SCHOOL OF MEDICINE
Department of Psychiatry and Neurobehavioral Sciences
Center for Diabetes Technology

EARLY FEASIBILITY STUDY OF ADAPTIVE ADVISORY/AUTOMATED (AAA) CONTROL OF TYPE 1 DIABETES

VERSION 1.5

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I. CLINICAL STUDY

A. Purpose/Objectives

The purpose of this study is to use an Advisory/Automated Adaptive (AAA) Control system for insulin delivery in adults with Type 1 Diabetes (T1DM) in an outpatient setting to evaluate the system's ability to significantly improve blood glucose levels. This protocol represents a culmination of prior clinical trials in development of this AAA system and benefits from the synthesis of those components.

B. Study Design

The study will proceed in sequential assessments to optimize work load and personnel availability, particularly during the experimental (closed-loop control) admissions. Figure 1 presents the design of the experimental admission and control study at home (the last two days of the 7 day study period).

For the experimental admission: Subjects will be admitted to a hotel or a guesthouse at 18:00 and will be discharged 40 hours later at 9:00 on day 3 of admission. AAA control will be initiated before dinner at 19:00 and will be discontinued at 7:00 before breakfast on day 3. Different modules of AAA control will be active at different times – a practice adopted in our previous studies of closed-loop control, which is consistent with the Modular Architecture of our algorithms.

For the control study at home: Subjects will remain at home and will follow the timeline noted in Figure 2. Study personnel will be in contact with the study subject during the time to ensure that time points are consistent. The study subject will remain on CGM plus their home insulin pump following their usual regimen.

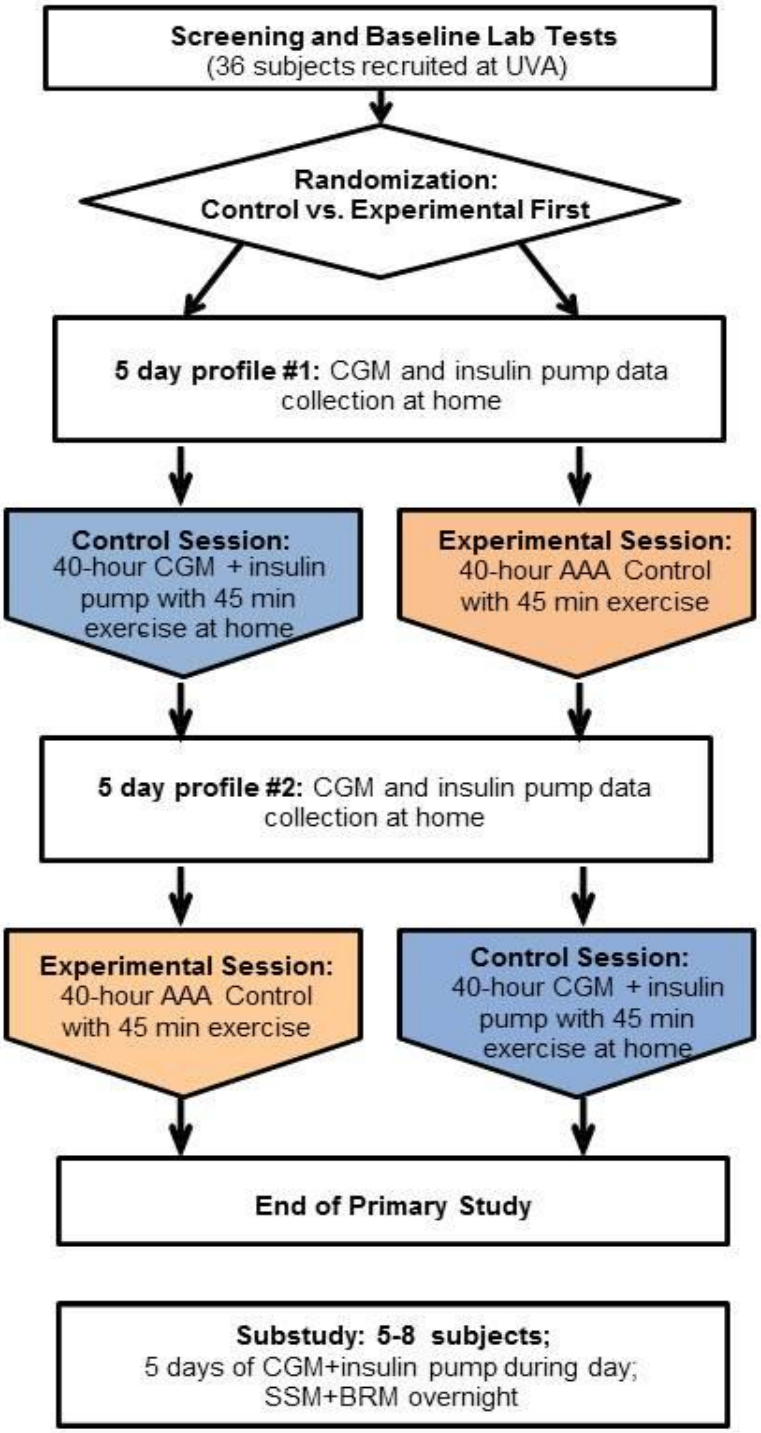

Figure 1: **Overall Flowchart of the Study**

C. Sample Size and Investigational Sites

The studies will be conducted at UVA and will require IRB approval prior to the initiation of the trial. Thirty-six subjects with Type 1 Diabetes Mellitus will be needed to complete the protocol.

Based on our experience with similar studies, we estimate an expected 20-30% screen failures, dropouts, or withdrawals (7 to 10 subjects at UVA); thus we intend to set a recruiting target of 45 subjects. One pilot subject will be enrolled to test system performance. More than one subject may be admitted at one time.

Specific Aim 1 (SA1): Hypoglycemic risk, Open vs. Closed Loop (exercise)
Specific Aim 2 (SA2): Time within target range, Open vs. Closed Loop control during the day
Specific Aim 3 (SA3): Time within target range at night
Specific Aim 4 (Substudy/exploratory): Assess the effect size of Control Modules 1+3 (SSM+BRM) preventing nocturnal hypoglycemia and increasing time within target (80-140mg/dl) overnight as compared to CGM-augmented pump alone.

The testing of the three specific aims of the main study (SA1, SA2, SA3) involves different periods of time as presented in Figure 3. Thus, in addition to complete data, availability of partial data would allow testing some of the study hypotheses. As a general rule, a session will be considered useful for data analysis if the subject completes more than 80% of the active study protocol (29 out of 36 hours for the experimental session). Sessions completing less than 80% of the protocol will be rescheduled. Specifically, comparing risk and occurrence of hypoglycemia during the 5-hour periods encompassing exercise (14:00-19:00) on open- vs. closed-loop control will address SA1. Comparing the time within target range (70-180mg/dl) during the day (7:00-23:00) on open- vs. advisory control will address SA2, and comparing the time within target range (80-140mg/dl) and the risk for hypoglycemia overnight will address SA3 (Figure 2).

To determine sample size we used power analysis based on data from our previous closed-loop control studies, which showed significant reduction in hypoglycemia (due to Module 1) and increase in time within target during the day and overnight [15]. With N=36 subjects, the power for proving SA1 is 97% and the power for SA3 is similar, while the power for SA2 is lower, but sufficient - 85%. The significance level was reduced to p=0.01 to account for multiple comparisons.

