Protocol #: 18-1798
Project Title: Hybrid Closed-Loop Therapy in Pregnancies Complicated by Type 1 Diabetes (T1D)
Study Title: PICLS (Pregnancy Intervention with a Closed-Loop System) Study
Principal Investigator: Sarit Polsky, MD, MPH
Version Date: 01-19-2021

I. Introductory Background:

Pregnancies associated with diabetes mellitus are accompanied by high risks of adverse maternal and fetal outcomes. Uncontrolled glucose levels in pregnancy can lead to fetal loss (miscarriage, stillbirth), congenital malformations, preterm delivery, cesarean section, macrosomia, neonatal hypoglycemia, and the like[1-4]. Given these high risks, the American Diabetes Association (ADA) recommends rigorous glucose control throughout gestation with a glycated hemoglobin A1C (A1C) of <6% for women with preexisting diabetes[5]. The strict glycemic targets are especially difficult to achieve for women dependent on insulin throughout gestation, such as those with Type 1 Diabetes (T1D). Their rates of severe hypoglycemia (SH, hypoglycemia requiring 3rd party assistance) are critically high[6-10]. Strategies are needed to optimize glucose control both pre- and post-prandially without significantly increasing the risk of hypoglycemia throughout gestation. Closed-loop (CL) insulin therapy employs a continuous subcutaneous insulin infusion pump with feedback from a continuous glucose monitor (CGM)[11]. Several CL systems evaluated in non-pregnant populations have been found to improve glucose control[11-17]. One of these Hybrid CL (HCL) systems was recently approved by the Federal Drug Administration (FDA) and has been evaluated in non-pregnant adolescents and adults[18, 19]. In this proposal, we aim to improve maternal and fetal health through a novel insulin delivery system, and to obtain pilot data to ultimately reduce birth complications.

The effects of CL therapy on glucose and pregnancy outcomes are largely unknown. Only one investigational CL system has been studied in women with diabetes throughout most of pregnancy[20]. This single hormone HCL system was found to increase the glucose target time in range (TIR) compared to sensor-augmented pump therapy (SAPT), however rates of large-for-gestational age (LGA) infants remained high[20]. There is currently one HCL system on the market approved by the FDA, the Medtronic 670G system with the Guardian sensor[21]. The 670G system can be used in auto, closed mode (HCL therapy) or manual, open mode (SAPT) using the same insulin pump and continuous glucose monitor, offering a unique opportunity to compare therapies with the same devices. Women across the United States are beginning to use this HCL therapy, which has never been studied in pregnancy. As rates of unintended pregnancy remain high in the United States (~45%)[22, 23], many women may be using the 670G without knowing they are pregnant for many weeks. Thus, it is critical that we understand how this system will perform throughout pregnancy with regards to safety, glucose control, quality of life, and maternal and fetal outcomes in comparison to SAPT therapy.

II. Hypotheses and Specific Aims:

The PICLS (Pregnancy Intervention with a Closed-Loop System) Study is a two-center, prospective, 'open-label', single-blind, investigator-initiated randomized controlled pilot

study evaluating hybrid closed-loop (HCL) insulin delivery among pregnant women with T1D compared with sensor-augmented pump therapy (SAPT) throughout gestation and the first 6 weeks of the post-partum period at the Barbara Davis Center for Diabetes and Ohio State University. The HCL system being used is the Medtronic 670G system, which has been FDA-approved in non-pregnant populations but has never been studied in pregnancy.

Specific Aim (SA) 1: Evaluate safety of HCL therapy (Medtronic 670G with Guardian sensor) compared to SAPT in women with T1D throughout the 2nd and 3rd trimesters of gestation and the early post-partum period.
Hypothesis SA 1.1: We hypothesize that time spent with glucose <54 mg/dL will be the same or reduced among women using the HCL system compared to those using SAPT.
Hypothesis SA 1.2: We hypothesize that the episodes of diabetic ketoacidosis and rates of adverse skin reactions will be similar between groups.

Specific Aim 2: Evaluate indices of glucose control and fear of hypoglycemia in pregnant women with T1D using HCL therapy compared to those using SAPT throughout the 2nd and 3rd trimesters of gestation and in the early post-partum period.
Hypothesis SA 2.1: We hypothesize that HCL therapy will increase time spent in the glucose target range (63-140 mg/dL), reduce time spent in mild and more severe hypoglycemia (<63 mg/dL and <54 mg/dL, respectively), and reduce time spent in hyperglycemia (>140 mg/dL) over time compared to SAPT.
Hypothesis SA 2.2: We hypothesize that HCL therapy will reduce fear of hypoglycemia as measured by the Hypoglycemia Fear Survey[24], starting in the 1st trimester of pregnancy compared to SAPT.

Specific Aim 3: Evaluate quality of life and device acceptability in pregnant women with T1D using HCL therapy compared to those using SAPT throughout the 2nd and 3rd trimesters of gestation and in the early post-partum period.
Hypothesis SA 3.1: We hypothesize that pregnant women with T1D randomized to HCL therapy or SAPT will report similar quality of life (general mental health and general health perceptions), as measured by the Medical Outcomes Study (MOS) Short-Form 36 (SF-36)[25], without a significant difference between groups.
Hypothesis SA 3.2: We hypothesize that HCL will be more acceptable to subjects than SAPT, as measured by Insulin Delivery Satisfaction Survey[26] and the Glucose Monitoring Satisfaction Survey[27].
Hypothesis SA 3.3: We hypothesize that HCL in mid-pregnancy, late pregnancy, and post-partum will be more acceptable to subjects than SAPT in the first trimester in the same women using both modes of therapy, as measured by the INSPIRE Questionnaire[28].

Specific Aim 4 (Exploratory Aim): Evaluate maternal and fetal outcomes in pregnant women with T1D using HCL therapy compared to those using SAPT throughout gestation and in the early post-partum period.
Hypothesis SA 4.1: We hypothesize that rates of fetal loss, preeclampsia, cesarean section, and neonatal hypoglycemia will be similar between groups.
Hypothesis SA 4.2: We hypothesize that rates of large-for-gestational age infants and macrosomia (birth weight >4,000 grams) will be similar between groups.

III. **Background and Significance**:

Pregnancies associated with type 1 diabetes (T1D) are accompanied by high risks of adverse maternal and fetal outcomes[4]. To reduce the risk of adverse health outcomes occurring, it is recommended that women obtain and maintain tight glycemic control throughout gestation[5]. This task is difficult given the ever-changing insulin requirements in pregnancy. The insulin-sensitive 1st trimester predisposes women to nocturnal hypoglycemia[29, 30]. Insulin resistance begins 14 to 20 weeks gestation because of increased placental-fetal unit demands, free fatty acid production, and placental/maternal hormonal influences[29, 31]. The early post-partum period cuts insulin requirements 35-90% from pre-pregnancy doses because of cessation of placental hormones[29, 30, 32]. Achieving tight glycemic targets under these conditions, without causing SH, is one of the biggest challenges of diabetes pregnancy care. For women with T1D, the high stakes and strict goals of pregnancy can negatively impact QOL and mental health[33]. CL therapy is a novel way to improve care and QOL among pregnant women with diabetes.

CL in Pregnancy: Three studies have been done in this field, all with crossover designs. (1) The Deltec Cozmo insulin pump and FreeStyle Navigator CGM (HCL system with a model predictive control algorithm) was worn by 10 women for 24 hours at a time at 14.8 and 28 weeks gestation. Plasma TIR (63-140 mg/dL) overnight increased (84% early to 100% in late gestation, p=0.09), though nocturnal hypo- and hyperglycemia did not change[34]. (2) The Animas 2020 Insulin Pump with FreeStyle Navigator CGM or CSII alone was used for 24 hours at a time at 19 and 23 weeks gestation (n=12). Hypoglycemia was significantly reduced with HCL wear (time spent <45 mg/dL, lower low blood glucose index, and fewer hypoglycemic episodes), but overnight plasma TIR was similar in both groups[35]. Overall, both sessions were in the plasma TIR 81% of the time. (3) Finally, 16 women were randomly assigned to HCL therapy (DANA Diabecare R Insulin Pump with FreeStyle Navigator II CGM) or SAPT (control condition) for 4 weeks of over-night use then crossed over after a washout period. Women were then allowed to continue HCL therapy, if they wanted to do so. The HCL system used was investigational[20] and utilized a model predictive control (MPC) algorithm[34]. Semi-structured interviews and validated questionnaire data from this study showed that HCL wear was associated with some modest benefits with respect to quality of life (feelings of better glucose control/excitement/empowerment and less worry about hypoglycemia occurring overnight) but also concerns about device visibility and varying degrees of attention to data and hypo-/hyperglycemia symptoms[36]. Time spent <63 mg/dL was low in both groups (1.9% HCL vs 1.8% SAPT, p=0.67). HCL wear significantly increased TIR (66.3% HCL vs 56.8% SAPT, p<0.001), decreased time >140 mg/dL (31.6% HCL vs 40.9% SAPT, p<0.001) and >180 mg/dL (12.6% HCL vs 17.3% SAPT, p=0.001), and lowered mean glucose (128 mg/dL HCL vs 137 mg/dL SAPT, p<0.001). After crossover, 87.5% (14/16) of the women continued using HCL therapy until delivery. There were 26 adverse events (skin reactions and minor illnesses) and 95 device deficiencies with no differences between groups. Serious adverse events were unrelated to the devices. For the 24 hours prior to delivery the median glucose level was 110 mg/dL (86.8% TIR). Adverse outcomes were: 5 cases of pre-eclampsia, 15 cesarean section deliveries (10 prior to onset of labor), 7 deliveries <37 weeks gestation, 13 LGA infants (birth weight >90th percentile), 14 infants with neonatal hypoglycemia, and 12 cases of neonatal intensive care admissions[20]. Thus, hypoglycemia was reduced with one[35] and TIR increased with two out of the three HCL systems [20, 34]. None of the HCL systems studied are approved in the United States. No HCL system has been compared to SAPT for the duration of a pregnancy and early post-partum or has been shown to improve maternal and fetal outcomes. None of the HCL systems studied in pregnancy used a PID control algorithm, which may perform differently

than then MPC algorithms in situations of dramatic shifts in insulin requirements such as pregnancies complicated by diabetes and the transition from extreme insulin resistance in the 3rd trimester to insulin sensitivity post-partum.

This novel study will compare the only approved HCL system (novel therapy) to SAPT (often-used therapy) throughout pregnancy and early post-partum. The FDA-approved device we will use has a proportional-integral-derivative (PID) controller, which has never been studied in pregnancy. We will assess **safety (SA 1)** by measuring: 1) SH, 2) episodes of diabetic ketoacidosis (DKA), and 3) adverse skin reactions. We will compare **indices of glycemic variability (SA 2)** and **fear of hypoglycemia (SA 2)** between groups. Pregnancy often leads to hypervigilance with self-care, but also increased emotional stress and burden[33]. This study will assess psychological factors **(QOL, SA 3)** during and after pregnancy: QOL (SF-36)[25] and device satisfaction (3 surveys for people with T1D[26-28]). We will collect data about **maternal and fetal health outcomes (SA 4)**.

III. **Preliminary Studies/Progress Report:**

(1) **CGM Therapy in Pregnancy with or without Remote Monitoring:** The Barbara Davis Center (BDC) for Diabetes has experience with research during pregnancy[37-39]. BDC's clinical staff has cared for hundreds of pregnant women with diabetes (mostly with T1D), 60-70 per year. The principal investigator (PI) of the proposed study directs the Pregnancy and Women's Health Clinic. The PI completed an open-label, investigator-initiated, study in pregnant women with T1D prospectively (n=40) stratified to (1) CGM Alone [women with Apple devices], or (2) CGM Share (DexCom, San Diego, CA) [women with an iPhone and followers with data-viewing devices), and retrospectively (n=8) to (3) no CGM. There were 48 women enrolled in the study (15 during preconception, 25 during the 1st trimester, 8 on retrospective chart review). All pregnant women were trained and started on a Dexcom G4 system. Women prospectively enrolled were given sensors throughout pregnancy for the G4 (provided by the study) or G5 system (provided by patient's health insurance). In the preconception group, 53% (8/15) became pregnant during the study period. Final analyses include 13 women in the CGM Alone group, 15 in CGM Share, and 8 in no CGM. SAPT was used in 86% (24/28) of the prospective and 75% (6/8) of the retrospective pregnancies. There were 3 episodes of SH (severe hypoglycemia, which is hypoglycemia requiring the assistance of a 3rd party) in 2 women. Interim data were presented at the ADA Scientific Sessions in 2016[38] and 2017[39], complete data were presented at ATTD in 2018[40]. A1C over time, time spent >180 mg/dL, hypoglycemia fear scores, and neonatal hypoxemia were significantly lower in CGM Share users. The BDC can recruit and retain pregnant women with T1D into studies, and train them on SAPT devices.

