulin sensitivity factor), insulin infusion basal rate profile, and HbA1c as a marker of overall glycemic control. Data from insulin pump and blood glucose meters will be downloaded using appropriate software and archived using an electronic process to avoid data recording errors.

We will obtain routine vital signs and draw blood for screening labs, including HbA1c, hematocrit, AST, creatinine and TSH. Since all these subjects will be pregnant, these tests may be available close to recruitment. If so, those tests will be used, and unnecessary testing will be avoided. HbA1c measured within one month +/- 1 week of screening and other tests within 3 months +/- 2 weeks of screening will be accepted. If the study physician feels it is necessary, a c-peptide lab (with simultaneous glucose for c-peptide validation) can also be conducted at screening to confirm a type 1 diabetes diagnosis. This study is not meant to find out if the participant has any other disease or problem. The study leaders will alert the participant if any of the research results are important to her health during the study. The participant may have a copy of the screening tests to discuss with her personal physician.

Participants will be provided a study glucometer and supplies. They will be trained on the use of the meter including to perform fingersticks on clean, dry hands and to use only finger sticks for glucose assessments. Participants will be required to perform SMBG 8 times a day (before meals, after meals, at bedtime and overnight between 2-4 am) on one day during every four week interval of their pregnancy. Subjects will be

supplied tests strips and permitted to perform additional fingersticks for testing as they desire as is standard of care for pregnant women with T1D.

Participants will be provided a study Dexcom G6 glucose sensor and supplies. They will be trained on proper insertion, calibration, and maintenance of the CGM sensor. Training will be tailored to their individual experiences (no prior CGM use, prior CGM use on different sensor). G6 can be calibrated or used with factory calibration with the choice being made at the start of each probe insertion by the subjects. This information will be captured.

Follow up visits:
Research staff will contact patients 1 day and 1 week after G6 initiation visit and thereafter every 14±4 days. These contacts can occur at participants' regularly scheduled follow up visits with maternal fetal medicine or at visits for diabetes management or over the phone. The number of follow up visits will depend on the week of pregnancy of the participant at enrollment.

During these contacts, study CGM and blood glucose meters will be downloaded (either in person or remotely) to have data from every week of pregnancy. Concerns regarding subjects' glycemic control will be conveyed to their provider for appropriate insulin titration.

Personal insulin pumps will be downloaded whenever CGM data are downloaded and whenever settings are changed (either in person or remotely). Pregnancy complications will be recorded. At clinic visits, CGM sites will be inspected. We will also collect self-reported food diary and activity log at least 2 times per pregnancy within 2 weeks ± 1 week of enrollment and at 30 weeks ±2 weeks to assess amount of carbohydrates consumed per day to see if the quantity changes during pregnancy. In addition, food and activity logs will be collected if available.

Study personnel will be available at all times throughout the trial to answer any question or troubleshoot any sensor problem.

Postpartum visit: After delivery, the participants will return study devices at or around the time of their routine post-partum follow up visit. Medical records including method of delivery, gestational age at delivery, neonatal intensive care unit (NICU) admissions, neonatal hypoglycemia, fetal weight, and length of hospital stay will be reviewed. The infant's medical record will also be accessed to retrieve post-delivery medical information. Subjects will also be asked if they were given any medications such as steroids that are known to cause insulin resistance which would impact blood glucose control. Subjects will be asked to complete the CGM-SAT survey (a survey assessing satisfaction with the glucose sensor) at this visit[12].

Data analysis:
Data from the 3 sites will be de-identified and collected in a central HIPPA compliant data repository.

Patterns of insulin and glucose control (including time in range 60-140 mg/dL, frequency of severe hypoglycemic events, time spent above target range, time spent in hypoglycemic range, episodes of clinically significant hyperglycemia with CGM >180 mg/dL, episodes of ketoacidosis requiring emergency room or hospital admission) will be analyzed and association with outcomes calculated.

Maternal and fetal outcomes include gestational age at delivery, birthweight of baby, fetal malformations, incidence of macrosomia [13], preterm birth, neonatal hypoglycemia (requiring IV dextrose), neonatal NICU stay, method of delivery, adverse events associated with delivery including shoulder dystocia, and maternal complications including preeclampsia and polyhydramnios.

CGM data will be compared to time-matched SMBG data in the pregnant population.

Dr. Walter Kremers from mayo Clinic Rochester is the Program Statistician and will be involved in the analyses.

Resources: *Describe the available resources to conduct the research (personnel, time, facilities, mentor commitment, etc.)*:

☐ (1a) This is a multisite study involving Mayo Clinic and non Mayo Clinic sites. *When checked, describe in detail the research procedures or activities that will be conducted by Mayo Clinic study staff.*
Mayo Clinic staff will perform the activities described above for 10 participants. The other sites will conduct the same activities on their participants. Mayo Clinic staff will also collect de-identified data from all sites for analysis.