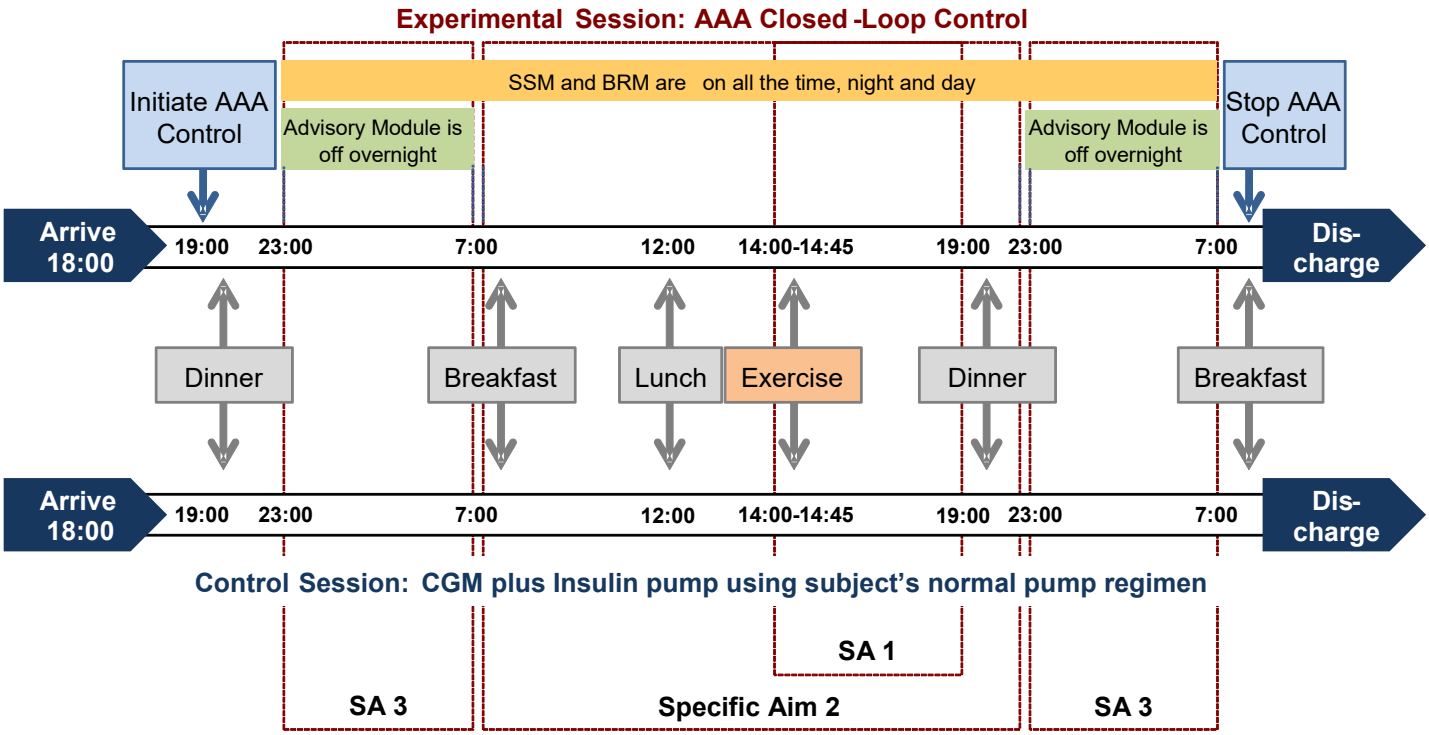

Figure 2: Experimental vs. Control sessions

D. Study Duration

As presented in Figure 1, the duration of the main study for each patient will be up to 6 weeks, which includes two active 1-week sessions, as well as time for screening and scheduling gap of up to 4 weeks between the sessions. There will be up to 5 visits, including screening, study training prior to the first study week, one outpatient (CDT Research House) experimental session and one visit following conclusion of the control week. The outpatient experimental session will last approximately 40 hours. For subjects participating in the substudy, an additional 5 day study period will occur any time after randomization..

E. Inclusion Criteria

1. ≥21 and <65 years old.
2. Clinical diagnosis of type 1 diabetes mellitus. For an individual to be enrolled at least one criterion from each list must be met.
   - Criteria for documented hyperglycemia (at least 1 must be met):
     i. Fasting glucose ≥126 mg/dL – confirmed
     ii. Two-hour OGTT glucose ≥200 mg/dL – confirmed
     iii. HbA1c ≥6.5% documented – confirmed
     iv. Random glucose ≥200 mg/dL with symptoms
     v. No data at diagnosis is available but the participant has a convincing history of hyperglycemia consistent with diabetes

- Criteria for requiring insulin at diagnosis (1 must be met):
  i. Participant required insulin at diagnosis and continually thereafter
  ii. Participant did not start insulin at diagnosis but upon investigator review likely needed insulin (significant hyperglycemia that did not respond to oral agents) and did require insulin eventually and used continually
  iii. Participant did not start insulin at diagnosis but continued to be hyperglycemic, had positive islet cell antibodies – consistent with latent autoimmune diabetes in adults (LADA) and did require insulin eventually and used continually

3. Use of an insulin pump to treat his/her diabetes for at least 1 year.
4. Familiarity with a bolus calculator with the current insulin pump with pre-defined parameters for carbohydrate [CHO] ratio, insulin sensitivity factor [ISF], target glucose and active insulin.
5. HbA1c <9% as measured with DCA2000 or equivalent device.
6. Not currently known to be pregnant, breast feeding, or intending to become pregnant (females).
7. Demonstration of proper mental status and cognition for the study.
8. Willingness to avoid consumption of acetaminophen-containing products 24 hours prior to and during CGM use.
9. Ability to access the Internet and upload CGM data via the DexCom company software during the data collection period.
10. If on antihypertensive, thyroid, anti-depressant or lipid lowering medication, have stability on the medication for at least 2 months prior to enrollment in the study.

F. Exclusion Criteria

1. Severe hypoglycemia resulting in seizure, loss of consciousness, or diabetic ketoacidosis within the 12 months prior to enrollment.
2. Pregnancy; breast feeding, or intention of becoming pregnant.
3. Uncontrolled arterial hypertension (Resting diastolic blood pressure >90 mmHg and/or systolic blood pressure >160 mmHg).
4. Conditions which may increase the risks associated with possible hypoglycemia, such as any active cardiac disorder/arrhythmia, uncontrolled coronary artery disease during the previous year (e.g. history of myocardial infarction, acute coronary syndrome, therapeutic coronary intervention, coronary bypass or stenting procedure, stable or unstable angina, episode of chest pain of cardiac etiology with documented EKG changes, or positive stress test or catheterization with coronary blockages >50%), congestive heart failure, history of cerebrovascular event, seizure disorder, syncope, uncontrolled adrenal insufficiency, neurologic disease or atrial fibrillation.
5. Self-reported hypoglycemia unawareness.
6. History of a systemic or deep tissue infection with methicillin-resistant staph aureus or Candida albicans.
7. Use of a device that may pose electromagnetic compatibility issues and/or radiofrequency interference with the CGM (implantable cardioverter-defibrillator, electronic pacemaker, neurostimulator, intrathecal pump, and cochlear implants).

8. Anticoagulant therapy other than aspirin.
9. Oral steroids.
10. Subjects currently taking Amylin.
11. Medical condition requiring use of an acetaminophen-containing medication that cannot be withheld for the study sessions.
12. Psychiatric disorders that would interfere with study tasks (e.g. inpatient psychiatric treatment within 6 months prior to enrollment).
13. Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation.
14. Known current or recent alcohol or drug abuse.
15. Medical conditions that would make operating a CGM, the DiAs cell phone or insulin pump difficult (e.g. blindness, severe arthritis, immobility).
16. Any skin condition that prevents sensor or pump placement on the abdomen or arm (e.g. bad sunburn, pre-existing dermatitis, intertrigo, psoriasis, extensive scarring, and cellulitis).
17. In adherence with the One Touch Ultra 2 User Guide that may be used in the experimental session and overnight during substudy, subjects with hematocrit levels less than 30% and above 55% will be excluded.
18. Impaired hepatic function measured as alanine aminotransferase or aspartate aminotransferase ≥three times the upper reference limit.
19. Impaired renal function measured as creatinine >1.2 times above the upper limit of normal.
20. Uncontrolled microvascular (diabetic) complications, such as current proliferative diabetic retinopathy or macular edema, known diabetic nephropathy (other than microalbuminuria with normal creatinine) or neuropathy requiring treatment.
21. Active gastroparesis requiring current medical therapy.
22. If on antihypertensive, thyroid, anti-depressant or lipid lowering medication, lack of stability on the medication for the past 2 months prior to enrollment in the study.
23. Uncontrolled thyroid disease.
24. Known bleeding diathesis or dyscrasia.
25. Known allergy to medical adhesives, components of the insulin pump insertion set or continuous glucose monitor sensor.
26. Active enrollment in another treatment clinical trial. Observational trials may be permitted at the discretion of the study physician.
27. Use of anti-diabetic agents other than CSII including long-acting insulin, intermediate-acting insulin, metformin, sulfonylureas, meglitinides, thiazolidinediones, DPP-IV inhibitors, glucagon-like peptide 1 agonists, and alpha-glucosidase inhibitors
28. Unwillingness to use an approved form of birth control during this study by a sexually active female participant.
29. Subjects with basal rates less than 0.01U/hr.

RESTRICTIONS ON USE OF OTHER DRUGS OR TREATMENTS

1. Use of anti-diabetic agents other than CSII including long-acting insulin, intermediate-acting insulin, metformin, sulfonylureas, meglitinides, thiazolidinediones, DPP-IV inhibitors, glucagon-like peptide 1 agonists, and alpha-glucosidase inhibitors.
2. Acetaminophen will be restricted starting 24 hours prior to CGM use.
3. Medications that block symptoms of hypoglycemia, including but not limited to beta blockers.