(2) **CL in non-Pregnant Adults:** The BDC has extensive experience studying insulin pump technology[11, 19, 41-45]. The BDC was 1 of the 10 sites involved in the pivotal study on the Medtronic 670G HCL system, which has been assessed in hotel[11] and free-living conditions[19]. The HCL system was studied in adolescents (n=30) and adults (n=94) with T1D for 3 months in free-living conditions. Adults were in the HCL mode a median of 88% of the time, A1C decreased from a mean of 7.3% to 6.8% ($p<0.001$), TIR (70-180 mg/dL) increased from 68.8% to 73.8% ($p<0.001$), and hypoglycemia (≤70 mg/dL) decreased from 6.4 to 3.4% ($p<0.001$) from run-in to study end[19]. For adults, fasting TIR significantly increased (70 ± 21.2% run-in to 84.4 ± 12.1% study end, $p<0.001$)[19]. There were no episodes of SH or DKA[19]. The sensor accuracy, measured as mean amplitude of relative

difference (MARD) ± standard deviation between the sensor glucose (SG) and i-STAT venous glucose values, was 10% ± 8.7% in adults (10.3% for SG >180 mg/dL and 12.2% for SG ≤70 mg/dL)[19]. The BDC can train subjects on the HCL system, follow glucose outcomes and device deficiencies, and retain subjects.

IV. Research Methods

A. Outcome Measure(s):

Primary Outcomes:

1) Safety of HCL therapy compared to SAPT in women with T1D throughout gestation and the early post-partum period assessed through episodes of severe hypoglycemia and time spent with glucose <54 mg/dL.
2) Indices of glucose control and fear of hypoglycemia in pregnant women with T1D using HCL or SAPT therapy throughout pregnancy and early post-partum. Indices of glucose control are time spent in the glucose target ranges <54 mg/dL and <63 mg/dL (hypoglycemia), 63-140 mg/dL (time in range), and >140 mg/dL and >180 mg/dL (hyperglycemia). Fear of hypoglycemia is assessed as behavior, worry, and total scores of fear of hypoglycemia determined by the Hypoglycemia Fear Survey.

Secondary Outcomes:

3) Safety of HCL therapy compared to SAPT in women with T1D throughout gestation and the early post-partum period assessed through episodes of diabetic ketoacidosis and skin reactions.
4) Indices of glucose control and fear of hypoglycemia in pregnant women with T1D using HCL or SAPT therapy throughout pregnancy and early post-partum. Secondary outcomes of indices of glucose control are mean glucose ± standard deviation, J index, High Blood Glucose Index (HBGI), Low Blood Glucose Index (LBGI), duration of hypoglycemic episodes, Mean Amplitude of Glycemic Excursions (MAGE), and Continuous Overall Net Glycemic Action ($CONGA_n$).
5) Quality of life and device acceptability in women with T1D throughout gestation and the early post-partum period as measured by scores from the MOS Short-Form 36 (quality of life) and Insulin Delivery Satisfaction Survey, Glucose Monitoring Satisfaction Survey, and INSPIRE (HCL only) questionnaires (device acceptability).
6) Maternal and fetal outcomes in pregnant women with T1D using HCL therapy compared to those using SAPT throughout gestation and in the early post-partum period. Maternal outcomes include preeclampsia/eclampsia, cesarean delivery, and gestational weight gain. Fetal outcomes include fetal loss (miscarriage or stillbirth), large-for-gestational age, and neonatal hypoglycemia.

B. Description of Population to be Enrolled:

We anticipate recruiting women with T1D for at least a year who are pregnant (11 weeks gestation or earlier) between the ages of 18 and 45 years old. We expect to screen up to 37 individuals, randomize up to 24 women, and have 20 completers (10 women per group).

C. Study Design and Research Methods

Overview: This is a two-center, prospective, 'open-label', single-blind, investigator-initiated randomized controlled pilot study evaluating HCL insulin delivery among pregnant women with T1D compared with SAPT throughout the 2nd and 3rd trimesters of gestation and the first 6 weeks of the post-partum period at the BDC and Ohio State University. Each institution will obtain IRB approval separately. The statistician will be blinded to treatment assignment, but the participants and clinical research team will not.

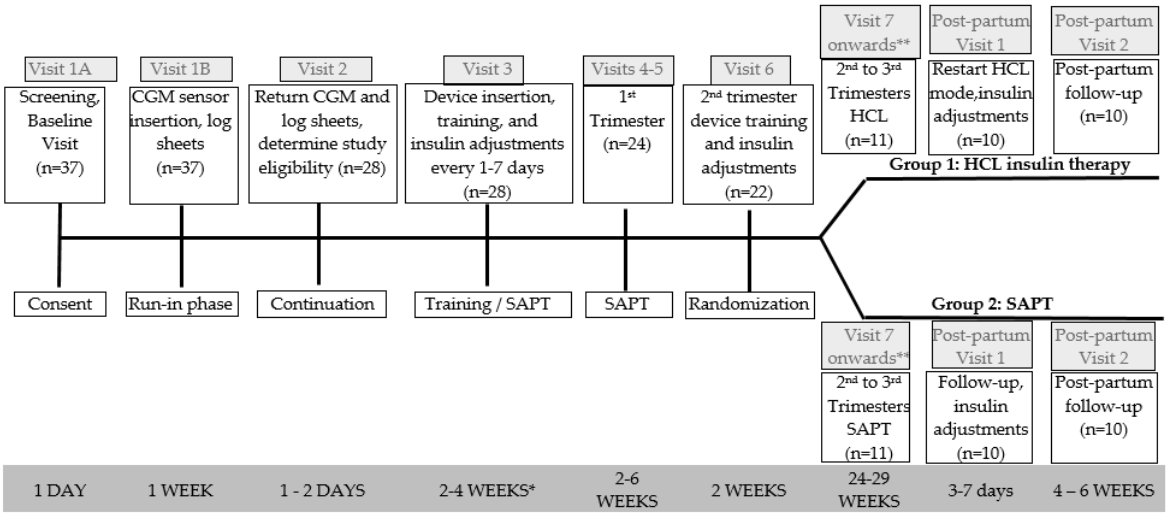
Study Design: Up to 37 women will be screened in the 1st trimester of pregnancy (≤11 weeks gestation) over 10 months. All subjects meeting the initial inclusion/exclusion criteria will be invited to sign informed consent and participate in the study. The consent form must be signed by all women who wish to participate in the study, however there are two optional consent procedures: (1) providing specimens (blood and urine) to be stored in a biorepository for future research studies and (2) providing permission to be contacted for other research studies in the future. Consent for the optional procedures will be voluntary and will not affect regular clinical care for participants in any way.

If potential subjects are not available or not able to consent in person, they will have the option of to do a phone consent or consent through a videoconference. A HIPAA-compliant videoconferencing tool formally approved by the University of Colorado (e.g., Zoom) will be used. In order for individuals to consent remotely, subjects who want to consent by phone or video will be e-mailed or mailed a PDF of the consent form, for them to read over. They will set up a time and date with the research personnel to thoroughly go over the consent form. The prospective subject will have a written copy of the consent form in-hand at the time of the informed consent discussion, and will ask any questions she may have. For video consenting, an impartial witness must be present (site-dependent stipulation), i.e., a friend or family member of the subject or someone on the research staff who is not involved in this study. If the subject agrees to participate, the witness must sign the copy of the consent form to verify that the subject's questions were answered, and that the subject agreed to participate. The subject will send the original consent form with her signature and the witness's signature back to the Barbara Davis Center.

All subjects will fill out a questionnaire about personal demographics and baseline health history. All women will be counseled on glucose targets in pregnancy, per standard of care. Women will be given handouts on general guidelines for care of pregnant women with diabetes and on specific conditions of which they should be aware during the first trimester (see appendix). If the woman was seen at the Barbara Davis Center or Ohio State University prior to the consent visit, we will do a retrospective chart review for medications, vital signs, height/weight, A1C, insulin doses, glucose meter downloads, insulin pump downloads (if applicable), and CGM downloads (if applicable) for the most-immediate pre-conception clinic visit and for previous visits during the current pregnancy, if she was not seen at either institution prior to signing the consent form, then we will have her fill her a medical release form to request these records. Women will be asked to participate in a run-in phase. The run-in phase requires CGM wear, but not insulin pump wear. Women previously using a CGM, but not the device to be used during the run-in phase, will receive a targeted educational and training session on the study CGM system and its differences from their previous systems. Women naïve to CGM wear will receive a targeted educational and training session on CGM systems in general, on sensor wear, and on the study CGM system in particular. Both institutions in this protocol are experienced in training and starting CGM systems in pregnant women with diabetes. Women will undergo a run-in phase wherein they will wear the study CGM for 1 week and

be asked to calibrate per device instructions, log self-monitored glucose values (7 per day), insulin doses, carbohydrate intake, and exercise. Women who are compliant with device wearing and log sheets, who do not have an adverse reaction to device adhesives or wearing, who are willing to wear the study devices, and who are otherwise deemed appropriate candidates by the study PI will be invited to continue in the study (see Figure 1). The operational definition of compliance for the run-in phase is device wearing for ≥80% of time during the run-in phase, changing infusion sets every 3-4 days, performance of a minimum of 2 finger-sticks per day (as the HCL system requires 2-4 calibrations per day), filling out ≥80% of the log sheets, successful remote uploading of the CGM data, and communication with the study team during the run-in phase. Women will also be asked to record dietary (food and beverage) intake for three days during the run-in phase using log sheets. Food records will be reviewed to assess dietary compliance with the personalized pregnancy nutrition goals provided to participants and carbohydrate counting skills. Targeted enrollment after the run-in phase will be 28 women and by the end of the study will be 20 women (10 completers per group allowing for a drop-out rate of 36% due screen failures, miscarriages, dropping out, or subjects being lost to follow up).

Figure 1: Overall Study Design



*2 weeks for pump-experienced participants at baseline and 4 weeks for pump-naïve participants at baseline.

**Visits 7 through 14 for pregnancy care and study follow-up.

Abbreviations: CGM, continuous glucose monitor; HCL, hybrid closed-loop insulin therapy; SAPT, sensor-augmented pump therapy

Women meeting the above criteria will be trained to start SAPT mode with the Medtronic Minimed 670G insulin pump and Guardian CGM and will continue SAPT mode throughout the remainder of the 1st trimester of pregnancy. Insulin adjustments will be made every 1-7 days for the first 2 weeks. Frequency of insulin adjustments will be guided by participant experience with pump therapy, glucose levels, level of insulin sensitivity, and willingness to contact study staff to ask for assistance, where (in general) women with less pump experience, a larger-than-expected number of glucose levels above or below ADA targets, dramatic insulin sensitivity, and unwilling to proactively contact study staff for assistance will be contacted more frequently for pump follow-up and adjustments as necessary. Women will be counseled on the maternal and fetal health risks in pregnancies associated with T1D, on the ability to reduce these risks with optimal glycemic control, on

the ADA-recommended targets for glycemic control (HbA1c <6.5% prior to conception/1st trimester, HbA1c <6% as pregnancy progresses, fasting glucose target <95 mg/dL, 1-hour postprandial glucose target <140 mg/dL, and 2-hour postprandial glucose target <120 mg/dL if these can be achieved without significant hypoglycemia), and on the need for multidisciplinary care in pregnancy (diabetes expert, CDE, RD, RN, social worker, high-risk OB, eye provider, and other specialists as needed). Women with hypoglycemia unawareness will be given modified glycemic targets per ADA guidelines and the discretion of the clinical investigator. Women will be counseled on their individualized gestational weight gain goals based on guidelines from the Institute of Medicine and the American College of Gynecology, their body mass indices, lifestyle, and stage of pregnancy. They will be advised to contact the study team or study clinicians as needed to trouble shoot (e.g., for further pump adjustments, for re-training about using the 670G system, etc.) and to report AEs and SAEs throughout the duration of the study.