☐ (1b) Mayo Clinic study staff will be engaged in research activity at a non Mayo Clinic site. *When checked, provide a detailed description of the activity that will be conducted by Mayo Clinic study staff.*

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: 300 subjects across 3-5 sites. We plan to enroll 60 patients each at Mount Sinai New York, Mayo Clinic Rochester, Sansum Diabetes Research Center, Santa Barbara, CA. In addition, we hope to extend the study to sites such as the Barbara Davis Center, Denver, Colorado and Joslin Clinic, Boston, MA.

Subject population (children, adults, groups): Pregnant women 18 years of age or older with T1D

Inclusion Criteria:

- Clinical diagnosis, based on investigator assessment, of T1D for at least one year and using insulin for at least 1 year.
- Criteria for documented hyperglycemia (at least 1 must be met):
  - Fasting glucose ≥126 mg/dL
  - Two-hour OGTT glucose ≥200 mg/dL
  - HbA1c ≥6.5% documented
  - Random glucose ≥200 mg/dL with symptoms

    - No data at diagnosis is available but the participant has a convincing history of hyperglycemia consistent with T1D
- Criteria for requiring insulin at diagnosis (1 must be met):
    - Participant required insulin at diagnosis and continually thereafter.
    - Participant did not start insulin at diagnosis but upon investigator review likely needed insulin (significant hyperglycemia that did not respond to oral agents) and did require insulin eventually and used continually.
    - Participant did not start insulin at diagnosis but continued to be hyperglycemic, had positive islet cell antibodies – consistent with latent autoimmune diabetes in adults (LADA) and did require insulin eventually and used continually.
- Currently using an insulin pump for diabetes management
- Currently using or willing to use an insulin-to-carbohydrate ratio to calculate meal bolus sizes
- Willing to change insulin infusion site at least every 3 days.
- Confirmed pregnancy
- Current gestational age ≤16 weeks
- Age 18-40 years
- HbA1c <10.0%
- Demonstration of proper mental status and cognition for the study
- Ability to access the internet and upload CGM data remotely if needed
- An understanding of and willingness to follow the protocol and sign the informed consent

Exclusion Criteria:

- 670 G users in Auto mode
- Current gestational age >16 weeks
- Cystic fibrosis
- A known medical condition that in the judgment of the investigator might interfere with the completion of the protocol such as the following examples:
    - Inpatient psychiatric treatment in the past 6 months
    - Abnormal renal function test results (calculated GFR <60 mL/min/1.73m2); testing required for subjects with diabetes duration of greater than 5 years post onset of puberty
    - Active gastroparesis
    - Abuse of alcohol or recreational drugs
    - Infectious process not anticipated to resolve prior to study procedures (e.g. meningitis, pneumonia, osteomyelitis)
    - Uncontrolled arterial hypertension (Resting diastolic blood pressure >95mmHg and/or systolic blood pressure >160 mmHg) at the time of screening
    - Chronic oral steroid use
- A recent injury to body or limb, muscular disorder, use of any medication, any carcinogenic disease, or other significant medical disorder if that injury, medication or disease in the judgment of the investigator will affect the completion of the protocol

Research Activity

Check all that apply and complete the appropriate sections as instructed.

1. ☐ **Drug & Device**: Drugs for which an investigational new drug application is not required. Device for which (i) an investigational device exemption application is not required; or the medical device is cleared/approved for marketing and being used in accordance with its cleared/approved labeling. (Specify in the Methods section)

2. ☐ **Blood**: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture.

3. ☐ **Biological specimens other than blood**: Prospective collection of human biological specimens by noninvasive means that may include: urine, sweat, saliva, buccal scraping, oral/anal/vaginal swab, sputum, hair and nail clippings, etc.

4. ☐ **Tests & Procedures:** Collection of data through noninvasive tests and procedures routinely employed in clinical practice that may include: MRI, surface EEG, echo, ultrasound, moderate exercise, muscular strength & flexibility testing, biometrics, cognition testing, eye exam, etc. (Specify in the Methods section)

5. ☐ **Data** (medical record, images, or specimens): Research involving use of existing and/or prospectively collected data.

6. ☐ **Digital Record**: Collection of electronic data from voice, video, digital, or image recording. (Specify in the Methods section)

7. ☐ **Survey, Interview, Focus Group:** Research on individual or group characteristics or behavior, survey, interview, oral history, focus group, program evaluation, etc. (Specify in the Methods section)

☐ NIH has issued a *Certificate of Confidentiality* (COC). *When checked, provide the institution and investigator named on the COC and explain why one was requested*. _____

Biospecimens – Categories 2 and 3

(2) Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.