G. STUDY TIMELINE

1. Screening / Enrollment Visit

At the Screening Visit, the following procedures will be performed / criteria will be checked and documented:

1. Signed and dated informed consent
2. Inclusion and exclusion criteria
3. Demographics (date of birth, gender, race and ethnicity)
4. Medical history
5. Details of the diabetic history: duration of disease (number of years), diagnosis details, current treatment (including basal rates, carbohydrate ratios, insulin sensitivity factors, target glucose, average daily insulin over 7 days, history of DKA, history of severe hypoglycemia, and self-monitoring blood glucose values)
6. Past and current medical conditions
7. Surgical history
8. Menstrual history (females)
9. Allergies
10. Medications and supplements
11. Social history including drinking, smoking, and drug habits
12. Review of systems
13. Physical examination
14. Weight and height
15. Vital signs
16. Blood draw for screening labs:
    a. HbA1c
    b. Comprehensive chemistry panel
    c. Qualitative serum HCG In women with childbearing potential. If not performed, document reason (i.e. hysterectomy, postmenopausal)
    d. Hematocrit
    e. TSH
17. Preferred foods for the subject's self-treatment of hypoglycemia will be documented

If a study subject has had a recent physical exam with vitals, the study physician may determine that it does not need to be repeated. Once all results of the screening evaluations are available, a decision will be made to determine the subject eligibility for the study. If an exclusionary condition is identified, the study subject will be excluded from participation with follow up and referred to their primary care physician as needed. If the study subject is pregnant, the study physician will discuss the results of the blood test with the subject and the subject will be asked to seek confirmation of the test and the appropriate medical care. If the study subject has an abnormal initial blood pressure, the subject will be allowed to relax for >10-15 minutes and have the blood pressure reassessed. If the blood pressure remains out of range, the subject will be excluded. Subjects may be re-screened at a later date if their clinical situation changes as determined by the study physician.

If a subject meets all the study criteria, he/she will be enrolled in the trial. The total amount of blood to be withdrawn during the screening visit is ~6 cc. The screening visit will last approximately 2 hours. If the subject cannot schedule the session within 8 weeks of screening, screening labs, vital signs, and recent medical illness/medications will be re-evaluated. The study physician will have the discretion to repeat any test as needed.

All subjects will also be given written instructions to avoid acetaminophen prior to their study intervention or to reschedule their study intervention if they require acetaminophen as there is potential for interference with glucose oxidase systems for measuring glucose such as the Dexcom CGM. These instructions will also advise the subject to contact the study team in the event of a febrile illness within 24 hours of the study intervention, so that the study week can be rescheduled. All subjects will be given written instructions to bring all of their current medications and pump supplies with them for use during the experimental session.

2. Activities Performed During the Study Weeks

Outpatient Study Training Visit including use of Continuous Glucose Monitor (CGM)

1. An outpatient visit will be scheduled at the beginning of the first study week (experimental or control depending on the randomization). For subjects who are prior Dexcom CGM users, this visit may occur over the phone.
2. The subject's insulin pump, CGM receivers, and the subject's personal glucometer will be set using atomic clocks as a reference.
3. Quality control testing will be performed on the subject's personal glucometer as recommended in the manufacturer guidelines. If available, a concentration in the hypoglycemic range will be tested. A tested glucometer will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling. session
4. Female subjects of childbearing potential will perform a urine pregnancy test. If positive, the subject will discontinue study participation. The subject will be asked to seek confirmation of the test and the appropriate medical care. No payment will be given if the subject is cancelled due to pregnancy.
5. Subjects who are proficient CGM users prior to the Study Training visit may elect to initiate the CGM sensor at home rather at the training visit.

6. For those subjects who are not proficient CGM users, the subject will be supervised during the initial CGM sensor placements. A CGM sensor will be inserted into fatty tissue under the skin on the abdomen and will stay attached until the end of the study week (7 days).
7. If the CGM devices experience a sensor failure while at home, the subject will contact the study team. The subject will replace the sensor at home with guidance from the study team if appropriate or return to the office and the study team will replace the sensor. For the experimental week, while two sensors are operational during the study, only one of them is connected to the AP Platform and provides data for the closed loop system.
8. The subject will be trained on the use of the study glucometer and will demonstrate proficiency with a fingerstick test. The subject will be instructed that all fingersticks should be preceded by handwashing with warm water and a dry towel. The subject will be instructed to obtain fingerstick, avoiding alternative sites, when obtaining blood values. The first drop will be discarded. The second hanging drop will be used to measure the glucose level.
9. The subject will be taught how to calibrate the CGMs per manufacturer's guidelines. The subject will be asked to perform all required calibrations with fingerstick glucose measurements via the study glucometer.
10. The subject will be informed that all treatment decisions should be based on fingerstick values and not on CGM values.
11. The subject will be taught to look for skin irritation after sensor removal.
12. The subject will be reminded to avoid products containing acetaminophen 24 hours prior to wearing the CGM and while the CGM is in use.
13. If the subject requires an MRI, the sensor will be removed from the patient and the reason for removal will be noted. This will not be an adverse event. The visit may be rescheduled.
14. Subject will be instructed on how to upload the CGM data using DexCom Studio Software which is commercially available.
15. Subject will be instructed on how to download their personal pump using commercially available software generally included with their pump.
16. The study team will discuss with the subject their usual meal content and methods for estimating carbohydrates. Users will be asked to define a small, medium and large carbohydrate meal as well as provide us with their perception of whether a particular meal will result in slow, medium or fast rise in glucose. Subjects will be provided with Figure 3 below. This will correspond with the meal grid presented to them in the DiAs during the 2-day experimental session.

The closed loop control algorithm will be informed based on the way the subjects make judgments about their meals. Subjects will estimate their meal carbohydrates to determine their meal bolus. To this end, subjects will be asked to define their pre-meal bolus after assessing ***their perception*** of their meal size and glycemic effect of the meal. To assist subjects, they will be provided the following definition of glycemic effect:

> ***There are two aspects of how food raises the blood sugar – how high the blood sugar goes up and how quickly the blood sugar goes up. For instance, some foods may raise the blood sugar quickly, but not increase the blood sugar very***

much. Other foods may increase the blood sugar slowly but will eventually increase the blood sugar to a high final level. We want you to rate both how high you think the blood sugar will increase, and how quickly it will increase after you eat each meal and snack.

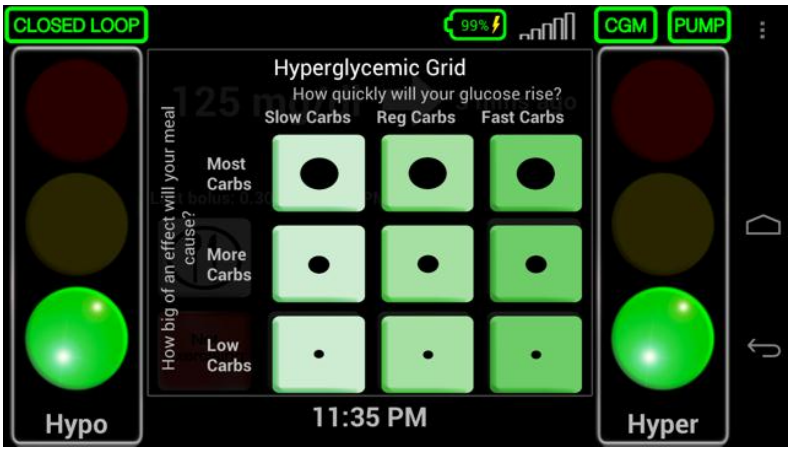

Figure 3: Hyperglycemic Grid

17. The outpatient visit will last approximately 1 – 3 hours depending on prior knowledge of the devices.
18. The subject will be given an instruction sheet with 24-hour contact information of the research team to address any problems or questions.
19. Unlimited additional appointments and telephone calls to the study team and study physician will be available.

3. Data Collection Period (Days 1-5)

Data Collection (before both control and experimental admissions)

A data collection period (5 days) will precede each of the control and experimental components of this study. All study subjects will be at home during these times. During the data collection period, subjects will be equipped with a DexCom Gen4 CGM. Subjects will be provided with instructions on how to upload CGM data through the DexCom software and how to download insulin pump data to record insulin pump information.

For the control session: an additional 2 days of data collection will continue while the subject follows the timeline in Figure 2. Subjects will be provided with specific instructions on how data should be recorded during the control days.

Data collection will include:

- *CGM Data:* The DexCom® stores glucose values every 5 minutes. This data will be uploaded via DexCom Studio software in the data collection system.
- *SMBG readings:*
  - Subjects will be asked to perform only SMBG (i.e., finger sticks), with no alternate site testing, for the entirety of the study.
  - They must complete four BG fingerstick readings per day to comply with the requirements for

participating in the study. Two of these measurements must be upon the subject's waking up and bedtime. Any home BG tests normally done by the participant should continue without interruption.

- *Meal times and Carbohydrate Administration:* Subjects will be asked to use the bolus calculator function of their pump and enter relevant carbohydrate information for meals.

- *Insulin administration*: information is stored within the subject's insulin pump any time the subject uses the suggested bolus calculator function. This data will be downloaded and sent to the study team the day before their session. Subjects will be asked to record any additional insulin administration that was not delivered via the insulin pump but was given by an insulin pen or needle injection.

To ensure that data are accurate, we will ask the subject to send us their pump download on day 2 or 3 of the 5 day glucose profile. These will be reviewed with for completeness by the study team.

The subjects who are in their experimental week will insert a second CGM on Day 3 or 4 (24-48 hours prior to their session). If the study subject would prefer, they may return to the office for study staff to insert the second sensor. This secondary CGM will be used as a back-up CGM during the experimental session if needed. Insertion of the secondary CGM in advance will allow for appropriate warm-up prior to the experimental session.

At the end of the 5 day collection period, subjects randomized to the experimental session first will proceed as described in "Procedures During the Experimental Session." For those subjects who were randomized to the control session first, they will proceed as described in "Procedures During the Control Session." These two 40-hour periods will complete the 7 day study week (5 days data collection + 2 day experimental or control session). Selected subjects who are participating in the Substudy will follow "Procedures During the Substudy".