Women will be counseled on nutrition goals in pregnancy and will be given personalized carbohydrate goals prior to training. Table 1 provides general guidelines for appropriate gestational weight gain and changes to caloric intake based on pre-pregnancy body mass index and stage of pregnancy, however modifications will be made based on each woman's individual situation. For example, women who are avid exercisers may have increased caloric intake goals. Guidelines are based on singleton pregnancies. Women will be given a dietary guidelines sheet describing general nutrition goals in pregnancies complicated by diabetes and their personalized goals (see appendix). Women will be asked to record all their food and beverage intake for 3 days (at least one weekday and at least one weekend day) at baseline (during the run-in phase and once each trimester). Training will include instructions for recommended infusion set changes with the appropriate time intervals and insulin reservoir fills per the relevant insulin and device labels, with set changes to be done according to the appropriate label or more frequently (if required). While in the SAPT mode, the suspend on low and suspend before low features will be disabled for the remainder or study. Women will be instructed to self-monitor blood glucose per standard of care in terms of sites allowed for sampling and frequency of checks. Women will be instructed to provide post-meal corrections as necessary, per standard of care.

Table 1: Guidelines for Weight Gain and Changes to Caloric Intake throughout Pregnancy*

Pre-Pregnancy Weight Status and BMI (kg/m^2)	1st Trimester		2nd Trimester		3rd Trimester		Total Pregnancy Weight Gain (pounds)
	Weight Gain per Week (pounds)	Additional Calories per Day (kcal)	Weight Gain per Week (pounds)	Additional Calories per Day (kcal)	Weight Gain per Week (pounds)	Additional Calories per Day (kcal)	
Underweight <18.5	1.0-1.3	100-200	1.0-1.3	300-400	1.0-1.3	300-500	28-40
Normal 18.5-24.9	0.8-1.0	0-100	0.8-1.0	200-300	0.8-1.0	300-450	25-35
Overweight 25-29.9	0.3-0.5	0	0.5-0.7	150-200	0.5-0.7	200-350	15-25
Obese >30	0.0-0.3	0	0.4-0.6	100-200	0.4-0.6	200-300	11-20

Abbreviations: BMI, body mass index.
*Based on recommendations by the Institutes of Medicine and the American College of Obstetricians and Gynecologists[46, 47].

At the beginning of the 2nd trimester, women will be randomized to HCL therapy or SAPT. Women who were on multiple daily injections at baseline will complete a minimum of 4 weeks of therapy in SAPT mode prior to being randomized. All women in the HCL arm will be trained on the HCL technology. For the first 2 weeks after training, women will be contacted daily for insulin adjustments (if applicable) and trouble-shooting of device wearing. Frequency of insulin adjustments will be guided by glucose levels, level of insulin resistance, and willingness to contact study staff to ask for assistance, where (in general) women with a larger-than-expected number of glucose levels above or below ADA targets, dramatic insulin resistance, and unwilling to proactively contact study staff for assistance will be contacted more frequently for pump follow-up and adjustments as necessary. For the HCL group, insulin adjustments will be changes to carbohydrate-to-insulin doses and/or active insulin time. For the SAPT group, insulin adjustments will be changes to basal rates, carbohydrate-to-insulin doses, correction factors, and/or active insulin time. The first 5 women in each arm of the study will be asked to complete 7-point profiles for 2 weeks after randomization. Women will attend research and clinic visits at the Barbara Davis Center and Ohio State University every 4 weeks for routine diabetes care in pregnancy, downloading of study devices, and outcomes measurements. CGM, glucose meter, and pump downloads will also be reviewed throughout the study to ensure compliance with treatment assignment and the study protocol. Insulin pump adjustments will be made at least once every 4 weeks at face-to-face clinic/research visits and every week in between face-to-face visits, as per routine clinical care. When recommendations for pump adjustments are made during the interim weekly remote monitoring, we will verify that participants correctly entered the new settings. Acceptable forms of verification will include, verbal or written confirmation of new pump settings by the participant, a new upload of settings in CareLink, sending screen shots or pictures of the new settings from the participant's pump. Women will be contacted every week in between research visits to inquire about open- and closed-loop wear (HCL group) and for pump adjustments as needed (both groups) (See Table 2 and Figure 2). As per routine clinical care, we will recommend that women start low-dose aspirin therapy (81-162 mg orally daily) between 12 and 16 weeks gestations, to reduce the risk of preeclampsia, unless there is a contraindication to aspirin therapy[48]. At the start of the 2nd and 3rd trimesters, women will be given handouts describing conditions of which they should be aware for that trimester (see appendix).

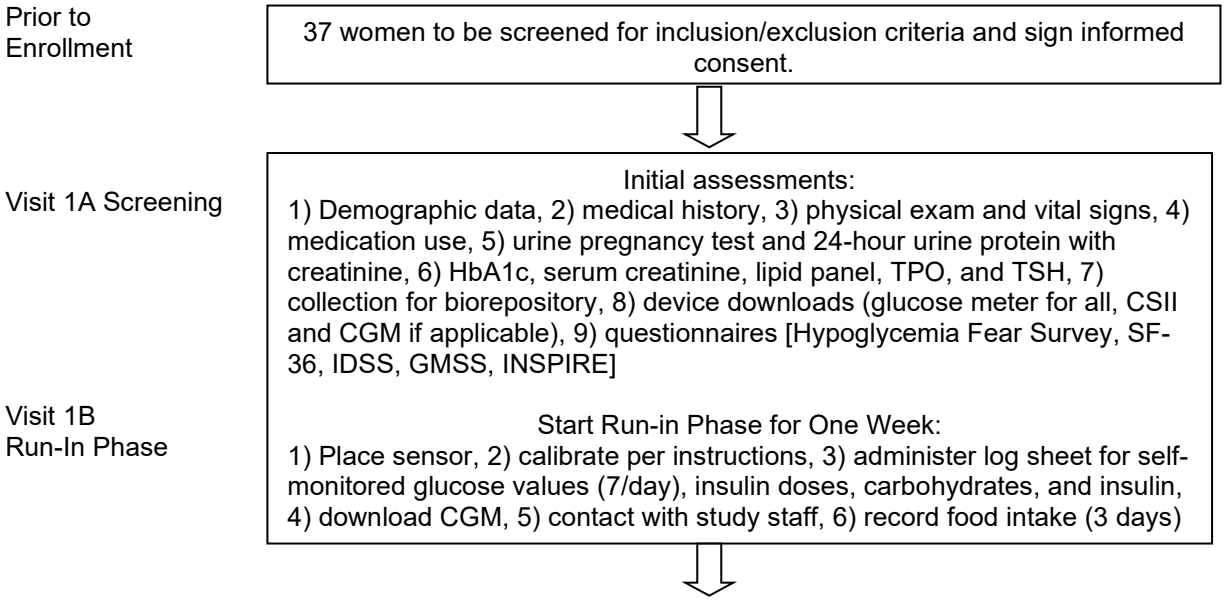
Table 2: Study Procedures for Subjects

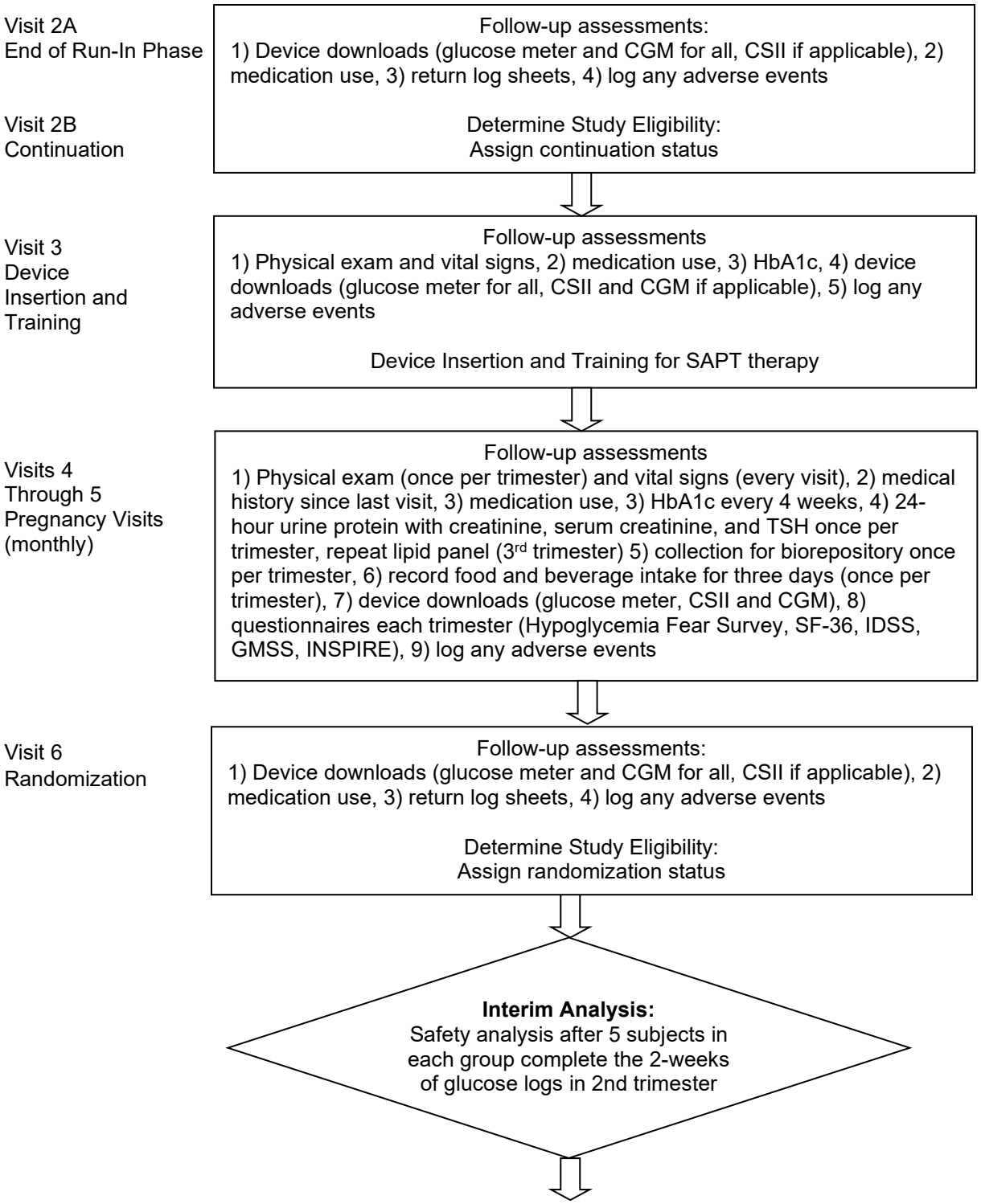
Visit‡	1	2	3	4-5	6	7-14	15	16
Study Week^	**0-1**	**1**	**1-5**	**3-9**	**5-11**	**7-36**	**30-32**	**36-42**
Informed Consent and Eligibility Criteria for Run-in Phase	X							
Urine or Blood Pregnancy Test, Demographic Data, Medical History	X							
CGM sensor insertion, use, and log sheets (Run-In Phase)	X							
Eligibility Criteria for Continuation		X						
Device insertion, training, insulin adjustments daily			X (SAPT)		X (HCL)		X	
Randomization (HCL and SAPT)					X			

