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

CLINICAL PROTOCOL

UNIFIED SAFETY SYSTEM (USS) VIRGINIA CLOSED-LOOP VERSUS SENSOR AUGMENTED PUMP (SAP) THERAPY FOR HYPOGLYCEMIA REDUCTION IN TYPE 1 DIABETES

NCT02302963
Version Date: 09/16/2016

A. Purpose/Objectives

The purpose of this study is to evaluate the effectiveness of the control system in reducing hypoglycemia by comparing, in a randomized study, 24 hour control with USS Virginia versus sensor augmented pump (SAP) therapy in subjects with type 1 diabetes and hypoglycemia unawareness and/or risk for hypoglycemia. We will also evaluate the effectiveness of the control system to improve hypoglycemia counterregulation, hypoglycemia awareness, and overall glycemic control. To achieve this goal, we will conduct pre- and post-intervention inpatient assessments of hypoglycemia counterregulation and symptom awareness. Subjects randomized to USS Virginia will participate in two training visits at a monitored outpatient setting for the step-wise deployment of the cell phone based on the Artificial Pancreas (AP) system at home. The first training visit includes training on the study pump and AP system followed by 1 week use of AP system at home in Pump mode. The second training visit includes additional training on USS Virginia+AP system and confirmation of independent use by the subject followed by 4 week use of AP system at home in Closed Loop mode. Subjects randomized to sensor-augmented pump therapy will complete 5 weeks of CGM with the home pump.

This protocol will complement our recently completed protocol (IDE G130143) in which results demonstrate significantly improved glucose control overnight. Additionally, this protocol represents a culmination of prior clinical trials in the development of this USS Virginia system and benefits from the synthesis of those components.

The DiAs platform is now licensed to a local startup company, TypeZero Technologies LLC, which has further locked down its design features and re-implemented the system under the name inControl, for increased reliability and clear requirements traceability.