Volume per blood draw: _____ml

Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.
   Volume per blood draw:
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.)

(3) Prospective collection of biological specimens other than blood: _____

Review of medical records, images, specimens – Category 5

For review of existing data: provide a date range or an end date for when the data was generated. The end date can be the date this application was submitted to the IRB. Example: *01/01/1999 to 12/31/2015* or all records through *mm/dd/yyyy*.

Date Range:

Check all that apply (data includes medical records, images, specimens).

__ (5a) Only data that exists before the IRB submission date will be collected.

__ (5b) The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples
- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

__ (5c) The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

__ Data __ Specimens __ Data & Specimens _____

__ Data __ Specimens __ Data & Specimens _____

__ Data __ Specimens __ Data & Specimens _____

MAYO CLINIC

☐ (5d) This study will obtain data generated from other sources. Examples may include receiving data from participating sites or an external collaborator, accessing an external database or registry, etc. Explain the source and how the data will be used in the Methods section.

☐ (6) Video audio recording: *Describe the plan to maintain subject privacy and data confidentiality, transcription, store or destroy, etc.*

HIPAA Identifiers and Protected Health Information (PHI)

Protected health information is medical data that can be linked to the subject directly or through a combination of indirect identifiers.

Recording identifiers (including a code) during the conduct of the study allows you to return to the medical record or data source to delete duplicate subjects, check a missing or questionable entry, add new data points, etc. De-identified data is medical information that has been stripped of all HIPAA identifiers so that it cannot be linked back to the subject. De-identified data is **rarely** used in the conduct of a research study involving a chart review.

Review the list of subject identifiers below and, if applicable, check the box next to each HIPAA identifier being recorded at the time of data collection or abstraction. Identifiers apply to any subject enrolled in the study including Mayo Clinic staff, patients and their relatives and household members.

Internal refers to the subject's identifier that will be recorded at Mayo Clinic by the study staff.
External refers to the subject's identifier that will be shared outside of Mayo Clinic.

Check all that apply:	INTERNAL	EXTERNAL
Name	X	
Mayo Clinic medical record or patient registration number, lab accession, specimen or radiologic image number	X	
Subject ID, subject code or any other person-specific unique identifying number, characteristic or code that can link the subject to their medical data	X	X
Dates: All elements of dates [month, day, and year] directly related to an individual, their birth date, date of death, date of diagnosis, etc. **Note:** Recording a year only is not a unique identifier.	X	
Social Security number		
Medical device identifiers and serial numbers	X	X
Biometric identifiers, including finger and voice prints, full face photographic images and any comparable images		
Web Universal Resource Locators (URLs), Internet Protocol (IP) address numbers, email address		
Street address, city, county, precinct, zip code, and their equivalent geocodes	X	
Phone or fax numbers	X	
Account, member, certificate or professional license numbers, health beneficiary numbers		

Vehicle identifiers and serial numbers, including license plate numbers		
Check 'None' when none of the identifiers listed above will be recorded, maintained, or shared during the conduct of this study. (exempt category 4)	___ None	___ None

Data Analysis

Power analyses may not be appropriate if this is a feasibility or pilot study, but end-point analysis plans are always appropriate even if only exploratory. Provide all information requested below, or provide justification if not including all of the information.

Power Statement: Previous studies have found a clear benefit between AP and standard using 16 patients per group, so the sample size of 40 patients for data collection and comparator should be sufficient.

Data Analysis Plan: Data from the 5 sites will be de-identified and collected at each site. CGM data will be compared to time-matched SMBG data to confirm accuracy in the pregnant population. Patterns of insulin and glucose control change will be analyzed and association with outcomes calculated. This data will also be used as a comparator for AP studies as a historical or active control group.

Endpoints
Primary:
Time in range defined as 63-140 mg/dL as determined by CGM analysis

Secondary:
Glycemic Outcomes:
-Frequency of hypoglycemia defined as <63 mg/dL and percent of time in the hypoglycemic range
-Frequency and duration of severe hypoglycemic events defined as requiring assistance from another, an emergency room visit or treatment with glucagon due to unconsciousness
-Time spent above target range defined as >140 mg/dL
-Episodes of clinically significant hyperglycemia with CGM> 180 mg/dL
-Extent of glucose variability
-Percent of time CGM active
-Concordance of CGM data in relation to SMBG data

Insulin Delivery Outcomes:
-Change in total daily insulin during pregnancy and the postpartum period
-Change in basal insulin during pregnancy and the postpartum period
-Change in insulin-to-carbohydrate ratio during pregnancy and the postpartum period
-Change in insulin sensitivity during pregnancy and the postpartum period
-Change in carbohydrate consumption during pregnancy and the postpartum period