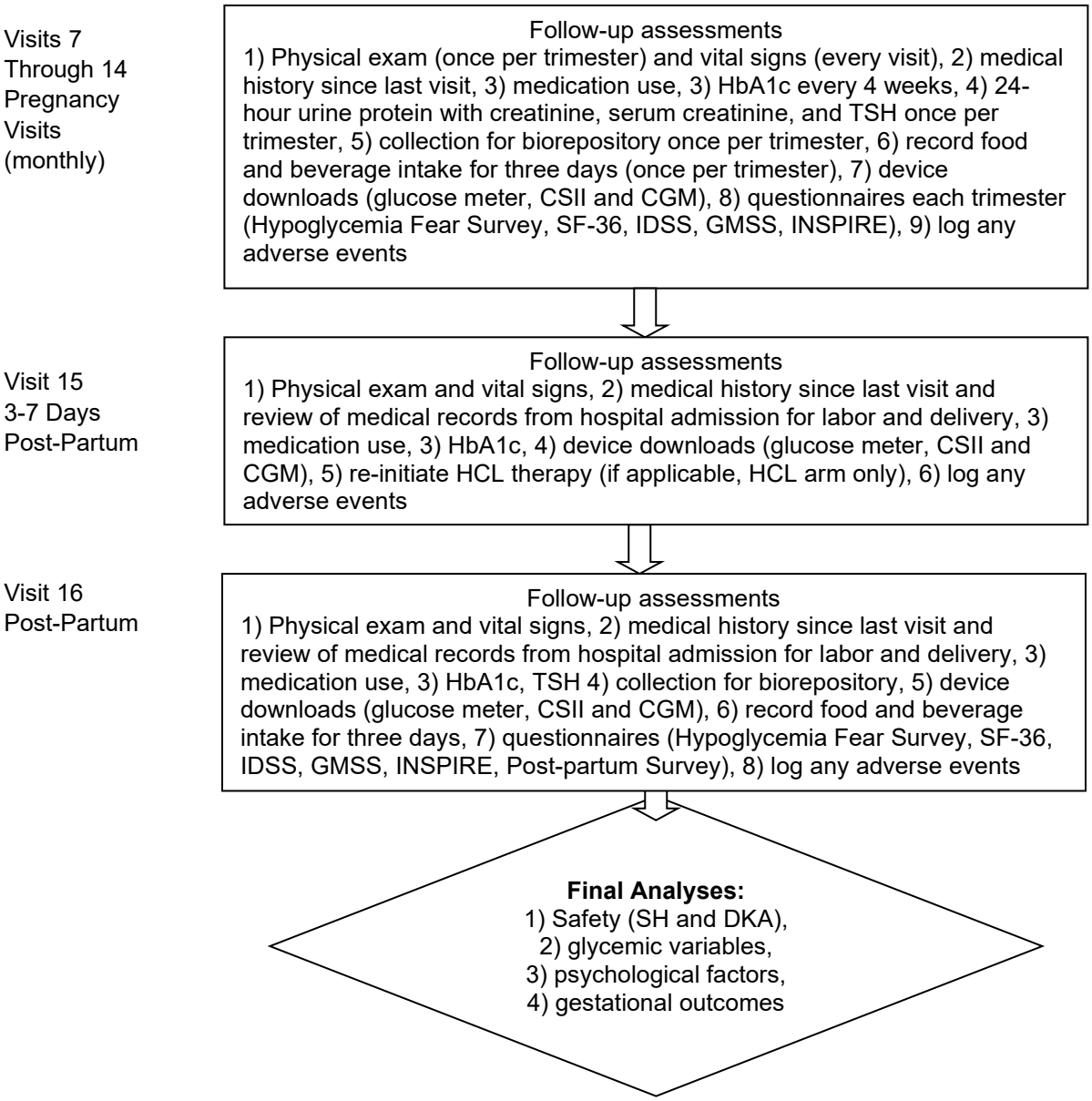
Device wearing, pump adjustments and mode (open vs closed) weekly				X (SAPT)	X	X	X	X
Concomitant Medications and Adverse Events	X	X	X	X	X	X	X	X
Hemoglobin A1C	X		X	X	X	X	X	X
Vital Signs, Height, Weight, Physical Exam*	X		X	X		X	X	X
Lab tests† (A1C, creatinine, 24-hour urine protein with creatinine, cholesterol panel, TSH, TPO)	X				X*	X*		X
Serum, plasma, and urine collection for biorepository	X		X*	X*	X	X*		X
Glucose Meter, Insulin Pump, and CGM Downloads	X	X	X	X	X	X	X	X
Questionnaires (Hypoglycemic Fear, SF-36, IDSS, GMSS, INSPIRE^^, Post-partum)	X			X*		X*		X**

‡ Visit may take place virtually by phone or Zoom, if an in-person visit is not possible. Participant will download devices remotely. Laboratory assessments can be collected by study site at a different time or can performed at commercial labs for virtual visits. Biorepository specimens can be collected at a different time or may not be collected for virtual visits. Physical assessments will not be performed at virtual visits.
^ Study week from visit 2 onwards depends on gestational age at enrollment, training period of 2-4 weeks for SAPT depending on mode of insulin delivery at baseline, completion of 4 weeks of SAPT training for MDI patients prior to randomization, weeks remaining in 1st trimester prior to randomization, and date of delivery.
* Once per trimester.
† Not all tests performed at each visit.
^^ SAPT and HCL arms at baseline, but after randomization HCL arm only.
** The only time point for the post-partum questionnaire.

Figure 2: Study Design Scheme and Timelines




Visit 2A
End of Run-In Phase
Visit 2B
Continuation
Follow-up assessments:
1) Device downloads (glucose meter and CGM for all, CSII if applicable), 2) medication use, 3) return log sheets, 4) log any adverse events
Determine Study Eligibility:
Assign continuation status
Visit 3
Device
Insertion and
Training
Follow-up assessments
1) Physical exam and vital signs, 2) medication use, 3) HbA1c, 4) device downloads (glucose meter for all, CSII and CGM if applicable), 5) log any adverse events
Device Insertion and Training for SAPT therapy
Visits 4
Through 5
Pregnancy Visits
(monthly)
Follow-up assessments
1) Physical exam (once per trimester) and vital signs (every visit), 2) medical history since last visit, 3) medication use, 3) HbA1c every 4 weeks, 4) 24-hour urine protein with creatinine, serum creatinine, and TSH once per trimester, repeat lipid panel (3rd trimester) 5) collection for biorepository once per trimester, 6) record food and beverage intake for three days (once per trimester), 7) device downloads (glucose meter, CSII and CGM), 8) questionnaires each trimester (Hypoglycemia Fear Survey, SF-36, IDSS, GMSS, INSPIRE), 9) log any adverse events
Visit 6
Randomization
Follow-up assessments:
1) Device downloads (glucose meter and CGM for all, CSII if applicable), 2) medication use, 3) return log sheets, 4) log any adverse events
Determine Study Eligibility:
Assign randomization status
Interim Analysis:
Safety analysis after 5 subjects in each group complete the 2-weeks of glucose logs in 2nd trimester



Study Device: The Medtronic 670G insulin pump with Medtronic Guardian® 3 Sensor and Contour® Next Link blood glucose meter (Medtronic, Northridge, CA) has 2 modes: open (manual) and closed (auto). The research team will set the necessary parameters for open mode (basal rates, glucose targets, active insulin time, carbohydrate-to-insulin ratios, and correction [sensitivity] factors) at baseline and throughout the study period. For closed mode, the team will set the active insulin time and carbohydrate-to-insulin ratios. The HCL system requires multiple days of data from open mode to personalize HCL control parameters in closed mode, therefore subjects will be started in open mode and transitioned to closed mode after 5 days. The HCL system algorithm utilizes sensor glucose to deliver microboluses every 5 minutes to achieve the target glucose level. The glucose target is fixed at 120 mg/dL but one can temporarily set the glucose target to 150 mg/dL for exercise. The closed mode requires calibrations (optimally 3-4 times daily) and announcements for carbohydrate consumption and exercise. Participants will be

counseled that finger stick blood glucose values must be checked and used for pre-meal and correction insulin boluses. Participants will be counseled that should they experience symptoms of hypoglycemia or hyperglycemia, then should confirm with a finger stick blood glucose measurement and treat according to the value obtained. Patients can stop closed mode therapy at any time and will be given specific instructions on when this is appropriate. The system exits open mode for a variety of reasons (e.g., lost sensor signal, persistent glucose readings below or above predesignated limits, pump occlusions, insulin delivery rates persistently below or above predesignated limits), which can be recorded. These parameters have been well-described in previous studies[19, 49, 50]. For this study, glucose targets will be set at 80-100 mg/dL during the day and 90-110 mg/dL over night for both arms of the study during pregnancy. Bolus targets will be set at 90-120 mg/dL during the day and 100-130 mg/dL over night in the post-partum period.

Subject Selection and Recruitment:

Inclusion/Exclusion Criteria: Inclusion criteria will be women with T1D, pregnant within the first 11 weeks of gestation, 18 – 45 years of age, diabetes duration >1 year, using MDI or CSII therapy, willingness to routinely check at least 3-8 blood glucose measurements per day, ability and willingness to receive routine and specialty obstetric care throughout the course of the study, ability and willingness to adhere to the protocol including scheduled study visits for the duration of the pregnancy and early post-partum period, A1C 5.5 – 9%, willing to participate in the run-in phase and full study (if eligible), and able to speak, read, and write English. Exclusion criteria will be women with T2D, gestational diabetes, or other type of diabetes (e.g., MODY), pregnancy beyond gestational week 11 or higher, age <18 years, age >45 years, T1D duration <1 year, screening A1C <5.5% or >9%, use of basal insulin alone, use of bolus insulin alone, extensive skin changes/diseases that inhibit wearing an infusion set, insulin pod, or sensor on normal skin, known severe allergic reaction to device adhesives within the last 3 months, unwillingness to use an insulin pump with tubing, unwillingness to be randomized to study group, unwillingness to switch from MDI to CSII and CGM use (if applicable), unwillingness to switch from MDI or to change from current insulin pump to HCL system (if applicable), severe hypoglycemic episode requiring the assistance of a 3rd party within the last 6 months, non-compliance with run-in phase, inadequate access to a phone and computer (for downloading devices and web-based communications), intention to move out of state within the next year, a multiple pregnancy (2 or more fetuses), and any other condition determined by the PI which could make the subject unsuitable for the trial or impairs the validity of the informed consent.

Insulin Pump Adjustments throughout the Study:

Insulin pump adjustments will be made weekly based on routine clinical care for both the SAPT and HCL arms of the study. The following conditions will encompass unusual situations or study-specific conditions and how to address the insulin pump settings for each condition, in order to ensure that procedures are similar between the two study sites.

There are times when women in the HCL arm will be unable to deliver an adequate insulin bolus using auto mode. Thus, they will be instructed to put in “fake carbohydrates” under these conditions, this means that they will administer a bolus putting carbohydrates into the pump even though they do not intend to consume these carbohydrates. Subjects will be asked to mark these episodes as “other” in the event marker of the insulin pump so that they can be identified. These conditions and their justifications are outlined in Table 3.

Table 3 Conditions for Administering "Fake Carbohydrates" in Auto Mode

Condition	Justification	Amount of Fake Carbohydrates*
Caffeine intake^	Caffeine can increase blood glucose levels by increasing hepatic glucose production, decreasing glucose uptake in skeletal muscle, and increasing glucose counter-regulatory hormone secretion[51]	Start: 10 grams per cup Range: 5-15 grams per cup
Glucose level of ≥135 mg/dL over night	Corrections for hyperglycemia with a bolus while in auto mode are determined by the pump and will always target a sensor glucose level of 150 mg/dL (though the automated basal target glucose remains 120 mg/dL), thus automated corrections for mildly elevated glucose are often very small or even nothing.	Start: 5 grams Range: 2-20 grams
Post-prandial glucose ≥200 mg/dL and no advised correction bolus^^	An individual can put in a blood glucose measurement into the pump while in auto mode and ask to give a bolus of insulin to correct hyperglycemia, but sometimes the pump will not advise a bolus (e.g., active insulin on board). It may thus be necessary to provide an extra bolus to amend the hyperglycemia more quickly.	Start: 10 grams Range: 5-20 grams
Exercise that increases glucose to ≥180 mg/dL^	Anaerobic exercise can raise blood glucose levels in some individuals because of metabolites that restrict glucose disposal and increases in glucose counter-regulatory hormones[52]. Auto mode will automatically increase micro-bolus insulin administration, but it may not be done rapidly enough to mitigate hyperglycemia.	Start: 5 grams Range: 2-20 grams

*Exact amount to be determined by subject's individual response to carbohydrate amount. If deemed safe by the investigator, subjects will be instructed to start with the amount denoted by "start" but the amount will be lowered or raised based on the individual response within the "range" indicated. If the starting amount is thought to be too aggressive, the investigator may recommend a different amount that is within the "Range" indicated above and alter as needed.
^Applicable for both SAPT and HCL therapy.
^^Subjects will be advised that timing should be 1-2 hours after a meal and should not be repeated for 2 hours afterwards. If the reason for the hyperglycemia was under-estimation of carbohydrates, then subjects should bolus for half the amount of carbohydrates missed because the automated basal likely increased basal insulin already in efforts to mitigate the hyperglycemia.