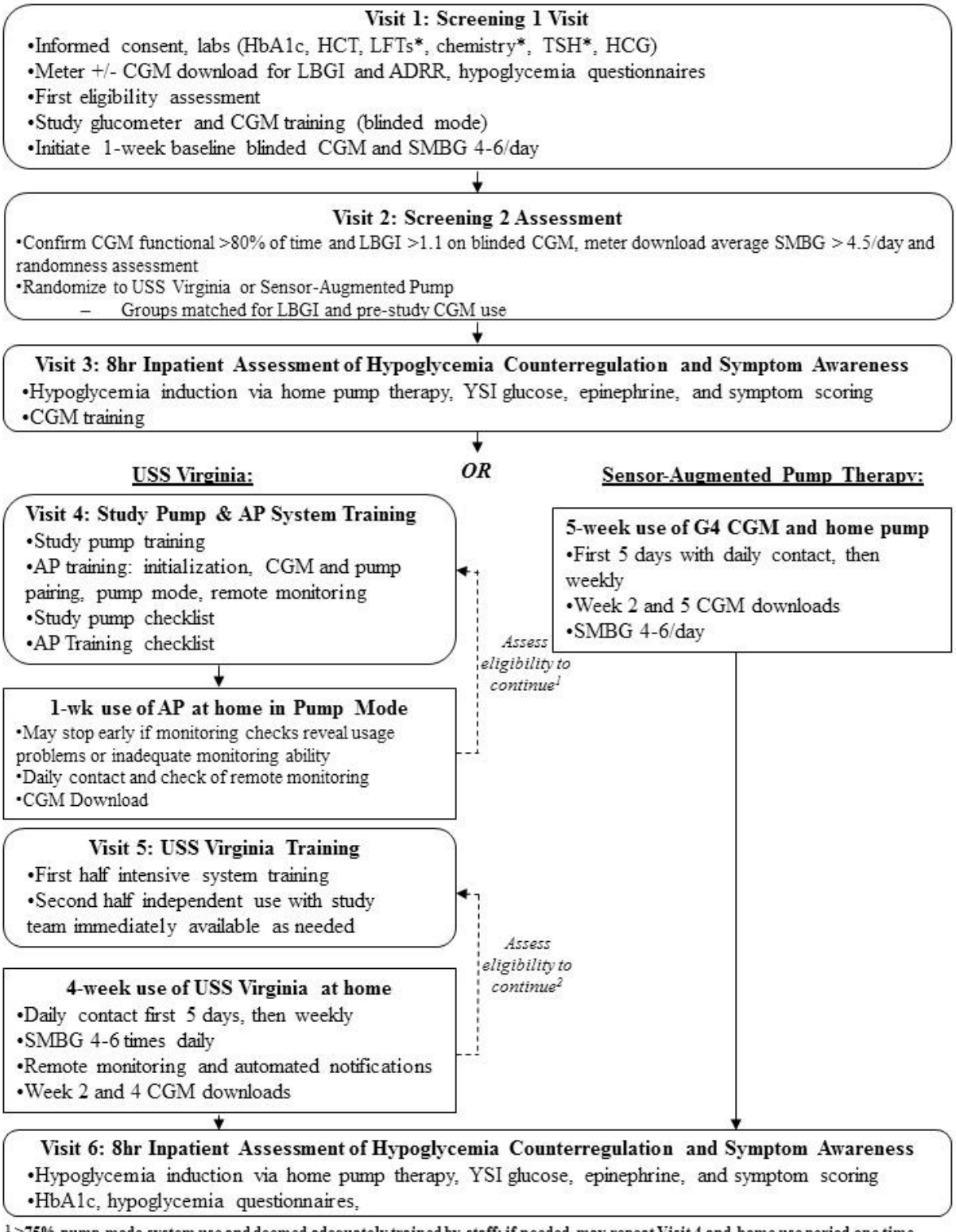
B. Study Design Overview

This is a randomized, controlled trial of Unified Safety System (USS) Virginia closed-loop versus sensor-augmented pump (SAP) therapy for hypoglycemia prevention in subjects with type 1 diabetes and hypoglycemia unawareness and/or risk for hypoglycemia.

Subjects: We will recruit up to 85 subjects aged 12-70 years old with type 1 diabetes for at least the past 1 year, on insulin for at least the past 1 year, and on insulin pump therapy for at least the past 6 months to achieve a goal of 44 completed subjects. Subjects will be recruited at two clinical sites: University of Virginia and Stanford University.

Procedure: Figure 1 below presents the overall flow of the study.

Figure 1: Study flow diagram



Visit 1: Screening 1 Visit. A meter ± CGM download will be performed to evaluate subject

eligibility (i.e. Average Daily Risk Range [ADRR] >40 or LBGI >2.5 from SMBG data or LBGI >1.1 from 1 week of CGM data within the prior 3 weeks) and to determine pre-study CGM use in the prior 4 weeks (active [CGM use ≥5 days/week] or no CGM use). Baseline HbA1c, hypoglycemia symptom awareness (presence of adrenergic symptoms at BG 60 mg/dL) and hypoglycemia questionnaires (Clarke Hypoglycemia Perception Awareness and Fear of Hypoglycemia – APPENDIX A-5) will be assessed. Those subjects that qualify will be trained to use the study glucometer and CGM in blinded mode and complete 1 week of baseline blinded CGM and SMBG at least 4 times daily.

Visit 2: Screening 2 Visit. The blinded CGM will be downloaded and if review of the data shows that the CGM was functional >80% of the time and the subject has confirmed risk of hypoglycemia with LBGI >1.1 (#2) (per 1 week of blinded CGM), the subject will be randomized to USS Virginia AP system experimental treatment or Sensor-Augmented Pump Therapy control treatment and proceed to Visit 3. The experimental and control groups will be matched for LBGI and pre-study CGM use. The study glucometer will be downloaded and assessed for average SMBG/day and randomness of data. Subjects with average SMBG <3.5/day and/or poor randomness of SMBG testing will be reminded of SMBG requirements 4-6 times daily (pre-meal, bedtime, before driving, before exercise, and as indicated). CGM data collection period may be repeated.

Visit 3: 8 hr Inpatient Assessment of Hypoglycemia Counterregulation and Symptom Awareness. The subjects will undergo hypoglycemia induction via a previously validated method (1) using subcutaneous insulin pump therapy with frequently sampled YSI glucose levels. Hypoglycemia counterregulation and symptoms will be assessed by epinephrine levels and hypoglycemia symptom scoring as the BG is decreased from 100-150 mg/dL to <60 mg/dL. Subjects will be trained on the Dexcom Share AP CGM and either proceed to Visit 4 if randomized to the experimental group or 5 weeks of CGM and home pump use if randomized to the control group.