Pregnancy Outcomes:
-Episodes of ketoacidosis requiring emergency room or hospital admission
-Maternal complications including preeclampsia, pregnancy induced hypertension and polyhydramnios
-Gestational weight gain

Delivery and Neonatal Outcomes to be collected:
-Gestational age at delivery
-Birth weight of baby
-Fetal malformations
-Incidence of Large for Gestational Age based on WHO criteria at time of delivery
-Incidence of Small for Gestational Age based on WHO criteria at time of delivery
-Preterm birth (<37 weeks and early preterm < 34 weeks)
-Neonatal hypoglycemia requiring IV dextrose
-Neonatal NICU stay > 24 hours and indication
-Method of delivery and adverse events associated with delivery including shoulder dystocia
-Mode of delivery including induction rates and incidence of primary cesarean section (and indication noted)
-Length of hospital stay

References:

[1] M. G. Dalfra, G. Sartore, G. Di Cianni, G. Mello, C. Lencioni, S. Ottanelli, *et al.*, "Glucose variability in diabetic pregnancy," *Diabetes Technol Ther,* vol. 13, pp. 853-9, Aug 2011.

[2] L. A. Barbour, C. E. McCurdy, T. L. Hernandez, J. P. Kirwan, P. M. Catalano, and J. E. Friedman, "Cellular Mechanisms for Insulin Resistance in Normal Pregnancy and Gestational Diabetes," *Diabetes Care,* vol. 30, pp. S112-S119, 2007.

[3] P. M. Catalano, E. D. Tyzbir, R. R. Wolfe, J. Calles, N. M. Roman, S. B. Amini, *et al.*, "Carbohydrate metabolism during pregnancy in control subjects and women with gestational diabetes," *Am J Physiol,* vol. 264, pp. E60-7, Jan 1993.

[4] A. García-Patterson, I. Gich, S. B. Amini, P. M. Catalano, A. d. Leiva, and R. Corcoy, "Insulin requirements throughout pregnancy in women with type 1 diabetes mellitus : three changes of direction," *Diabetologia,* vol. 53, pp. 446-451, 2010.

[5] G. O'Malley, V. Dadlani, Y. C. Kudva, E. Dassau, K. Murari, D. Brooks, *et al.*, "Diurnal changes in insulin pump settings throughout pregnancy in patients with type I diabetes," in *American Association of Clinical Endocrinologists 27th Annual Scientific and Clinical Congress*, 2018.

[6] D. S. Feig, L. E. Donovan, R. Corcoy, K. E. Murphy, S. A. Amiel, K. F. Hunt, *et al.*, "Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial," *The Lancet,* vol. 390, pp. 2347-2359, 2017.

[7] H. R. Murphy, D. Elleri, J. M. Allen, J. Harris, D. Simmons, G. Rayman, *et al.*, "Closed-loop insulin delivery during pregnancy complicated by type 1 diabetes," *Diabetes Care,* vol. 34, pp. 406-11, Feb 2011.

[8] Z. A. Stewart, M. E. Wilinska, S. Hartnell, R. C. Temple, G. Rayman, K. P. Stanley, *et al.*, "Closed-Loop Insulin Delivery during Pregnancy in Women with Type 1 Diabetes," *New England Journal of Medicine,* vol. 375, pp. 644-654, 2016.

[9] Z. A. Stewart, M. E. Wilinska, S. Hartnell, L. K. O'Neil, G. Rayman, E. M. Scott, *et al.*, "Day-and-Night Closed-Loop Insulin Delivery in a Broad Population of Pregnant Women With Type 1 Diabetes: A Randomized Controlled Crossover Trial," *Diabetes Care,* p. dc172534, Mar 2018.

[10] S. Polsky, R. Garcetti. "CGM, Pregnancy, and Remote Monitoring", *Diabetes Technology & Therapeutics,* Vol. 19, No. S3 , pp S49-S59, 2017.

[11] M. Tansey, L. Laffel, J. Cheng, R. Beck, J. Coffey, E. Huang, et al. "Satisfaction with continuous glucose monitoring in adults and youths with Type 1 diabetes ,"*Diabet. Medicine,* vol. 28, pp1118–1122, 2011.

[12] B. M. Mulla, N. Noor, T. James-Todd, E. Isganaitis, T. C. Takoudes, A. Curran, et al." Continuous Glucose Monitoring, Glycemic Variability, and Excessive Fetal Growth in pregnancies complicated by type 1 diabetes. *Diabetes Technology & Therapeutics,* Volume 20, Number 6, pp 413-419, 2018

[13] www.who.int/reproductivehealth/topics/best.../weight_percentiles_calculator.xls