4. Procedures During the Experimental Session (Days 5-7)

EXPERIMENTAL SESSION DAY 5:

1. The study subject will perform a final upload of CGM, SMBG and insulin pump information on the evening prior to the session. If the subject is unable to do so then we will ask them to come earlier on the day of session (Day 5 of data collection period) for the study team to download the information at the office. If a subject does not provide the download until the day of session, a delay of up to 2 hours on the start time of the session may be required.
2. The subject will meet the study team and check in to the CDT Research House at 18:00.
3. The subject will be asked to perform a fingerstick using the study glucometer shortly after arrival. SMBG needs to be between 80-249 mg/dL prior to initiation of AAA control and glucose not expected to be <70 within two hours of initiation of AAA. AAA control may be delayed up to two hours until these conditions are met.
4. The study team will confirm that the subject brought his/her insulin, insulin pump supplies, and regular medications. The study team will also confirm the absence of a febrile illness and absence of acetaminophen use while wearing the CGM sensor. If all criteria are not met, the subject will be rescheduled.

5. Female subjects of childbearing potential will perform urine pregnancy test. If positive, the subject will discontinue study participation. The subject will be asked to seek confirmation of the test and the appropriate medical care.
6. The subject will be instructed that all fingersticks should be preceded by hand washing with warm water and a dry towel. The subject will be instructed to obtain fingerstick, avoiding alternative sites, when obtaining blood values. The first drop of blood will be discarded. The second hanging drop will be used to measure the glucose level.
7. The subject will be reminded that all treatment decisions should be based on fingerstick values and not on CGM values.
8. The subject may take additional fingerstick readings as desired.
9. The subject will use the CGMs throughout the experimental session with the hypoglycemia alarm set at 90 mg/dL and the hyperglycemia alarm set at 260 mg/dL. If either the primary or secondary CGM alarms, a fingerstick value will be obtained. The Hypoglycemia or Hyperglycemia Safety Protocol will be followed (Appendices A-6).
10. In addition to device-required calibrations, an additional calibration will be performed prior to the evening meal +/- 30 minutes to minimize the likelihood that a calibration is requested close to the time of the study meal. Additional calibrations may be performed at the discretion of the investigator and will be documented in source documents. Both CGM devices will be calibrated at the same time, using a blood glucose value determined from the study glucometer. The CGM will be calibrated per manufacturer's guidelines with the study glucometer.
11. If the sensors disagree by more than 20% or if the error of a given sensor is >20% compared with a fingerstick, a second fingerstick will be obtained. If this value also shows a discrepancy with the sensor greater than 20%, the sensors will be calibrated using the average of the two values, with a maximum of one calibration every 6 hours. If the two sensors disagree by >20% in less than 6 hours after calibration, fingersticks will be obtained every hour until the difference between the sensors resolves or the next calibration point can be administered.
12. The CDT Research House will be stocked with the subject's preferred hypoglycemia treatment foods (e.g. juice, glucose tablets, milk, etc…). Study medical personnel will additionally have glucose tablets, glucose gel/liquid, and a glucagon emergency kit available for treatment (Appendix A-6: Treatment Safety Protocols).
13. The subject will have access to ad lib glucose-free beverages.
14. The study MD will be available for any clinical concerns.
15. The senior engineer with remote monitoring capability will view the study from another location. A technician will be on site for system issues.
16. The subject will be accompanied by a medically qualified staff member and a computer technician during the entire session.
17. Care partners (e.g. spouse) can accompany study subject during the trial. The guest will be required to sign the Care Partner Consent Form.

Equipment Specifications:

1. All study equipment including the DiAs cell phone, computers, insulin pump, and CGM receivers will use atomic clocks as a reference.
2. The investigator or delegate determines which one of the two CGM units will be used in the DiAs System during the clinical trial, and documents the rationale for decision. For example, the most accurate CGM may be used, and may be determined by the closest sensor glucose value to the meter glucose value performed at the time. A problem with radiofrequency communication resulting in loss of sensor glucose values or other sensor problem may lead to the alternate CGM being used. If both CGM units are performing equally, either unit may be selected. If during the outpatient session, the selected CGM exhibits abnormalities, the alternate CGM will be used for the remainder of the visit. If the alternate CGM also exhibits abnormalities, the outpatient visit will be terminated and rescheduled.
3. DiAs will be initialized with the subject's insulin pump parameters and will be connected to the study pump. The study pump will be initiated, and the subject's home pump will be removed.
4. During the Experimental Admission, DiAs takes the place of the Aviva Combo device and assumes control of the pump via the same Bluetooth connection that the pump uses to communicate with the Aviva meter. The Aviva Combo device is unpaired with the pump and will be unable to communicate with the pump during the time when DiAs is active. The subject will use the One Touch Ultra 2 or the Aviva Combo glucometer for fingersticks only during the DiAs control of the insulin pump.
5. The subject will be trained to use the DiAs interface; the training will continue approximately an hour, or until all questions are answered – the DiAs User Manual is included in Appendix A-7.
6. The subject will be trained on DiAs and on how to respond to the AAA alerts. The study team will provide supervision during the session.
7. The subject will be primarily responsible for using the system at this time, with the study team serving as a back-up when needed. The subject will be re-educated as needed and will be provided printed reminders/instructions as a reference.
8. At approximately 19:00, the computer tech will initiate the closed-loop (AAA control) on DiAs.
9. The Safety Supervision Module (SSM) will be running through the remainder of the trial (approximately 19:00 on the day of session until 7:00 on the day of discharge).
10. Dinner will be provided between 19:00 and 20:30. Dinner will consist of prepackaged meals and carbohydrate estimation will be determined by the subject.
11. Carbohydrate information and fingerstick values will be entered into the DiAs by the subject prior to the meal as described under Meal and Snack boluses.
12. Premeal insulin suggested by the DiAs will be confirmed by the subject.
13. At 23:00, DiAs will detune the AM module. The SSM and the BRM will continue to run overnight and is responsible for lowering the basal rate or insulin delivery to avoid hypoglycemia (SSM) or augmenting basal rate to compensate for changes in insulin sensitivity overnight, e.g. dawn phenomenon (BRM).
14. At approximately 23:00, lights will be turned out, and the subject will be encouraged to sleep.
15. The staff will be checking the readings of the secondary CGM receiver at 03:00AM and 05:00AM during the night; Additional readings may be taken as necessary.
16. Remote monitoring of the subject will be active all night.

Meal Times During the Study:

- Breakfast (07:00 – 08:00); Lunch (12:00 – 13:00); Dinner (19:00 – 20:30); optional snack (22:00 – 23:00). Subjects will be permitted to snack between scheduled meals.
- Snacks will not be permitted overnight (11 PM – 7 AM).
- Meals and snacks will be prepackaged meals purchased by the study team and will be brought in to the study site.
- Meals and snacks eaten during the experimental session will need to be exactly the same during the control session at home and should occur at the same time each day. This will be discussed with the study subject prior to the session.
- Study subject will determine the carbohydrate estimation for each meal. Subjects will be asked to use the same carbohydrate information for those meals and snacks for insulin dosing.

Meal and Snack Boluses:

- Using the DiAs interface, the subject will enter carbohydrate estimation and fingerstick value; the carbohydrate estimation will be from a 3x3 grid shown below. Subjects will be instructed that the type of the meal (slow, regular, fast) is color coded with 3 levels of increased intensity of the green color from left to right. The size of the meals is coded with increased sizes of dots placed in the middle of the nine buttons. To announce the meal, the user presses one of the 9 buttons which corresponds to his/her perception of the meal. Upon pressing the button, the time is automatically recorded and the system is informed about the time, size, and type of the meal.
- The user will be also presented with meal graphic user interface (MGUI) windows that:
- Request confirmation of a correction bolus requested by the controller that would also allow the user to change the size of the bolus (or cancel it).
- Request from the user to enter a SMBG value after the meal is announced via the main Meal GUI window (Figure 3).
- Provide information on the estimated meal size
- DiAs will recommend bolus treatment;
- Subject will confirm bolus treatment in the DiAs.
- After the subject confirms the bolus, the insulin will be injected.

Fingerstick Collection Times:

Once a fingerstick is obtained for any reason, Hypoglycemia and Hyperglycemia Safety Protocols will be followed to determine timing of subsequent fingersticks.

- Scheduled times: meal time, two hour post-meal time, 2300 and 0300.
- Prior to any elective snacks.
- Red Light Hypoglycemia Alarm on the DiAs
- Red Light Hyperglycemia Alarm on the DiAs
- CGM alarms >260 and will repeat hourly if CGM persistently >260
- CGM alarms <90 during Experimental Sessions and will repeat hourly if CGM persistently <90
- If the two CGMs differ by more than 20%, a fingerstick will be obtained and calibration

performed if ≥ 6 hours since last calibration. The frequency of subsequent fingersticks will depend on the actual fingerstick according to Hypoglycemia and Hyperglycemia Safety Protocols. Fingerstick will occur hourly if the CGMs continue to differ by 20%.