In the event of consumption of a high-fat/high-carbohydrate meal, like pizza or Mexican food, subjects will be instructed to divide the amount of the carbohydrate load into two boluses. The first carbohydrate bolus will be 50% ± 15% of the entire bolus, and the second carbohydrate bolus will be 50 ± 15% of the entire bolus administered 1-2 hours later, per the discretion of the study clinician. The distribution of the bolus for the first and second carbohydrate loads can be altered based on each subject's individual response to the meal. This mimics a "dual-wave bolus" that can be utilized in manual mode, which is an automated split bolus administered by the pump for certain meal conditions. While consumption of these types of meals will be discouraged in this population, this study does not provide food/drink to subjects. Thus, parameters for appropriate glucose management in real-world settings are important.

For subjects in the HCL arm in auto mode, the targeted glucose value is 120 mg/dL with the insulin pump algorithm. However, subjects may temporarily raise the target to 150 mg/dL using the "temp target" function of the pump for a pre-determined amount of time. Conditions for using temp target and parameters of use are outlined in Table 4.

Table 4: Conditions for Entering "Temp Target" in Auto Mode

Condition	Justification	Duration of Use*
Exercise	Aerobic exercise causes blood glucose concentrations to fall in most people with type 1 diabetes[52]. While auto mode will automatically reduce micro-bolus insulin administration if sensor glucose values fall, it cannot take away active insulin from the circulation and thus may not act quickly enough to prevent hypoglycemia.	Start up to 60 minutes prior to activity, continue throughout exercise bout, stop up to 2 hours after exercise.
Impending hypoglycemia (glucose ≤70 mg/dL)	Auto mode will automatically reduce or shut off micro-bolus insulin delivery when hypoglycemia is predicted, however it cannot take away active insulin from the circulation and thus may not act quickly enough to prevent hypoglycemia. In the event that it is still delivering insulin, engaging "temp target" will reduce the amount of insulin delivered. In the event that insulin has been shut off, then engaging "temp target" for a prolonged period will allow micro-boluses to be smaller when automatic delivery resumes.	If sensor or blood glucose is 101-120 mg/dL and sensor glucose is trending down, start for 30 minutes. If sensor or blood glucose is <100 mg/dL and sensor glucose is trending down, start for 45 minutes.
Hypoglycemia (glucose ≤70 mg/dL) for more than 15 minutes	Auto mode does significantly reduce time spent in the hypoglycemic range in studies of non-pregnant populations[19], but hypoglycemia may still occur. In the event that this occurs, subjects will be instructed to confirm with a blood glucose measurement, consume carbohydrates, and start a temp target. Engaging "temp target" for a prolonged period will allow micro-boluses to be smaller when automatic delivery resumes.	If blood glucose level is <50 mg/dL, start for 30 minutes. If blood glucose level is 51-69 mg/dL, start for 15 minutes.

*Exact duration to be determined by subject's individual responses for each condition.

Exercise is encouraged in pregnant women with diabetes[5], however it may induce hypoglycemia or hyperglycemia[52]. Subjects will be asked to mark exercise at the start and stop of each exercise bout using the "exercise" marker in the pump, regardless of study arm (SAPT or HCL), throughout the study. Subjects in the HCL arm may additionally require the use of the temp target for exercise-induced hypoglycemia (see Table 4) or administration of "fake carbohydrates" for exercise-induced hyperglycemia (see Table 3). Subjects in the SAPT arm may use a "temp basal" mode for exercise. "Temp basal" is a mode wherein a user can tell the insulin pump to administer more or less insulin for a pre-determined amount of time. Subjects who experience exercise-induced hypoglycemia will be instructed to start a temp basal rate of 50% less insulin 30 minutes prior to activity, continue it for the duration of activity, and 1 hour afterwards. Based on an individual's response, she will be instructed to change the amount within the range of 10 to 100% less insulin, pre-exercise duration 15-60 minutes, and post-exercise duration 0-2 hours. Subjects who experience exercise-induced hyperglycemia will be instructed to start a temp basal rate of 20% more insulin at the start of activity, continue it for the duration of activity, and stop it at the end of activity. Based on an individual's response, she will be

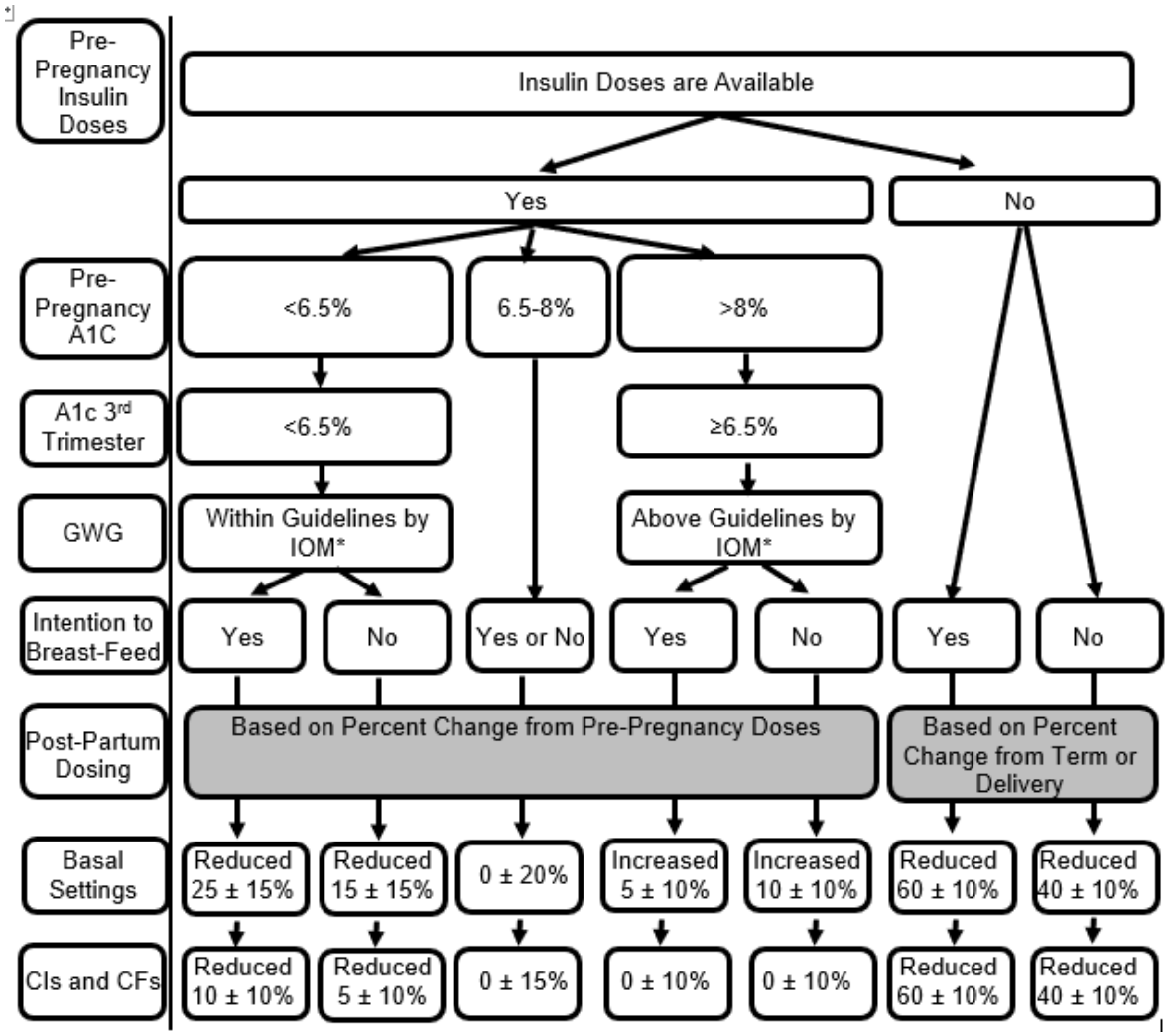
instructed to change the amount within the range of 10 to 50% less more, pre-exercise duration 0-30 minutes, and post-exercise duration 0-1 hour.

As preterm deliveries are common among pregnant women with diabetes[1-4], between 30 and 33 weeks gestation women will be given an instruction sheet detailing how to manage their insulin pumps during labor and delivery, goals for glucose management during labor and delivery, and post-partum doses and instructions (see appendix). The study staff will provide the same instructions sheets to each woman's obstetric team. We will also discuss with women their intended plan for post-study insulin delivery and glucose monitoring. Should they choose to continue therapy with a new insulin pump or glucose monitoring system, based on personal preference and health insurance coverage, we will work them to initiate paperwork for the new devices around the time of labor and delivery. They will be given instructions for transitioning to the post-study mode of insulin delivery and new glucose monitoring system (if applicable) at the final study visit. Women randomized to HCL therapy will be instructed to switch from auto mode to manual mode (until they contact the study clinician) if they are given high-dose steroids, such as betamethasone, to induce fetal lung maturation. Women in either the SAPT or HCL arms of the study will be advised to contact the study provider for instructions on pump adjustments to reduce steroid-induced hyperglycemia. The study clinician will determine when auto mode should be re-started based on the relative stability of glucose levels following steroid administration.

Women will be instructed to use manual mode for labor and delivery and until post-partum insulin sensitivity stabilizes in the immediately post-partum period. Women in the SAPT arm will remain in manual mode throughout the hospital admission if the hospital protocol allows it. Women in the HCL arm will switch to and then remain in manual mode throughout the hospital admission if the hospital protocol allows it. Women will return to clinic (or have a visit remotely by phone or Zoom) between 3 and 7 days post-partum: (1) for review of CGM, glucose meter, and pump downloads, (2) for pump adjustments to be made per the discretion of the clinical investigator, and (3) to re-initiate auto mode for women in the HCL arm per the discretion of the clinical investigator.

The study MD or PA will examine each woman's glucose control prior to conception, during conception, and throughout pregnancy, along with A1C in the 3rd trimester, amount of gestational weight gain, and intention to breastfeed to determine the post-partum dosing. Breastfeeding often induces hypoglycemia[32], thus post-partum dosing will be lower for women intending to breastfeed. Because numerous clinical factors are taken into account, post-partum dosing must be individualized for each women based on the basic parameters described above and the clinical judgement of the provider. Thus, Table 4 describes basic conditions with general guidelines for post-partum pump recommendations based on changes from pre-pregnancy (or first trimester insulin pump settings, if known). If the pre-pregnancy pump settings are unknown, pump settings from term or delivery will be reduced 50-70% for the post-partum settings, with more aggressive changes in women who are intending to breastfeed. Active insulin time ranges for each individual, but typically ranges from 3-4 hours. The post-partum active insulin time recommended will be 3:15 hours ± 15 minutes (HCL group) and 3:45 hours ± 15 minutes (SAPT), per the provider's clinical judgement. We will recommend blood glucose targets over 90-120 mg/dL during the day and 100-130 mg/dL over night for the post-partum doses.