Visit 4: Study Pump & AP System Training. Subjects in the USS Virginia group will present to the monitored outpatient setting to complete a training session including study pump training and AP system training. Subjects will be provide a copy of the AP system manual. Subjects will then use AP system at home in Pump mode, connected to the study CGM and study pump. During this week, study staff will contact the subject daily to answer any questions and enquire about any device complaints, adverse events, and whether the adverse event was related to AP system use. Study staff will also check the number of SMBG tests entered on the AP system and will remind the subject to perform 4-6 SMBG daily. The ability of AP system to be remotely monitored in the subject's daily environment will also be assessed with daily checks of the remote monitoring site. After completion of 1 week of AP Pump mode home use, study staff will determine whether additional training

and practice with the AP system is needed and whether the subject will repeat all or portions of Visit 4 and 1 week of home use (up to 1 time if needed) or proceed to Visit 5. Subject's that cannot be adequately monitored at least 75% of the time in their local environment will not be allowed to proceed.

Visit 5: USS Virginia Training. Visit 5 may occur remotely via GoToMeeting or similar HIPAA compliant web conferencing. This visit may also occur with visit 4 as determined by the study team. Subjects in the USS Virginia group will present to the monitored outpatient setting to complete a training session including an initial AP system closed-loop training followed by independent use of the system and completion of the AP Training Checklist. The study team will be immediately available as needed. Subjects will then use the AP system at home in Closed Loop mode, connected to the study CGM and study pump.

There will be an initial 3-5 day trial of the system at home in Closed Loop mode during which, the subject will receive daily contact from study staff and remote monitoring automated alerts will be in place. Study staff will also check the number of SMBG tests entered on the AP system and will remind the subject to perform 4-6 SMBG daily. Study staff will then determine whether additional training and practice is needed and whether the subject will repeat all or portions of Visit 5 and 3-5 days of the AP system home use (up to 1 time) or proceed with the remainder of the 4 weeks of the system Closed Loop home use. During the 4 weeks of home use, study staff will continue to contact the subject (daily for the first 5 days, then weekly) to answer any questions and enquire about any device complaints, adverse events, and whether the adverse event was related to the AP system use. Study staff will check the number of SMBG entered on the AP system daily and contact the subject if <4 SMBG are observed on any day. The subject's CGM data and meter data will be collected at week 2 and week 4. Subjects will be required to have average SMBG >4.5/day and random SMBG data to continue.

Visit 6: 8 hr Inpatient Assessment of Hypoglycemia Counterregulation and Symptom Awareness. Within approximately one week of completing either USS Virginia or sensor-augmented pump therapy at home, the subjects will undergo a final hypoglycemia induction using the home pump therapy with frequently sampled YSI glucose levels. Hypoglycemia counterregulation and symptoms will be assessed by epinephrine levels and hypoglycemia symptom scoring as the BG is decreased from 100-150 mg/dL to <60 mg/dL. Post-intervention HbA1c, and hypoglycemia questionnaires, and a DiAs Usability questionnaire (DiAs users only) will be completed. If a subject completes more than 1 week of either USS Virginia or sensor-augmented pump therapy and subsequently withdraws from the study intervention, they will be asked to complete Visit 6 within one week of discontinuing the intervention.

C. Pilot subjects

Each site will study two initial Pilot subjects: one aged 21-65 years old and one aged 15-20 years old. The Pilot subjects and their respective diabetes care partners will be used to test the adequacy of the AP system training period and the system performance (in Pump mode) in the subject's local environment. If significant changes are made to the system or to the protocol after the Pilot subjects or the AP system did not meet success criteria in the local environment, an additional two Pilot subjects (one aged 21-70 years old and one aged 12-20 years old) will be studied at each site. Pilot subjects may be repeated as necessary until no further changes are needed. Those sites that have already used the identical closed-loop system (phone, pump, sensor, MAF version of AP system) in two subjects at home for at least 1 week (336 hours) each do not need to complete the Pilot subjects as the system has already been tested in the home environment.

Pilot subjects will participate in Visit 1 (Consent and Screening). The study inclusion and exclusion criteria will apply to the Pilot subjects with the following exceptions: 1) the Pilot subjects will not have a significant risk of hypoglycemia (as assessed by LBGI <1.1 and ADRR <20 from the prior 30 days of meter data), and 2) the Pilot subjects will not have hypoglycemia unawareness (as assessed by a Clarke Hypoglycemia Perception Awareness score of 2 or less). If the Pilot subject is CGM-naïve, s/he may be trained on the study glucometer and study CGM and wear an unblinded CGM for up to a week at home at the discretion of the investigator. Prior CGM wearers may skip the home CGM use if they have previously been trained on the study CGM. Within 4 weeks of Visit 1, the Pilot subjects will proceed directly to Visit 4 (Study Pump and AP Training) with a subsequent 5 days of the AP system use in Pump mode in the subject's local environment and with remote monitoring and automated notifications in place. The Pilot subjects will receive daily contact by the study team and the remote monitoring site will be checked daily. Success of the Pilot subjects will be determined by >80% time of functional system components including: CGM, pump, AP system, connectivity with the CGM, and AP system connectivity with the pump. There will also need to be remote monitoring capability at least 75% of the time.