- Prior to calibration of CGM
- A subject may request any additional fingersticks as desired
- Study personnel may also request additional fingersticks at their discretion.

EXPERIMENTAL SESSION DAY 6:

1. The subject will be awakened shortly before 7:00 AM and allowed time for routine hygiene.
2. A fingerstick value will be obtained upon waking while the subject is still fasting.
3. At 7:00 AM, DiAs will activate the Advisory Module (AM). The AM will be active from 7:00 AM through 23:00 PM. BRM will be detuned.
4. The Advisory Module (AM) is running in the background and is accessed by the subject when they desire advice. When the advice button is pressed, the subject will be asked whether this is meal advice or correction advice. The subject will be required to request correction advice from the AM if the Hyperglycemia Red Light Alarm occurs. In that scenario, correction boluses may be suggested by the AM between those hours and must be confirmed by the study subject prior to injection. There is no limit on the number of times that a subject can request advice from the AM.
5. Breakfast will occur approximately 8:00 AM (between 07:00 and 08:30) and insulin administration will occur as described for all meals.
6. Lunch will occur approximately 12:00 PM (between 12:00 PM and 13:00 PM).
7. At approximately 14:00, the subject will be required to take a 45 minute walk or similar activity with staff. The subject may walk in the neighborhood near the hotel or guest house or inside the house but must be accompanied by medical personnel. During any walks, the system will be observed remotely by the study technician. Staff will carry hypoglycemia treatment supplies, including a glucagon emergency kit. Subjects will be permitted to snack before, during, or after the walk without insulin to prevent hypoglycemia.
8. Dinner will occur at approximately 19:00 PM (between 19:00 PM and 20:30 PM).
9. At 23:00, DiAs will detune the AM control. The SSM and the BRM will continue to run overnight and is responsible for lowering the basal rate or insulin delivery to avoid hypoglycemia or augmenting the basal rate to compensate for changes in insulin sensitivity overnight (e.g. dawn phenomenon).
10. At approximately 23:00, lights will be turned out, and the subject will be encouraged to sleep.
11. The staff will be checking the readings of the secondary CGM receiver at 03:00 AM and 05:00 AM during the night. Additional readings may be taken as necessary.
12. Remote monitoring of the subject will be active.

EXPERIMENTAL SESSION DAY 7:

1. The subject will be awakened shortly before 7:00 AM and allowed time for routine hygiene.
2. A fingerstick value will be obtained upon waking while the subject is still fasting.
3. At 7:00 AM, the DiAs will stop AAA control. The system components (CGM sensors, study pump) will be removed.
4. The subject will resume his/her normal home pump therapy.
5. A fingerstick value will be obtained prior to discharge.
6. The subject will be discharged by approximately 9:00 AM if the following 3 conditions below are met:
    a. the fingerstick value is 80-249 mg/dL
    b. the glucose trend is stable
    c. Insulin on Board is appropriate as determined by the MD
7. If the subject's glucose is out of the specified parameters, the Hypoglycemia or Hyperglycemia Safety Protocol will be followed until the subject is in the specified range.
8. Staff will request that subject remain at the Research House until approximately 9 AM so subject can be observed while eating breakfast.
9. Study staff will contact the subject within 24-48 hours after discharge.

5. Procedures During the Control session at Home (Days 5-7)

1. The study subject will start a new pump site on the morning of Day 5 to avoid initiation of a new site during the Control session at Home.
2. The study subject will follow the same schedule for timing of meals, snacks, exercise and bedtime as the experimental session.
3. The study subject will consume the identical meals and snacks as the experimental session. In the unlikely event, that the identical food is unavailable, the closest match of carbohydrate content will be chosen.
4. The study subject will administer insulin through their home insulin pump using their usual parameters.
5. Subjects will be allowed to use temporary basal rates at home.
6. The study subject will perform fingersticks using the study glucometer at a minimum at the identical scheduled times as the experimental session.
7. The subject will be instructed that all fingersticks should be preceded by hand washing with warm water and a dry towel. The subject will be instructed to obtain fingerstick, avoiding alternative sites, when obtaining blood values. The first drop of blood will be discarded. The second hanging drop will be used to measure the glucose level.
8. The subject will be reminded that all treatment decisions should be based on fingerstick values and not on CGM values.
9. The subject may take additional fingerstick readings as desired.
10. The subject will use the CGM throughout the study days with the hypoglycemia alarm set at 90 mg/dL and the hyperglycemia alarm set at 260 mg/dL. If either the CGM alarms, a fingerstick value will be obtained.

11. The study subject will be instructed to follow a similar hypoglycemia and hyperglycemia safety protocol as the experimental session (the Home Glycemic Safety Protocol, Appendix A-6).
12. In addition to device-required calibrations, an additional calibration will be performed prior to the evening meal +/- 30 minutes to minimize the likelihood that a calibration is requested close to the time of the study meal. The CGM will be calibrated per manufacturer's guidelines with the study glucometer.
13. The subject will have access to ad lib glucose-free beverages.
14. The study subject will continue with the data collection process as described during Days 1-5.
15. Study personnel will be in frequent contact with the study subject during this phase of the study.
16. The study subject will be asked to confirm the time and content of meals and snacks when they occur. They will also notify study personnel of SMBG values.
17. Study subject will be asked to be at home with comparable physical activity level as the experimental session.
18. The study subject will return to the office on approximately Day 7. Data will be downloaded from all devices.

Pilot Session:

Up to two subjects will participate in a pilot experimental session. These subjects will follow the same procedures as Outpatient Study Visit for Continuous Glucose Monitor (CGM) Training. Data Collection Period (Days 1-5) does not need to be collected. Procedures for Pilot Session will be the same as and are described in "Procedures for the Experimental Session*" except for the procedures detailed below.* A pilot subject may also participate in 40-hour trial.

- Closed loop (AAA) will be initiated at 19:00 and proceed through Day 2 at 17:00 (22 hours). Components of the AAA system will be active at the same corresponding times within that timeframe:
  - SSM and BRM will be active throughout the study period (19:00 Day 1 through 17:00 Day 2).
  - AM will be active 19:00 Day 1 through 23:00 Day 1 and 7:00 Day 2 through 17:00 Day 2.
  - The same procedures will be followed as described in "Procedures for the Experimental Session".
- Discharge will begin at 17:00. The DiAs will stop AAA control. The system components (CGM sensors, study pump) will be removed.
  - The subject will resume his/her normal home pump therapy.
  - A fingerstick value will be obtained.
  - The subject will be discharged by approximately 18:00 if the following 3 conditions below are met:
    - the fingerstick value is 80-249 mg/dL
    - the glucose trend is stable
    - Insulin on Board is appropriate as determined by the MD
  - If the subject's glucose is out of the specified parameters, the Hypoglycemia or Hyperglycemia Safety Protocol will be followed until the subject is in the specified

range.

- Study staff will request that the subject remains at the Research House until approximately 18:00. Subjects will be offered dinner.
- Study staff will contact the subject within 24-48 hours after discharge.

Procedures Related to the Substudy:

Five to eight subjects may enroll in the substudy at any time after randomization.

1. Subjects will wear the Accu-Chek Spirit Combo pump during the entire substudy (5 days). Specific training will be given for the Accu-Chek Spirit Combo including the Accu-Chek Aviva Combo device which subjects will use during the day. This training will occur as a separate outpatient visit or while admitted to the CDT Research House during the primary study based on subject convenience. A study pump used for training purposes may be utilized. A qualified staff member will conduct the training and in particular discuss differences from their home pump in important aspects such as calculation of insulin on board.
2. The Accu-Chek Spirit pump will be programmed with the study subject's usual basal rates from 07:00 to 22:00. DiAs will be turned on in open loop between 20:00 - 22:00 and therefore the study pump will be programmed for a basal rate of 0 from the initiation of DiAs control until 07:00. This will allow for DiAs to operate. If there is any unforeseen delay of more than 15min in initiating DiAs in open loop, a basal rate will be entered into the Accu-Chek Spirit Pump until connection can be established.
3. After 07:00, the study subject may leave the research study house and participate in their usual activities (work, home) during the day. Activities should be similar to the 5 day period #1 of CGM-augmented insulin pump therapy during the main study. Subjects will be requested to remain within the greater Charlottesville area (~approximately 25 miles radius) during this time. The subjects will have unlimited access to study MD and qualified medical study personnel by phone, email, text or in person if needed to address any concerns during the day with use of the pump or other clinical concerns.
4. Subjects will be asked to return to the research study house by approximately18:00.
5. The study pump and CGM will be downloaded.
6. Dinner will occur between approximately18:00-19:00.
7. Hypoglycemic treatments can occur at any time per the subject's request. In addition, the Home Glycemic Safety Protocol will be followed by the study subject
8. The subject will be started on DiAs in open loop mode between 20:00 – 22:00. When DiAs is operating, the Accu-Chek Aviva Combo Device is not paired to the pump and is unable to communicate with the pump. The subject will use the One Touch Ultra 2 or Aviva Combo glucometer for fingersticks while the DiAs is operating.
9. Subject may administer correction boluses per their usual regimen at any time prior to closed loop control initiation which is approximately 23:00.
10. The system will turn on SSM+BRM at 23:00 to 07:00.
11. At approximately 23:00, lights will be turned out, and the subject will be encouraged to sleep.