Figure 3: Conditions with General Guidelines for Post-Partum Pump Dosing (Changes noted from pre-pregnancy settings, if known)



Abbreviations: CFs, correction factors; CIs, carbohydrate-to-insulin ratios; IOM, Institute of Medicine

*IOM guidelines for weight gain during pregnancy based on maternal body mass index[46]

Hemoglobin A1C will be measured every 4 weeks in pregnancy and 4-6 weeks post-partum. The A1C measurements will be those used for clinical point of care at each site. These assays are DCCT aligned for both sites. Routine blood and urine tests will be performed in all subjects in each trimester (see Table 2), and serum, plasma, and urine samples will be collected and stored at -80 degrees as a biorepository for future assays. The Hypoglycemia Fear Questionnaire[24], Insulin Delivery Satisfaction Survey[26], Glucose Monitoring Satisfaction Survey[27], INSPIRE Questionnaire (HCL only)[28], and Medical Outcomes Study (MOS) Short Form-36 (SF-36)[25] will be administered at baseline, once every trimester (6-8 weeks, 18-20 weeks, 30-32 weeks) and 4-6 weeks post-partum. We will screen for diabetes complications at baseline, once per trimester, and post-partum. Women will be administered a questionnaire inquiring about breastfeeding at their final post-partum visit. We will request records of the hospital admission at delivery to collect data about maternal and fetal outcomes. Should subjects experience emotional distress during the pregnancy or post-partum period, a licensed clinical psychologist will provide

them with resources for therapy either at the Barbara Davis Center or closer to where they live per subject preference.

We will assess safety of HCL therapy by collecting data about episodes of SH requiring the assistance of a 3rd party and time spent <54 mg/dL (SH range), DKA, and skin reactions throughout the study. After the first 5 participants in each group complete 2 weeks of therapy after randomization, we will analyze interim data to compare SMBG measurements for time in the American Diabetes Association's recommended pregnancy target ranges (fasting <95 mg/dL and 2-hour post-prandial <120 mg/dL) and compare groups (see Table 2). Bedtime values will be considered post-prandial if they are within 2 hours of a meal ± 30 minutes but will be considered fasting (pre-meal) if they are >3.5 hours after a meal. If the average fasting blood glucose levels are 20% higher and the average 2-hour post-prandial values are 20% higher in the HCL arm compared to the SAPT arm, this would be considered worsening of glycemic control in the HCL arm. In the event that these interim analyses demonstrate worsening of glycemic control in the HCL arm, the study would be suspended until further investigation into the safety of the participants is undertaken. After the first 5 participants in each group have completed the 2nd trimester, we will analyze the interim data and compare episodes of SH between groups to ensure no increased risk of SH with HCL therapy (see Table 1). Episodes of SH will be used for the interim analysis as SH events can be life-threatening for pregnant women and their fetuses.

Virtual (Remote) Visits: For the duration of the study, in-person visits are the preferred mode of conducting study visits. However, in the event that a study visit cannot take place in-person, a virtual visit by phone or a HIPAA-compliant video platform (e.g., Zoom) will be accepted. Examples of reasons why a virtual visit may be required include, but are not limited to, a participant or a research staff member has a confirmed or suspected COVID-19 infection, a participant or research staff member is required to quarantine for COVID-19 infection or exposure to someone with a COVID-19 infection, participant is required to be on bed rest per instructions of a medical provider (e.g., obstetrician), and weather conditions prohibit safe travel to the study site (e.g., snow storm). The mode of study visit should be noted. Participants will be required to upload study devices to CareLink for each virtual study visit. Vital signs will not be performed. A physical exam, if required for that study visit, will not be performed. Laboratory assessments can be performed at the study site at a different time or at a commercial lab. A commercial laboratory assessment will be noted as a protocol deviation. Laboratory assessments collected out of the study window time frame will be considered protocol deviations. Biorepository samples will either be collected at the study site at a different time or will not be collected for that study visit (if required). As biorepository collections are optional procedures, if the specimens are not collected they will be considered missed samples and will not be considered as protocol deviations. Study supplies can be picked up at the study site by the participant at a different time or will be mailed to the participant. In the event that handouts are due to be given to the participant at the time of the study visit, they can be e-mailed or sent in the mail to the participant per her preference.

Data Collection and Analyses: All glycemic data will be collected at each study visit. All other data will be collected at enrollment, 1st trimester (6-8 weeks gestation), 2nd trimester (18-20 weeks gestation), 3rd trimester (30-32 weeks gestation), and post-partum (4-6 weeks after delivery) except where otherwise indicated. Subjects enrolled between 8 weeks 1 day gestation and 11 weeks gestation who continue in the study after the run-in phase, will be allowed to complete the 1st trimester study assessments at the completion

of the run-in phase (outside the 6-8 week gestational time point). Each category of data and the pertinent specific aim (SA) to which it applies are outlined below.

(1) Screening (enrollment only): We will screen subjects with a history, physical exam, and urine or blood pregnancy test. Gestational age will be calculated based on the last menstrual period (or by viewing records of a uterine ultrasound). Subjects meeting inclusion/exclusion criteria will be invited to participate in the run-in phase. In our experience most women present to their diabetes provider for care during pregnancy prior to getting an ultrasound with an obstetrician. Eight to 11 weeks is the time frame when ultrasound dating is most accurate, but in our previous study 76.7% (33/43) of women presented prior to 8 weeks gestation. Thus, the LMP will be used for determining initial eligibility based on inclusion/exclusion criteria. Once an ultrasound is obtained, it will be used to determine the final gestational ages for each study visit.

(2) Run-in Phase: Subjects will wear the Medtronic Guardian CGM sensor continuously for 7 consecutive days. Subjects will calibrate per device instructions. Subjects will record self-monitoring blood glucose (SMBG) measurements (before meals, 2 hours after meals, and at bedtime), insulin doses, carbohydrate intake, and exercise on standardized log sheets. Subjects will be asked to download devices (glucose meter, insulin pump, and CGM) once during the run-in phase. The research staff will contact each subject after 2 days to ensure that they have access to communication methods in between research visits. Subjects will fill out a questionnaire about adverse reactions to device adhesives and wearing, as well as willingness to proceed further in the study.

(3) Safety Factors (SA 1): Subjects will be asked at each visit if they had any episodes of SH requiring the assistance of a 3rd party, DKA, adverse skin reactions, or hospitalizations since the last study visit. DKA in pregnancy will be defined as positive symptoms (nausea, vomiting, malaise, polyuria, polydipsia, abdominal pain, change in mental status) with positive laboratory findings (glucose >300 mg/dL, arterial pH <7.3, anion gap >12 mEq/L, elevated blood or urine ketone levels, serum bicarbonate <15 mEq/L) or medical documentation of DKA by a healthcare facility. Subjects will be instructed to contact study staff immediately should any of these events occur in between study visits. We will request records of any urgent care visits, emergency room visits, and hospital admissions that occurred. Time spent <54 mg/dL (SH range) will be collected through CGM data.

(4) Glycemic Factors (SA 2): Insulin pumps, glucose meters, and CGMs will be downloaded at each visit. Data collected will be used to calculate percent of time spent in glucose ranges (hypoglycemic: <54 and <63; in range: 63-140 (per recommendations from the International Consensus on Time in Range[53]); hyperglycemic: >140, and >180 mg/dL), mean glucose ± standard deviation, J index, High Blood Glucose Index (HBGI), Low Blood Glucose Index (LBGI), duration of hypoglycemic episodes, Mean Amplitude of Glycemic Excursions (MAGE), and Continuous Overall Net Glycemic Action ($CONGA_n$). Subjects will download from study devices weekly from home using CareLink® Clinical Software. At study visits and weekly in between study visits, subjects will provide data on frequency and duration of open-mode and closed-loop HCL mode. Data will be confirmed through HCL pump downloads, along with the reasons HCL mode was exited.

(5) Psychological Factors (SA 2 and 3):

(a) Fear of hypoglycemia: We will measure fear with the Hypoglycemia Fear Survey[24] which is a psychometric instrument wherein subjects rank frequency of 10 behaviors and 17 worries based on a 5-point Likert scale.
(b) Quality of life (QOL): We will measure QOL over the past 4 weeks with the MOS Short-Form 36 (SF-36)[25] which uses a multi-item scale from 36 questions to assess 8 health concepts (physical functioning, physical role, emotional role, pain, general health, vitality, social functioning, and emotional well-being)[54].
(c) Device acceptability: We will measure HCL and SAPT device acceptability with the Insulin Delivery Satisfaction Survey (IDSS)[26] and the Glucose Monitoring Satisfaction Survey (GMSS)[27] in both the SAPT and HCL arms of the PICLS Study. The IDSS provides a 14-item questionnaire for people with T1D to assess patient attitudes and perspectives about insulin-related devices. The IDSS provides a total score, as well as subscales related to devices being effective, burdensome, and inconvenient[26]. The GMSS asks 15 questions about glucose monitoring device satisfaction and provides a total score and subscales related to device openness, emotional burden, behavioral burden, and trust[27]. We will measure HCL device acceptability with the INSPIRE Questionnaire[28]. The INSPIRE Questionnaire provides a 22-item questionnaire for people with diabetes to assess patient thoughts and feelings specifically about how automated insulin delivery systems, such as HCL therapy, affect their worries/concerns, burdens, and management of diabetes[28].

(6) Maternal and Fetal Outcomes (SA 4): We will administer a survey we previously developed for the CGM pregnancy study in the preliminary data section. It inquires about breastfeeding. We will obtain records of the hospital admission at delivery for mother and baby to collect data about the labor and delivery process, maternal and fetal complications before and after delivery, baby's anthropometrics at birth (weight and length), and baby's age at delivery.

Data will be entered into REDCap (Research Electronic Data Capture). REDCap is an internal secure, computerized database system at the University of Colorado Denver. This system allows data entry, questionnaire building, data exportation to statistical packages, and is HIPAA compliant.

Data and Safety Monitoring Plan:

A Data Safety Monitoring Board (DSMB) with providers not connected with the study will oversee safety data throughout the study by convening once each quarter to review adverse events and severe adverse events. If after the first 6 months, the DSMB notes no increased harm from study participation then ongoing meetings will convene once every 6 months thereafter. It will also review stopping rules based on the number of SH events and other criteria as below (Table 5), either for an individual or for the total study group, and provide recommendations about study continuation.

This study's risks are minimized by use of extensive inclusion and exclusion criteria and close monitoring of research subjects. The key personnel are qualified and experienced in all of the study procedures. We will reduce the risk of severe hypoglycemia by setting a low glucose alarm of 80 mg/dL for women with hypoglycemia unawareness and 70 mg/dL for all other women, rather than relying on the mandatory 55 mg/dL low glucose alarm pre-set by the Medtronic 670G system. We will also ask each participant to keep an active glucagon kit if she already possesses one or to get an active glucagon kit if she does not have a kit or if it expired. Further, we will instruct all subjects in the HCL arm of the study that should they develop conditions that significantly reduce

insulin requirements, such as hyperemesis gravidarum, adrenal insufficiency, or placental insufficiency, that they should go into manual mode and contact the study provider for further instructions/pump adjustments. We will reduce the risk of DKA and excessive post-prandial glucose excursions by setting a high glucose alarm of 180 mg/dL for all women. We will also instruct subjects to contact the study provider if they have symptoms of DKA, elevated glucose that does not resolve with appropriate treatment, and moderate or severe ketones on testing.

The collaborators and consultants provide necessary expertise for ensuring the safety of subjects and the integrity of the study procedures. We will also use a volunteer Safety Officer to oversee the study's safety. The Safety Officer will be an independent investigator (not a member of the research team) with experience in similar clinical research. S/he will review reports of adverse events, recruitment and enrollment statistics (ethnicity and numbers of subjects disqualified, withdrawn, randomized, and who completed the study) every 6 months. This information will be reviewed during meetings with study investigators and recorded by the Safety Officer in meeting minutes.