After the Pilot subjects at each site have successfully completed Visit 4 and 5 days of use at home in Pump mode, study enrollment and randomization may proceed at each site. The data from the Pilot subjects will not be used in the final analysis. Pilot subjects will not be counted in the enrollment tally.

D. Sample Size and Investigational Sites

The studies will be conducted at University of Virginia and Stanford and will require IRB approval at each site prior to the initiation of the trial.

At the University of Virginia, all inpatient studies (Visit 3 and Visit 6) will be performed at the Clinical Research Unit (CRU) of the University of Virginia Health System with website

at: (http://research.med.virginia.edu/clinicalresearch/research-resources/offices-supporting-clinical-research/clinical-research-unit/). The street address is:
UVA Medical Center
1215 Lee St, Barringer Wing
Charlottesville, VA 22903

The monitored outpatient studies (Visit 4 and Visit 5) will occur at a UVa CRU.

At Stanford, all inpatient studies (Visit 3 and Visit 6) will be performed at The Stanford Center for Clinical and Translational Research and Education (CTRU) with website at: http://spectrum.stanford.edu/accordions/clinical-and-translational-research-unit.

The monitored outpatient studies (Visit 4 and Visit 5) will in 3 rooms available for outpatient research studies through "ACCESS", a clinical research resource available at Stanford. These rooms are available in the same building as the Endocrine Division and are adjacent to the CTRU.

Forty-four subjects (N=44) with type 1 diabetes mellitus will be needed to complete the protocol.

Based on our experience with similar studies and the additional requirement of hypoglycemia unawareness or risk for hypoglycemia, we estimate an expected ~40% screen failures, dropouts, or withdrawals, thus we intend to set a recruiting target of 70 subjects.

Hypothesis:
We hypothesize that in patients with hypoglycemia unawareness and a risk for hypoglycemia, the AP system equipped with USS Virginia compared with CGM-augmented pump therapy will result in:

1. Reduced risk for hypoglycemia and exposure to hypoglycemia (measured by the Low Blood Glucose Index and by CGM time in hypoglycemia).
2. Restoration of hypoglycemia counterregulation (as assessed by epinephrine response measured in a hospital setting), restoration of hypoglycemia awareness, and reduced fear of hypoglycemia.

Primary Specific Aim:
Reduction in hypoglycemia during the study on USS Virginia versus SAP as assessed by:

- LBGI from CGM during 1 week of baseline blinded use versus during the last week of intervention.

Secondary Specific Aims:
Reduction in hypoglycemia during the study on USS Virginia versus SAP as assessed by:

- CGM time <70 mg/dL and <50 mg/dL by retrofitted CGM and SMBG trace during a 24 hour period and the overnight period (11PM – 7AM) from 1 week of baseline blinded use versus the last week of intervention.

Improvement in counterregulatory response to hypoglycemia at baseline versus follow-up as assessed by:

- Peak epinephrine
- Epinephrine area under the curve (AUC)
- Epinephrine increase over baseline

Improvement in hypoglycemia awareness at baseline versus follow-up as assessed by:

- Hypoglycemia symptom ratings
- Clarke Hypoglycemia Perception Awareness and Fear of Hypoglycemia scores

Improvement in glycemic control at baseline versus the last week of intervention as assessed by:

- Time within target (70-180 mg/dL) over a 24 hour period.
- Time within target (80-140 mg/dL) in the overnight period (11PM – 7AM)
- Distribution of wake-up glucose levels at 7AM

Sample size determination is based on literature data (#3) and on results from our previous studies of hypoglycemia unawareness (#4)**Error! Reference source not found.**. We estimate, conservatively, that the effect size of using the AP system+USS Virginia vs. CGM in terms of restoration of epinephrine response will be moderate ~0.35. Power calculations assuming α=0.05, and power of 80% yield a required sample size of N=36 (using G*Power 3 software [#5]). With this sample size, the power for finding significant effects on frequency and extent of hypoglycemia (Low BG Index [#6]) exceeds 0.9. Assuming a proportion of noncompliance R=20% for Intention-to-Treat (ITT) analysis (#7), 44 completed subjects will adequately address the specific aims of this study. Per-protocol analysis will also be performed. In order to achieve 44 completed subjects, up to 70 subjects may sign consent given an expected screen failure, withdrawal and drop-out rate of ~40% due to the rigorous exclusion criteria and requirements imposed for the AP system use in the subject's local environment.