12. The staff will be checking the readings of the secondary CGM receiver at 03:00 AM and 05:00 AM during the night and will monitor remotely the subject.
13. CGM will be calibrated in the same manner as described in Procedures Related to the Experimental Session.
14. The subject will be awakened shortly before 7:00 AM and allowed time for routine hygiene.
15. A fingerstick value will be obtained upon waking while the subject is still fasting.
16. At 7:00 AM, DiAs will be stopped and the subject will resume CGM-augmented insulin pump therapy. These same procedures will be repeated for 5 consecutive nights. Subjects will be able to leave the CDT each morning if SMBG is 80-249 mg/dL, and glucose trend is stable. A meal will be offered.

Procedures Related to Discharge (Day 6 of substudy)

1. The subject will be awakened shortly before 7:00 AM and allowed time for routine hygiene.
2. A fingerstick value will be obtained upon waking while the subject is still fasting.
3. At 7:00 AM, DiAs will be stopped and the system components (CGM, pump) will be removed.
4. The subject will resume his/her normal home pump therapy.
5. A fingerstick value will be obtained.
6. The subject will be discharged by approximately 9:00 AM if the following 3 conditions below are met:
   a. the fingerstick value is 80-249 mg/dL
   b. the glucose trend is stable
   c. Insulin on Board is appropriate as determined by the MD
7. If the subject's glucose is out of the specified parameters, the Hypoglycemia or Hyperglycemia Safety Protocol will be followed until the subject is in the specified range.
8. The subject will be offered a meal prior to discharge.
9. Study staff will contact the subject within 24-48 hours after discharge.

H. SAFETY MONITORING / RISK ANALYSIS

- Glucose Monitoring Risk:

  LifeScan's One-Touch Ultra 2 Glucose Monitor will be used to measure blood glucose values. It is a FDA 510K Class II Medical Device (510K number K053529).

- Hypoglycemic/Hyperglycemic Risk:

  The Hypoglycemia and Hyperglycemia Safety Protocols will be followed during the Experimental Session and the overnight portion of the substudy when SSM+BRM are active. The Home Glycemia Safety Protocols will be followed during the Control session Days (Day 5-7) and during the substudy days from 07:00-23:00.

Treatment Safety Protocols are present in Appendix A-6.

- Calibration of CGM Risk:

  The CGM will be calibrated using fingerstick values per manufacturer's guidelines.

- Sterilization Risk:

  Study equipment cannot be sterilized in an autoclave. Cleaning instructions for study equipment provided to study the subject are provided below.

- Device Reuse Risk

The DexCom Gen 4 is labeled for single use only. The sensor (the component of the system that enters the skin) will be single use only. The transmitter and receiver will be reused after cleaning as described below. The transmitter is attached to the sensor but does not enter the skin and the receiver is a hand held device. The transmitter and receiver will be cleaned adhering to hospital protocol as described below. Subjects will be informed that the FDA has approved these devices for single use and that by using them among multiple patients, bloodborne pathogens (i.e. Hepatitis B) may be spread through the use of multiple users.

The Accu-Chek Combo System is labeled for single-patient use. During the substudy when the Accu-Chek Spirit Insulin Pump is used in combination with the Aviva Combo Device, the system (the Aviva Combo device) will be single patient use. During the 2 day experimental session, the Accu-Chek Spirit Insulin Pump is not used with the Aviva Combo Device. In this configuration, the insulin pump is handheld. The subject interactions are primarily with the DiAs interface, not with the Accu-Chek Spirit Insulin Pump menu interface itself. Since there is no use of the Aviva Combo Device and minimal interaction with the handheld pump during the 2 day experimental session, the Accu-Chek Spirit Insulin Pump handheld device will be reused after cleaning adhering to hospital protocol as described below. All infusion set equipment will be single patient use only (infusion set insertion kits, tubing, cartridges etc.)

Cleaning Procedure: Equipment that touches intact skin will be cleaned with ethyl or isopropyl alcohol (70-90%), quaternary ammonium germicidal detergent (i.e. CaviCide) or household bleach. The contact time on the surface depends on the method used to clean the equipment. CaviCide requires three minutes on the surface. Clorox Germicidal Bleach Wipes require two minutes on the equipment. The surface should remain wet (i.e. slightly damp) with the disinfectant to be considered effective though not wet enough to leave drops of liquid. Equipment will be stored in a clean zipped bag.

The home glucose meters are single user devices.

Hb1Ac Risk: The University of Virginia central labs have College of American Pathologist (CAP) and the Clinical Laboratory Improvement Amendments (CLIA) certifications. While the central lab is not NGSP certified, the calibrators for the HbA1c assay are traceable to NGSP. The equipment (Tosoh G7) is NGSP

certified.

- Misuse Risk:

CGM training:

Subjects will be introduced to the CGM by a qualified member of the study team. The subject will be instructed how the device is inserted, calibrated and removed. Subject will be trained how to upload the CGM data via the DexCom Studio software. The subject will verbalize understanding of how the device is used, how to insert the device, how to calibrate the device and how to remove the device to the study team. The subject, with the guidance of the study team, will then insert the sensor and begin wearing the CGM. The study team will confirm that all questions have been answered and that the subject has understood the training. The subject will be given a contact sheet containing phone numbers for the study team to call with any questions 24 hours per day.

Study Glucometer training:

The subject will be using their personal glucometer for the home portions. The Accu-Chek Aviva Combo will be used during the substudy and relevant subjects will be trained on that device. At the training session, trained study staff will demonstrate proper use of the meter as described in the user manual. The subject will then be required to demonstrate proficiency on the use of the device. The subject will be instructed to wash their skin with warm water and a clean towel prior to obtaining fingerstick values. The subject will be instructed to obtain a fingerstick, avoiding alternative sites, when obtaining blood values. The first drop will be discarded. The second hanging drop will be used to measure the glucose level. QC will be completed prior to subject receiving the study glucometer and when study glucometer results are suspect. The study team will confirm that all questions have been answered and that the subject has understood the training.

Insulin Pump training:

The training with the study insulin pump is part of the DiAs training (below) and will occur with a qualified clinical member of the study team. During the Experimental Session, the subjects' interactions with the study pump will be carried out through the DiAs GUI. Other pump- related topics that are not covered by DiAs will be discussed, including but not limited to: temporary basal rates, bolus calculator function, administering extended bolus, insulin action duration, bolus increment, low reservoir warnings / alarms, auto off function, and changing the pump. The study team will confirm that all questions have been answered and that the subject has understood the training.

DiAs training:

During the experimental session and the substudy, the DiAs training will occur with a qualified clinical member of the study team and with the DiAs manual in hand (Appendix A-7). DiAs will be pre-programmed by the study team with all the subject's individual pump settings. Working interactively with DiAs, the subject will be instructed how to navigate the DiAs GUI. The subject's basal rates and pump parameters will be confirmed at this time. To minimize risk associated with the use of DiAs:

- The study team will confirm with the subject the pump parameters entered in DiAs. The selected pump parameters will be discussed with the study physician.
- The subject will be trained on the use of the DiAs GUI.
- The subject will also be asked to inform the system of any calibrations that are made to the

primary CGM unit by activating a calibration button on the user interface.

- The subject will be instructed how to access the CGM trace from the primary sensor via the DiAs user interface by activating the CGM button.
- The subject will activate the meal screen of the system any time insulin will be given with a meal or any time additional correction insulin is desired.
- The subject will inform the system of hypoglycemia treatment by activating a hypoglycemia treatment button after each ~16 grams of glucose is consumed.
- The subject will be assessed for understanding of the DiAs GUI and how to react to the SSM messages. The subject will be re-educated as needed and will be given printed User Guide as a reference. The subject will be primarily responsible for using the system, with a medically qualified staff member and computer technician serving as back-up when needed. Once the study team feels that the subject is comfortable using all components of the study system, the study will be initiated.

- Risks of blood sampling collection, contamination from sampling techniques
  - Hand washing with either soap & water or waterless hand sanitizer will be used prior to caring for the study subject. Gloves will be worn during blood sample collection and processing. Medical personnel will continue to practice hygiene for the patient's protection (i.e. hand washing, changing gloves frequently, disposing needles properly). Gloves will be removed and hands washed prior to leaving and upon return to the subject's room. Soiled linen will be changed to minimize the transfer of pathogenic organisms.
  - Study personnel with direct subject contact are required to complete Blood borne Pathogens and Infection Control training annually.

Medical Personnel Training

All study nurses will be currently licensed RNs. All RNs that are employed by the study are oriented to the care of the T1D research subject. Certification of their skill level is supervised by the study Nurse Manager. Other medical personnel may be licensed Emergency Medical Technicians. All medical personnel who will have direct contact with the study subject have current certification in Basic Life Support including CPR and AED. Study physicians will be available during the trial.