Table 5: Stopping Rules for Individual Subjects and for the Study

	State of the Study	Conditions to Meet for Stopping Rules
Criteria for Individual Stopping Rules	Pre-Randomization	• Subject is unable to demonstrate safe use of the study CGM during the run-in phase, as judged by the investigator • Subject fails to demonstrate compliance with using the study CGM during the run-in phase, as defined in the protocol
	Pre- and Post-Randomization	• Significant protocol violation or non-compliance • Any severe hypoglycemic event related to the use of the HCL system* • Three severe hypoglycemic events from any cause • DKA unrelated to an infusion site failure and related to the use of the HCL system** • Two episodes of DKA regardless of the cause • Four pump occlusions • Decision by the investigator or the sponsor that termination of study participation is in the subject's best medical interest • Allergic reaction to insulin • Severe allergic reaction to adhesive surface of the infusion set or glucose sensor that prohibits further use of the HCL system
Criteria for Total Study Stopping Rules	Pre-Randomization	• Four subjects are unable to demonstrate safe use of the study CGM during the run-in phase, as judged by the investigator
	Pre- and Post-Randomization	• Seven severe hypoglycemic events in the total cohort in at least two different subjects • Four DKA episodes in at least two different subjects • Decision by the investigator or the sponsor that termination of study participation is in the subjects' best medical interest

Abbreviations: CGM, continuous glucose monitor; DKA, diabetic ketoacidosis; HCL, hybrid closed-loop.

* A severe hypoglycemic event related to the use of the HCL system refers to the following device deficiencies: CGM transmission failure of low sensor glucose values, an absence of low-glucose alarms when the low-alert function is turned on, or delivery of the maximum basal rate when the sensor glucose is falling that results in a severe hypoglycemic event.
** DKA unrelated to an infusion site failure and related to the use of the HCL system refers to the following device deficiencies: CGM transmission failure of high sensor glucose values, an absence of high-glucose alarms when the high-alert function is turned on, or delivery of the minimum basal rate when the sensor glucose is rising and there is adequate intake of carbohydrates by the research participant that results in a DKA event.

Device-related adverse events will be monitored and addressed promptly. These include:

1) a severe hypoglycemic event occurring from CGM transmission failure of low sensor glucose values (SAPT and HCL), an absence of low-glucose alarms when the low-alert function is turned on (SAPT and HCL), or delivery of the maximum basal rate when the sensor glucose is falling (HCL only).
2) hypoglycemia <54 mg/dL lasting >20 minutes that did not result in the need for 3rd party assistance but that occurred from CGM transmission failure of low sensor glucose values (SAPT and HCL), an absence of low-glucose alarms when the low-alert function is turned on (SAPT and HCL), or delivery of the maximum basal rate when the sensor glucose is falling (HCL only).
3) an episode of DKA unrelated to an infusion site failure and related to CGM transmission failure of high sensor glucose values (SAPT and HCL), an absence of high-glucose alarms when the high-alert function is turned on (SAPT and HCL), or delivery of the minimum basal rate when the sensor glucose is rising (HCL only) and there is adequate intake of carbohydrates by the research participant.
4) an episode of DKA related to the absence of an infusion site occlusion alarm (SAPT and HCL) and there is adequate intake of carbohydrates by the research participant.
5) hyperglycemia >300 mg/dL lasting >2 hours that did not result in DKA and was not from an infusion site failure but that occurred from CGM transmission failure of high sensor glucose values (SAPT and HCL), an absence of high-glucose alarms when the high-alert function is turned on (SAPT and HCL), or delivery of the minimum basal rate when the sensor glucose is rising (HCL only) and there is adequate intake of carbohydrates by the research participant.
6) hyperglycemia >300 mg/dL lasting >2 hours that did not result in DKA but that occurred from an infusion site failure and an absence of an infusion site occlusion alarm (SAPT and HCL) and there is adequate intake of carbohydrates by the research participant.

Should any of these criteria be met, the participant will be given the appropriate replacement device(s) (e.g., insulin pump, transmitter, or sensor). Participants in the HCL arm will be instructed to exit auto mode until replacement device(s) are provided and the malfunction is investigated.

A Data and Safety Monitoring Board (DSMB) will also be established and led by the Safety Officer. The DSMB will be comprised of the Safety Officer (from the University of Colorado), and additional faculty members from outside the BDC (Barbara Davis Center for Diabetes at the University of Colorado) or OSU (Ohio State University) who are selected by the JAEB Center for Health Research. The Juvenile Diabetes Research Foundation (JDRF) is funding this study. JDRF created an Artificial Pancreas Project

Consortium, where artificial pancreas projects include HCL therapy and closed-loop therapy, which is coordinated by the JAEB Center for Health Research. JAEB is an organization that conducts diabetes-related human clinical trials. This partnership allows investigators with artificial pancreas projects funded by JDRF to utilize resources from the JAEB Center for Health Research without added cost to the investigator. For this study, the JAEB Center for Health Research has provided feedback for the Investigational Device Exception application submitted to the Food and Drug Administration, feedback on the statistical analyses, and will work with the study PI and JDRF to form the DSMB. It will be notified immediately of severe adverse events (SAEs). It will review the details of the SAE and the study protocol to determine if the SAE was possibly, definitely, or not related to study procedures. It will advise the study PI of its determination and of corrective action that needs to take place (if at all). The DSMB will be notified of SAEs within 1 business day. They will review the details of the SAE and the study protocol to determine if the SAE was possibly, definitely, or not related to study procedures. It will advise the study PI of its determination and of corrective action that needs to take place (if at all). The study PI will manage and report the SAEs and adverse events (AEs) to the IRB. Additionally, the DSMB will conduct phone or video conference calls every quarter to every 6 months to review all the SAEs and AEs that have taken place. The DSMB will also review the planned interim analyses of data (severe hypoglycemic events) after the first trimester in the first 5 participants of each group.

There are study MDs at each study site who will closely oversee and monitor the study. The study PI will continually review all adverse events during screening, data collection, and insulin delivery with SAPT or HCL therapy. Subjects who fail screening will be informed of the reasons for failure. Adverse events will be reported to the Safety Officer as they occur for each individual occurrence and monthly in aggregate form, as well as documented by standard IRB procedures and reported to them during the annual protocol review. All serious adverse events will be immediately reported to the Safety Officer, COMIRB, OSU's IRB (if applicable), and JDRF using the COMIRB Serious Adverse Report Event (SAE) form. The PI will sign each SAE and include a copy of the signed consent form of the subject with relevant sections highlighted. Serious adverse events are defined as death, life threatening injuries, inpatient hospitalization (other than that related to planned labor and delivery), persistent or significant disability/incapacity, and congenital anomaly/birth defect. All serious adverse events determined by COMIRB to be definitely, probably, or possibly related to the study or intervention will be addressed by COMIRB as appropriate with actions including but not limited to: protocol modification, consent form modification, modification of the timetable for continuing review requirements, new study enrollment suspension, or study suspension or termination. If the study is suspended or terminated, prompt reporting to the JDRF will be provided. Events not requiring suspension or termination shall be reported during the annual progress report.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

Risks:

Wearing insulin infusion sets and sensors can cause adverse skin reactions such as pain at the site of infusion set or sensor insertion. The adhesive pads may cause skin erythema for 1 to 2 days or more. An allergic reaction to 1 or more parts of CSII and CGM devices may occur which can be mild, moderate, or severe (rare). In rare cases, an infection at the infusion set or sensor site may occur. In rare cases, the sensor or needle may break inside the body and would require a minor surgical procedure to remove it.

These risks are likely during the run-in phase, but individuals unable to wear devices will not continue on. We also screen out individuals with a history of serious skin reactions to adhesives. These issues remain possible as the study continues, but will be less likely in those women able to be randomized.

Severe hypoglycemia is defined as a hypoglycemic episode requiring assistance of a 3rd party or hospitalization with or without an SMBG. The risk of severe hypoglycemia is high in pregnancy, especially in the 1st trimester. It will be reported as a severe adverse event (SAE). A hypoglycemic event "requiring assistance" is determined when the subject is unable to treat the event on her own. We have determined our sample size based on the ability to compare rates of severe hypoglycemia between groups. Severe hypoglycemia can lead to coma, seizure, or death, however the likelihood of these extreme adverse events is low. Any untoward event resulting in hospitalization, extension of hospitalization, death, or threat of death will also be considered an SAE. SAEs will be reported to the Drug Safety Monitoring Board (DSMB).

Medtronic CGM systems may experience reduced sensor accuracy (falsely elevated glucose levels) if the user takes acetaminophen-containing products. The level of sensor glucose inaccuracy may vary by participant and may depend on the quantity of acetaminophen administered. Therefore, all participants will be advised to mark acetaminophen use on paper and in the insulin pump as an "Injection" event marker. They will also be advised to rely on fingerstick glucose measurements for 12 hours after acetaminophen use for insulin dosing.

Pregnancies complicated by diabetes are inherently high-risk for adverse outcomes such as fetal loss, gestational hypertensive disorders, congenital malformations, abnormal fetal size, cesarean delivery, neonatal jaundice, neonatal hypoglycemia, and the like. SAPT has been used in pregnancy in previous studies and does not appear to significantly increase these risks in most cases. We do not anticipate that the HCL therapy used in this study will significantly increase these risks either. A viable pregnancy is defined as a pregnancy with detectable blood or urine human chorionic gonadotropin (hCG) level and confirmation of a fetal heart beat by Doppler ultrasound. Fetal loss is defined as loss of a viable pregnancy.

There is a risk of a breach in confidentiality. Thus, a confidential subject database will be established to maintain study data. Data will be entered into REDCap (Research Electronic Data Capture). REDCap is an internal secure, computerized database system at the University of Colorado Denver. This system allows data entry, survey/questionnaire building, data exportation to statistical packages, and is HIPAA compliant. Each subject will be assigned an identification number, which will be used to code and identify all of that subject's records. This will avoid the continual use of subject names. REDCap surveys can be sent to study participants via e-mail for direct input into the database. All study data will be locked in the PIs' offices and all relevant computer study files will be input on staff computers, which are password protected and contain encryption software. Data storage will be take place on a secured server maintained by the University of Colorado. The server is backed up nightly and a copy of the back-up file is kept off site in a secure facility. Data access will be limited to study personnel. Study results may be presented in the form of posters, abstracts, oral presentations, or publications at academic meetings or in journals. In all forms of study result reporting, subject identification will not be disclosed. A study subject may access his/her protected health information at any time by requesting said information in writing of the investigator. The investigative team has been trained in IRB and HIPAA compliance issues and will maintain confidentiality and protect health information. The above-stated procedures have been highly effective in preventing

breaches of patient confidentiality for the prior and current research studies in which the PI has been and continues to be involved.

All AEs, reported spontaneously by the subject, as well as those noted by the investigator or study staff, regardless of seriousness, severity or expectedness will be recorded on source documents from the time of obtaining the informed consent.

Protection Against Risks:

Consenting Procedures:

Subjects will be recruited from the BDC and OSU diabetes clinics, which both contain experts in gestational diabetes care (site PIs). Some subjects may be referred to each center by maternal fetal medicine specialists who are aware of the study, but only the site PIs will be allowed to determine possible eligibility for study participation. Subjects will have to be patients at each center to be included in the study. Subjects meetings initial inclusion/exclusion criteria will be invited to sign informed consent. They will be taken to a private room where the consent form will be discussed with them in detail, they will be asked to state their understanding of the study procedures, and will be asked if they have any inquiries. All questions will be answered. If they do not feel comfortable to sign the consent form at that point, they will be allowed to take it home and re-read it, then contact us with any further questions and with their decision about enrollment. All subjects will be provided a copy of the signed consent form.

Site PIs will determine initial eligibility for study inclusion. They will go over the inclusion and exclusion criteria with each potential subject and discuss the study procedures with women interested in participating. Private consenting procedures will be performed by trained research staff (PIs or professional research assistants). Completed, signed consent forms will be kept in their original form by study staff and a copy will be provided to subjects. The date of consent procedure completion will be recorded in REDCap.

Safety Monitoring:

This study's risks are minimized by use of extensive inclusion and exclusion criteria and close monitoring of research subjects. The key personnel are qualified and experienced in all of the study procedures. The collaborators and consultants provide necessary expertise for ensuring the safety of subjects and the integrity of the study procedures. We will also use a volunteer Safety Officer to oversee the study's safety. The Safety Officer will be an independent investigator (not a member of the research team) with experience in similar clinical research. S/he will review reports of adverse events, recruitment and enrollment statistics (ethnicity and numbers of subjects disqualified, withdrawn, randomized, and who completed the study) every 6 months. This information will be reviewed during meetings with study investigators and recorded by the Safety Officer in meeting minutes. A Data and Safety Monitoring Board (DSMB) will also be established and led by the Safety Officer. The DSMB will be comprised of the Safety Officer (from the University of Colorado), and additional faculty members from outside the BDC or OSU who are selected by the JAEB Center for Health Research. It will be notified immediately of severe adverse events (SAEs). It will review the details of the SAE and the study protocol to determine if the SAE was possibly, definitely, or not related to study procedures. It will advise the study PI of its determination and of corrective action that needs to take place (if at all). The DSMB will be notified of SAEs within 1 business day. They will review the details of the SAE and the study protocol to determine if the SAE was possibly, definitely, or not related to study procedures. It will advise the study PI of its determination and of corrective action that needs to take place (if at all). The study PI will

manage and report the SAEs and AEs to the IRB. Study staff will also identify, evaluate, and report anticipated and unanticipated device-related AEs. Additionally, the DSMB will conduct phone or video conference calls every quarter to review all the SAEs and AEs that have taken place. The DSMB will also review the planned interim analyses of data (especially glucose <63 m/dL) after the first trimester in the first 5 participants of each group.

There are study MDs at each study site who will closely oversee and monitor the study. The study PI will continually review all adverse events during screening, data collection, and insulin delivery with SAPT or HCL therapy. Subjects who fail screening will be informed of the reasons for failure. Adverse events will be reported to the Safety Officer as they occur for each individual occurrence and monthly in aggregate form, as well as documented by standard IRB procedures and reported to them during the annual protocol review. All serious adverse events will be immediately reported to the Safety Officer, COMIRB, and OSU's IRB (if applicable) using the COMIRB Serious Adverse Report Event (SAE) form. The PI will sign each SAE and include a copy of the signed consent form of the subject with relevant sections highlighted. Serious adverse events are defined as death, life threatening injuries, inpatient hospitalization (other than that related to planned labor and delivery), persistent or significant disability/incapacity, and congenital anomaly/birth defect. All serious adverse events determined by COMIRB to be definitely, probably, or possibly related to the study or intervention will be addressed by COMIRB as appropriate with actions including but not limited to: protocol modification, consent form modification, modification of the timetable for continuing review requirements, new study enrollment suspension, or study suspension or termination. If the study is suspended or terminated, prompt reporting to the JDRF (the Juvenile Diabetes Research Foundation, who is sponsoring this study) will be provided. Events not requiring suspension or termination shall be reported during the annual progress report.

Data Monitoring

Data will be collected and managed using REDCap (Research Electronic Data Capture). The database is hosted at the University of Colorado Denver Development and Informatics Service Center (DISC), which will be a central location for data processing and management. This server has a high level of security, controlled access, daily back-up, and long-term retention of back-up files. All members of the BDC research team in this study have individual computers that are part of the institution network with institutional oversight of security. Field and range checks will be programmed to minimize data entry errors. Data distribution will be checked periodically and outliers verified; missing data will be tracked and checked.

Justification of Procedures:

There may not be benefits to subjects. However, CSII and CGM therapies have both been shown to have benefits over MDI and SMBG, respectively, thus for women who were not on these technologies prior to study inclusion, they will likely experience better glucose control and potential better gestational outcomes.

Both CSII and CGM therapies have been investigated in pregnancies associated with diabetes, as has SAPT. Thus, the SAPT arm incurs no extra risks. Only investigational HCL systems have ever been studied in pregnancy before now. The knowledge gained from a study examining a device being used by the public but in a new capacity is extremely valuable. The subjects would receive the same, high-quality care throughout pregnancy regardless of study participation, but would additionally be under closer supervision because of the new therapy being used. This supervision would include

prompt reporting of AEs and SAEs to the study MDs, DSMB, and IRBs, as well as interim safety analyses. Thus, the risks to the subjects would be minimized as much as possible, while the knowledge gained would be high impact and extremely important.

Given the importance of tight glycemic control in pregnancy, there are risks of HCL therapy that has never been studied during pregnancy. However, subjects will get additional education and personalized nutrition guidelines for carbohydrate counting and adhering to ADA guidelines for nutrition with limitations on carbohydrate content for each meal and snack to limit post-prandial excursions. In addition, they will be in contact with research staff who are also experienced clinicians every week during the pregnancy to change pump settings, optimize care, and reduce extreme glycemic variations that could have adverse effects. Finally, in studies outside of pregnancy, HCL therapy has been shown to improve glucose control and reduce hypoglycemia over CSII alone and SAPT, thus we feel that under controlled conditions, HCL therapy has great potential to have similar effects in pregnancy, which would outweigh the potential risks.

E. Potential Scientific Problems:

Potential Pitfall #1: The HCL system does not allow a lower glucose target than 120 mg/dL. An estimated average glucose of 120 mg/dL correlates to an A1C of 5.8%, which is within the recommended target range in pregnancy[5]. A study among women with T1D using CGM found that they spent ~8 hours/day with a glucose >140 mg/dL and ~3.25 hours/day with glucose <70 mg/dL in each trimester[55]. Both extremes are detrimental. Maternal hypoglycemia is one of the major barriers to achieving optimal glucose control. Maternal SH can lead to coma, road traffic accidents, and death[30]. Animal studies link hypoglycemia early in gestation with growth retardation and congenital anomalies[56]. In multiple studies demonstrating good overall glucose control among women with diabetes, rates of infant LGA and macrosomia remained high[20, 56-59]. This phenomenon may result from maternal hypoglycemia leading to treatment with carbohydrate consumption, fetal hyperinsulinemia, and then excess fetal growth[60]. Moreover, there is evidence that an intervention that improves TIR (even without a large difference in A1C) can improve maternal and fetal outcomes[57]. Studies in non-pregnant groups using the 670G system demonstrate little hypoglycemia among adults (3.4% time ≤70 and 0.6% ≤50 mg/dL) with increased TIR and decreased hyperglycemia[19], thus this system will potentially also improve overall maternal glucose control and reduce adverse pregnancy outcomes. Benefits of HCL therapy will likely outweigh risks. The study protocol includes collection of safety measurements throughout and review of these data through an independent DSMB. Should evidence arise that HCL is associated with significant harm, directive measures will be taken immediately.

Potential Pitfall #2: The HCL system may not remain in auto mode continuously. The HCL system is designed to leave HCL mode under certain conditions that would affect its efficacy (e.g., prolonged loss of sensor signal). Thus, all subjects randomized to HCL therapy will also have regular adjustments made to their basal patterns and bolus wizard settings for the manual mode. Manual mode is equivalent to SAPT. Data will be collected weekly to assess frequency and etiology for leaving HCL mode. HCL exits due to subject behaviors will be addressed promptly (e.g., not wearing the sensor). A previous study done under free-living conditions wherein patients had significant alternations in glucose from exercise, medication changes, and the like showed that participants remained in HCL mode ~88% of the time[19]. Subjects in this proposal who have HCL mode enabled ≤80% of the time will be identified so that corrective measures can be taken (e.g., if HCL

is exited from under-calibrations then the subject will be reminded that she must calibrate 3-4 times each day).

F. Data Analysis Plan:

Statistical Analysis Plan:

Data will be blinded to the study statistician. For the **interim safety analysis**, after the first 5 participants in each group have completed the 1st trimester, we will analyze the interim data to compare episodes of SH between groups to ensure no increased risk of SH with HCL therapy. Episodes of SH will be used for the interim analysis as SH events can be life-threatening for pregnant women and their fetuses. If interim safety analyses demonstrate no increased harm in either group, then the statistician will remain blinded until the end of the study. If the interim safety analyses demonstrate increased harm in one group necessitating evaluation of whether the study should be stopped, then the statistician will be unblinded at that point.

To address **Specific Aim 1**, we will compare percent of time spent in the SH range of <54 mg/dL on CGM (primary outcome) using a non-inferiority t-test with a margin of 1%. Counts of DKA and adverse skin reactions (secondary outcomes) will be compared between groups (HCL vs. SAPT) using t-tests for normally distributed variables and Wilcoxon Rank-Sum test for non-normal variables. As the purpose of this study is to demonstrate that HCL has a similar safety profile compared to SAPT during pregnancy, we will use a non-inferiority test. As a secondary analysis of events such as SH, DKA, and skin reactions, we will account for potential differential follow-up times due to miscarriage, drop-out, and withdrawal using Poisson regression with an offset for follow-up time. To address **Specific Aim 2**, we will compare CGM glucose variables (primary outcomes for glucose variables will be time spent <54, <63, 63-140, >140, >180 mg/dL; secondary outcomes will be glucose SD, J index, HBGI, LBGI, MAGE, and $CONGA_n$) and fear of hypoglycemia score between groups (HCL vs. SAPT) using t-tests for normally distributed variables and Wilcoxon Rank-Sum test for non-normally distributed variables. We will examine the buckets of time spent in each range (hypoglycemia, in range, and hyperglycemia) by day and night, as well as day-to-day variation. Mean glucose variables and hypoglycemia fear scores will be compared during each trimester of pregnancy and 4-6 weeks post-partum using mixed models. To address **Specific Aim 3**, we will compare SF-36 scores, insulin device satisfaction and glucose device satisfaction by group (HCL vs. SAPT) using t-tests if scores are normally distributed and Wilcoxon Rank-Sum test if scores are non-normal. We will analyze changes in INSPIRE Questionnaire scores over time in the HCL group. **Specific Aim 4** is an exploratory aim, and for this aim we will examine rates of fetal loss, preeclampsia, cesarean section, LGA, and neonatal hypoglycemia using Chi-square tests. We will account for potential differential follow-up times due to miscarriage, drop-out, and withdrawal using Poisson regression with an offset for follow-up time as a sensitivity analysis, in addition to the proposed chi-square tests in the exploratory analyses of fetal loss, preeclampsia, Caesarean section, LGA, and neonatal hypoglycemia. We will use mixed models to analyze changes in repeated measures, such as glycemia variables and hypoglycemia fear scores by trimester. We will evaluate the percent of time spent in closed loop by trimester as a feasibility outcome that is important to the next step of a larger clinical trial with efficacy outcomes.

For women who discontinue CGM therapy during the study, we will do an intention to treat analysis of above-stated outcomes. The alpha level will be 0.05 for all analyses, except the non-inferiority tests (alpha = 0.025). The use of mixed models and Poisson regression will allow for analysis of data for the portion of the study completed with CGM therapy.

Power and Sample Size Calculations: The primary outcome for **Specific Aim 1** is percent of time spent <54 mg/dL on CGM. With a sample size of 10 women per group (20 study completers), we will have 80% power to detect non-inferiority using a one-sided alpha of 0.025 and a non-inferiority margin of 1.5% of time spent <54 mg/dL for HCL compared to SAPT, using estimates of variability from the PI's current study of CGM use during pregnancy. The standard deviation of time spent <54 mg/dL based on data from the PI's current study of CGM use during pregnancy was 1.1%. For **Specific Aim 2**, with a sample size of 10 women per group (20 study completers), we will have 83% power to detect a difference in time spent in target glucose range (65-140 mg/dL, this range was used in the power calculations because at that time there was no consensus on optimal time in range in pregnancy) of 3.3 hours/day (13.8%) between HCL to SAPT, assuming a standard deviation of 2.5 hours/day (effect size=1.0 SD). This is similar to effect sizes reported in another artificial pancreas study showing a difference of 2.5 hours/day (10.4%) between groups[61] and a study of HCL in pregnancy (in a crossover design) showing a difference of 3.6 hours/day (15.2%)[20]. While this study is not powered to detect significant differences in maternal-fetal outcomes as described in **Specific Aim 4**, our goal is to provide estimates and preliminary data on these outcomes to inform the sample size needed for a larger trial focused on these outcomes, once the safety of the HCL system in pregnancy has been established.

G. Summarize Knowledge to be Gained:

This would be the first study to compare an FDA-approved HCL system to SAPT throughout pregnancy and the early post-partum period. Women across the USA are already using the HCL system being investigated in this proposal, and most pregnancies are unplanned, thus there are likely many women getting pregnant while on HCL therapy without knowing its effects on gestation. This study would demonstrate if the HCL system is safe in pregnancy. This study would provide pilot data to design and implement a larger, randomized controlled trial with adequate power to detect differences in maternal and fetal outcomes.

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