I. STOPPING RULES

Entire study

The study will be stopped if three similar AE's occur that are deemed moderate or severe or if there is system communication failures, which may trigger revision of the system software. Additionally, the Principal Investigator, IRB-HSR, Safety Officer, or sponsor may decide to stop the trial or part of the trial at any time. In this case, the Principal Investigator will promptly inform the subjects and assure appropriate therapy and follow-up. Additionally the Principal Investigator will notify the IRB if the study is temporarily stopped. The pertinent regulatory authorities will be informed according to national regulations.

Early study stop will be documented and following information will be collected:

- Date and cause of the ending

- Description of any serious adverse event leading to the study ending

A subject who does not complete the protocol may be replaced or rescheduled. Available data will be exploited.

In the case of an unanticipated adverse device effects (UADE), the overall study may be suspended while the problem is diagnosed and the PI investigates the UADE. If the PI determines that the UADE poses an unreasonable risk to subjects, the study should be suspended until this UADE can be resolved. If it cannot be resolved, the study should be terminated. Termination should occur no later than 5 working days after PI makes the decision. The result of the investigation and the PI's decision to terminate the study shall be reported the site IRB, and the FDA per 21CFR 812.46(b) (2). The medical monitor must determine if the UADE presents an unreasonable risk to subjects. If so, the medical monitor must ensure that all investigations, or parts of investigations presenting that risk, are terminated as soon as possible but no later than 5 working days after the medical monitor makes this determination and no later than 15 working days after first receipt notice of the UADE.

The study may resume if the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension. The IRB will be notified if the study is stopped, and permission to resume will be obtained from the FDA and IRB prior to restarting.

SUBJECT WITHDRAWAL CRITERIA

An individual subject can be stopped from study participation at subject, PI, study MD, or sponsor's request.

The Principal Investigator, IRB-HSR, or Safety Officer may decide to stop the trial or part of the trial at any time. In this case, the Study MD will promptly inform the subject and assure appropriate therapy and follow-up. Additionally, the Principal Investigator will promptly inform the IRB and provide a detailed written explanation. The pertinent regulatory authorities will be informed according to national regulations.

The subject may request to be withdrawn from the study at any time for any/no reason. A subject will be withdrawn at the subject's request (withdrawal of informed consent) or at the request of the PI or sponsor.

Study procedures other than those required for subject safety would be stopped if:

- The subject had a serious adverse event deemed related to study.
- Glucagon is required to treat hypoglycemia.
- The subject experiences a hypoglycemic seizure.
- The subject becomes unconscious due to hypoglycemia.
- SMBG <45 mg/dL at any time during the experimental session
- SMBG >300 mg/dL for more than 2 hours during the experimental session
- SMBG ≥400 mg/dL at any time during the experimental session
- The subject develops emesis, nausea and abdominal pain during the experimental session.
- Confirmed β-ketone level≥0.6 mmol/L for more than 2 hours during the experimental session
- Confirmed β-ketone level >1.5 mmol/L at any time

- System is in 'Stopped Mode' for more than 2 consecutive hours during the experimental sessions

- The subject has a positive pregnancy test.

Subjects who were not able to complete the study for reasons other than a serious adverse event (i.e. hypoglycemic seizure, etc.) will be permitted to repeat the session.

Reason Study Stopped	Repeat Session?
Equipment Failure or similarly related issues that invalidate study data	Can repeat session
Hyperglycemic Events that did not result in Serious Adverse Event	Can repeat session
Hypoglycemic Events that did not result in Serious Adverse Event	Can repeat session
PI initiated discontinuation of study due to patient or equipment concerns	Can repeat session
Serious or unanticipated adverse event deemed related to the study	Unable to repeat session

Table 1: Repeat Session Table

CATASTROPHIC EVENT PLAN

The Outpatient Emergency Plan will go into effect should a catastrophic event occur during the experimental session. A catastrophic event is defined as any event that requires emergency treatment by medical professionals that exceed the expected parameters of the protocol. A copy of this plan will be located at the monitoring desk. Staff will be aware of its location at all times.

Event	RN Response	Tech Response
Respiratory Arrest	1) Tell Tech to call 911 2) Begin Basic Life Support	Refer to Study Physician on-site
Cardiac Arrest	1) Tell Tech to call 911 2) Begin Basic Life Support	Refer to Study Physician on-site
Severe Hypoglycemic Event as defined by hypoglycemia accompanied by unconsciousness or seizure	1) Tell Tech to call 911 2) Administer glucagon IM (described in Hypoglycemia Safety	Refer to Study Physician on-site
Severe Hyperglycemic Event as defined by β-ketone level ≥0.6 mmol/L for >2 hours or >1.5 mmol/L, or symptoms of vomiting or abdominal pain are present	1) Discuss correction dose of insulin to administer s.c. via syringe with study M.D. 2) Encourage p.o. water intake	Refer to Study Physician on-site

Table 2: Outpatient Emergency Plan

In the unlikely event of a disruption in 911 phone service, the Charlottesville-UVA-Albemarle Emergency Communications Center can be reached via their non-emergency number 434-977-9041. This number feeds into their main call area where 911 dispatchers are available 24/7.

J. ENDPOINTS

This study is an early feasibility study that will test the efficacy of DiAs - a *smart-phone-based system* compared to CGM-enhanced insulin pump treatment in an outpatient setting. Specifically, the main study will have randomized cross-over design with each patient participating in two study weeks: 1) experimental involving 5 days of data collection followed by 2 days of AAA control using insulin pump and available CGM (however, treatment based on CGM will be discouraged) and 2) Control week involving 5 days of data collection followed by 2 structured days of study at home. This series of sessions will provide data for the regulatory approval of the AAA system and for its deployment in a longer-term trial of AAA at home. In addition, the data will be used to estimate the effect size of the AAA vs. CGM-enhanced insulin pump treatment in an outpatient setting.

The *basic unit for most analyses is the glucose trace of an individual*, i.e. a time-stamped series of CGM data recorded for each person. Summary characteristics and group-level analyses are derived after the individual traces are processed to produce meaningful individual markers of average glycemia and glucose variation. The following primary endpoints will be assessed:

- Risk for hypoglycemia as measured by the Low BG Index associated with exercise (SA1);
- Time spent within 70-180 mg/dl during the day (SA2);
- Risk for hypoglycemia overnight and time spent within the target range of 80-140 mg/dl overnight (SA3).

In addition, the following secondary endpoints will be assessed:

- Extent postprandial glucose excursions during the day;
- Overall number and extent of hypoglycemic episodes;
- System reliability, including failure rates of system components, frequency analysis of lost or inaccurate CGM records, percent time of active control, and inter-device connections between DiAs and the CGM and between DiAs and the insulin pump;
- System functionality, including the DiAs GUI in terms of patient comfort with operating the system, and
- The DiAs remote monitoring by medical personnel/technicians to confirm appropriate functioning outside of the hospital setting.

The specific aim SA4 of the Substudy is exploratory – no significant results are expected, but we will assess the effect size of Control Modules 1+3 (SSM+BRM) preventing nocturnal hypoglycemia and increasing time within target (80-140mg/dl) overnight as compared to CGM-augmented pump alone.

K. SUCCESS CRITERIA / GOAL

We hypothesize that, compared to CGM-augmented insulin pump treatment, AAA control will result in moderate effect size of approximately 0.3-0.5 in terms of:

- Prevention of hypoglycemia during and following exercise more efficiently than state-of the-art care based on CGM and insulin pump;
- Increased time within the target range of 70-180 mg/dl during the day;
- Prevention of nocturnal hypoglycemia and increase of the time within target range (80-140mg/dl) overnight.

As a general rule, a session will be considered useful for data analysis if the subject completes more than 80% of the active study protocol (29 out of 36 hours for the experimental session). Sessions completing less than 80% of the protocol will be rescheduled.

L. STATISTICAL ANALYSIS PLAN

The testing of the three specific aims of the main study involves different periods of time as presented in Figure 2. Thus, in addition to complete data, availability of partial data would allow testing some of the study hypotheses. Measures of time within target range, risk and occurrence of hypoglycemia, glucose variability and system stability will be computed as previously described and will be accompanied by appropriate plots [20]. Repeated measures ANOVA with contrasts will be used to compare the different study periods on the basis of these measures. Specifically:

- Comparing risk and occurrence of hypoglycemia during the 5-hour periods encompassing exercise (14:00-19:00) on open- vs. closed-loop control will address SA1;
- Comparing the time within target range (70-180mg/dl) during the day (7:00-23:00) on open- vs. advisory control will address SA2, and
- Comparing the time within target range (80-140mg/dl) and the risk for hypoglycemia overnight will address SA3 (see Figure 2).

II. INFORMED CONSENT

The Pilot Consent, the Informed Consent, and the Care Partner Consent are presented in Appendix A-8.

III. PATIENT CASE REPORT FORMS

Patient Case Report Forms are presented in Appendix A-9.

IV. INVESTIGATOR AGREEMENT FORMS

Investigators Agreements Forms are presented in Appendix A-10.

V. MONITORING INFORMATION

Data and Safety Monitoring Plan

A. Defi**nition of adverse events (AE) for this study**

An adverse event will be defined as: 1) any adverse finding (sign, symptom, abnormal assessment, (i.e. lab, vital signs, ECG, etc., or cluster of these) temporarily associated with interventions and procedures of the research protocol, and 2) an unanticipated problem involving risks to subjects, or breaches of protocol which might entail risk to participant.

B. Definition of serious adverse events

A serious adverse event will be considered any undesirable sign, symptom, or medical condition which is fatal, is life-threatening, requires or prolongs inpatient hospitalization, results in persistent or significant disability/incapacity, constitutes a congenital anomaly or birth defect, is medically significant and which the investigator regards as serious based on appropriate medical judgment.

An important medical event is any AE that may not result in death, life-threatening, or require hospitalization but may be considered SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions of SAEs.

C. Definition of an unanticipated problem

An unanticipated problem is any event, experience that meets ALL 3 criteria below:

- Is unexpected in terms of nature, severity or frequency given the research procedures that are described in the protocol-related documents AND in the characteristics of the subject population

being studies

- Related or possibly related to participation in research. This means that there is a reasonable possibility that the incident may have been caused by the procedures involved in the research study.
- The incident suggests that the research placed the subject or others at greater risk of harm than was previously known or recognized OR results in actual harm to the subject or others.

D. Definition of a protocol violation

A protocol violation is defined as any change, deviation, or departure from the study design or procedures of a research project that is NOT approved by the IRB-HSR prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations. Protocol violations may or may not be under the control of the study team. These protocol violations may be major or minor violations. Table 3 details the timeline and reporting agencies of these events.

Type of Event	To whom will it be reported:	Time Frame for Reporting	How reported?
Any internal event resulting in death that is deemed DEFINITELY related	IRB-HSR	Within 24 hours	IRB Online and phone call
Internal, Serious, Unexpected adverse event	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event	IRB Online
For Device Studies: Unanticipated adverse device effects	IRB-HSR	Within 10 day calendar days of the study team receiving knowledge of the	IRB Online
Unanticipated Problems that are not adverse events or protocol violations (this would include a Data	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the	Unanticipated Problem report form.
Protocol Violations or Enrollment Exceptions	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the	Protocol Violation and Enrollment Exception Reporting Form

Data Breach	Compliance and Privacy Office; Police if breach includes equipment (stolen computers).	As soon as possible and no later than 24 hours from the time the incident is identified.	Compliance and Privacy Office
OUTSIDE SPONSOR			
All Serious adverse events	Sponsor	Within 7 calendar days from the time the study team received knowledge of the	Sponsor-determined procedure.
External, Serious and Unexpected adverse event resulting in change to the protocol or consent.	Sponsor	Within 7 calendar days from the time the study team received knowledge of the	Sponsor-determined procedure.
For Device Studies: Unanticipated adverse device effects (internal)	Sponsor	Within 10 day of the study team receiving knowledge of the event	Sponsor-determined procedure.
Unanticipated Problem	Sponsor	Within 10 day of the study team receiving knowledge of the	Sponsor-determined procedure.
Protocol violations	Sponsor	Within 10 day of the study team receiving knowledge of the	Sponsor-determined procedure.
IND/IDE			
Life-threatening and/or fatal unexpected events related or possibly related to the use of	FDA	Within 7 calendar days of the study team learning of the event	Form FDA 3500A (Med Watch) or narrative
Serious, unexpected and related or possibly related adverse events	FDA	Within 15 calendar days after the study team receives knowledge of the event	Form FDA 3500A (Med Watch) or narrative
For Device Studies: Unanticipated adverse device effects (internal or external)	FDA	Within 10 working days of the study team receiving knowledge	Form FDA 3500A (Med Watch) or narrative
All adverse events	FDA	Annually	IDE annual report

Table 3: Reporting Table

E. Definition of a Protocol Enrollment Exception

An enrollment exception is the sponsor's prospective approval for the enrollment of a research subject that fails to meet current IRB-HSR approved protocol inclusion criteria, or falls under protocol exclusion criteria. Enrollment exceptions only apply to a single individual. Such a request should be rare and justified

in terms of serving the best interests of the potential study participant. Enrollment exceptions will be evaluated by the study medical monitor prior to enrollment.

F. Definition of a Data Breach

A data breach is defined in the HITECH Act (43 USC 17932) as an unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

G. Data Collection

Identifiable endpoint data be collected/recorded in the form of source documents and will be stored on a database on a Health Systems Computing Services (HS/CS) secure managed server that is configured to store PHI. De-identified data will be stored on password-protected network.

Safety Data Oversight will be completed by the Study Medical Monitor or designee. The medical monitor's designee will be a staff member from the institutional Clinical Trials Office. Monitoring Form example presented in Appendix A-11.

The PI will conduct an aggregate review of the following data:

- All adverse events
- Unanticipated Problems
- Protocol violations
- Audit results
- Early withdrawals
- Endpoint data

Other: In addition to the above, the reports will include subject enrollment. The principal investigator will also include the results of the safety reviews in the annual progress reports submitted to the IRB. The annual report will address:

- Whether adverse event rates are consistent with pre-study assumptions
- Reason for dropouts from the study
- Whether all subjects met entry criteria
- Whether continuation of the study is justified
- Conditions whereby the study might be terminated prematurely

The relevant device regulation for reporting adverse events to the FDA will also be followed.

Data from each subject will be reviewed by the PI after completion of participation to determine whether the DiAs system was working properly and whether there were safety concerns.

IRB-HSR will be updated annually on the IRB-HSR continuation status form.

H. Adverse Events / Unanticipated Problems

Recording, Reporting, and Grading

Only adverse events that are deemed related AND serious will be recorded, reported, and graded. The principal investigator will be responsible for the overall safety monitoring of the study. He, along with the sub-investigators, will review the individual adverse events as they occur. Any event that merits adverse event report will be collected and recorded in the IRB database by completing the IRB Adverse Event Reporting form online. The principal investigator can then use this database to produce a report of all adverse events reported on the study to do an aggregate review. If the AE is unexpected and serious, a signed hard copy of the IRB Adverse Event Reporting form will be submitted to the IRB within 7 calendar days.

I. Grading of Adverse Events

- Mild/Moderate/Severe
- Serious/Not serious
- The PI will determine the relationship of adverse events to the study using the following scale:
  - Related: AE is clearly related to the intervention
  - Possibly related: AE may be related to the intervention
  - Unrelated: AE is clearly not related to intervention

Reporting/recording of adverse events/unanticipated problems will begin after the subject begins study drug/device placement/intervention/study-related procedure/specimen collection.
Reporting/recording of adverse events/unanticipated problems will end at the end of study drug/device/intervention/participation.

VI. INSTITUTIONAL REVIEW BOARD DESCRIPTION

Institutional Review Board description is presented in Appendix A-12.

VII. LABELING

"CAUTION-Investigational Device. Limited by Federal (or United States) law to investigational use."

The investigational device is a system comprised of FDA-Approved and investigational component devices. The intended use of the system is the regulation of blood glucose levels in Type 1 diabetes via subcutaneous continuous glucose monitoring (CGM) and subcutaneous delivery of insulin. The use of the system is strictly limited to the clinical testing of a closed-loop control algorithm in controlled outpatient conditions.

- The FDA-Approved component devices that are used without modification are:
- Dexcom Gen4® Plus, Dexcom Inc. (PMA Number P050012)
- Roche Accu-Chek Spirit Combo insulin pump (PMA Number K111353).

We certify that we have copies of all product labeling for each approved/cleared device, which are available to any end-user/healthcare provider upon request.

The investigational component devices are:

- Smart-phone medical platform – DiAs (Diabetes Assistant);
- Three interacting control modules:
  - **Module 1 –** Automated Safety Supervision (SSM) responsible for prevention of hypoglycemia, which can be adapted (individualized) with prior data for each subject;
  - **Module 2 –**Advisory Module (AM) responsible for pre-meal boluses and postprandial corrections, which can be adapted (individualized) with prior data for each subject;
  - **Module 3:** Automated Basal Rate Module (BRM) responsible for augmentation of basal rate to compensate for changes in insulin sensitivity, particularly overnight (e.g. dawn phenomenon), which can be adapted with prior data for each subject.

In addition, the investigational system:

- Displays information about glucose level and insulin delivery to the user;
- Assist the user with computing pre-meal insulin boluses and asks for confirmation of the suggested pre-meal insulin;
- Stores session data, including glucose readings and insulin delivery, and
- Ensures real-time remote monitoring of patient state and technical information.

VIII. ANTICIPATED CHANGES

When satellite devices – the CGM and the insulin pump - evolve, we will adapt DiAs with appropriate software updates (i.e. Low-power Bluetooth or ANT+ communication).

Any relevant changes in the study protocol will be reported and validated by the investigator, coordinator and sponsor. They will be documented as an amendment to the protocol.

Any changes that affect the intent or scientific soundness of the clinical study, or that may affect the welfare, safety and/or rights of the patient, will be submitted for approval by the IRB and by appropriate regulatory bodies, before implementing the changes into the clinical trial.

IX. MANUFACTURING

Not Applicable

APPENDIX B: GLOSSARY OF TERMS

Presented in Appendix A-13