E. Study Duration

Subject participation will last roughly 7-14 weeks depending on whether Visit 4 and/or Visit 5 and the subsequent home use portions of the study need to be repeated as per Figure 1 above. This includes: 1 day screening visit, 1 week baseline blinded CGM use, 1 day eligibility assessment and randomization visit, 1 day inpatient assessment of hypoglycemia counterregulation and symptom awareness, then either 5 weeks of sensor augmented pump

therapy at home or the AP system+USS Virginia training and use at home. The AP system +USS Virginia training and use includes: 1 day outpatient study pump and the AP system training, 1 week use of the system at home in Pump mode, 1 day outpatient AP system +USS Virginia training and 4 weeks use of the AP system +USS Virginia at home. Each group will additionally complete a final 1 day inpatient assessment of hypoglycemia counterregulation and symptom awareness. Up to 14 days are able to be repeated in the scheme above, up to 4 weeks may elapse between Visit 1 and Visit 3, and up to 1 week may elapse between completion of the study intervention and Visit 6.

Participation for the Pilot subjects will last up to 6 weeks including: 1 day screening visit, 0-1 week use of study CGM at home,1 day outpatient study pump and AP training, and 5 day use of the AP system at home in Pump mode. Up to 4 weeks may elapse between the screening and the AP training visit.

F. Inclusion and Exclusion Criteria

Inclusion Criteria: To be eligible for the study, a subject must meet the following criteria:

- Clinical diagnosis of type 1 diabetes for at least 1 year. 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):
        - Fasting glucose ≥126 mg/dL – confirmed
        - Two-hour OGTT glucose ≥200 mg/dL – confirmed
        - HbA1c ≥6.5% – confirmed
        - Random glucose ≥200 mg/dL with symptoms
        - No data at diagnosis is available but the participant has a convincing history of hyperglycemia consistent with diabetes or in the opinion of the investigator participant has history consistent with type 1 diabetes.
    - Criteria for requiring insulin at diagnosis (at least 1 must be met):
        - Participant required insulin at diagnosis and continually thereafter
        - Participant did not start insulin at diagnosis but upon investigator review likely needed insulin (significant hyperglycemia that did not respond to oral agents) and did require insulin eventually and used continually
        - Participant required 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 thereafter
- Use of insulin for the last 12 months or more
- Use of an insulin infusion pump for the last 6 months or longer
- Age 12-70 years old

- HbA1c <10.0% as measured with DCA2000 or equivalent device; if HbA1c <6.0% then total daily insulin must be ≥0.5 U/kg
- Risk of hypoglycemia or hypoglycemia unawareness as defined by any of the following:
    - Clarke Hypoglycemia Perception Awareness questionnaire score of ≥4 (#8).
    - Average Daily Risk Range (ADRR) >40 as assessed from SMBG readings from the prior month (#9). Subject must have a glucometer that can be downloaded for this assessment. The subjects may alternatively provide a spreadsheet of their past 30 days of blood glucose values.
    - Low Blood Glucose Index (LBGI) >2.5 as assessed from SMBG from the prior month or LBGI >1.1 as assessed from 1 week of CGM readings from the prior three weeks. Subject must have a glucometer or CGM that can be downloaded for this assessment. For the glucometer data, the subjects may alternatively provide a spreadsheet of their past 30 days of blood glucose values.
    - Subject reports no recognition of hypoglycemia until the glucose is <60 mg/dL and no adrenergic symptoms at glucose of 60 mg/dL (shakiness, palpitations, diaphoresis).
- Able to speak and read English and use basic technology such as a cell phone.
- Currently using an insulin-to-carbohydrate ratio to calculate meal bolus sizes.
- Access to Internet or cell phone service in the subject's local environment.
- Willingness to maintain uninterrupted availability via personal cell phone at all times during the study.
- Willingness to perform SMBG testing 4-6 times daily (before meals, bedtime, before driving, before exercise, and as indicated) during the interventional phases of the study.
- Living with a diabetes care partner ≥18 years old who meets the following inclusion criteria:
    - Committed to potentially (if randomized to the AP system) participating in all training activities involving components and emergency procedures,
    - Knowledgeable at all times of the participant's location during the day when closed loop is in use,
    - Committed to maintaining uninterrupted availability via personal cell phone,
    - Being present and available to provide assistance when the closed loop system is being used at night,
    - Able to speak and read English and use basic technology such as a cell phone, and
    - Absence of known medical condition that in the judgment of the investigator might interfere with the completion of the protocol such as the following examples:
        - Inpatient psychiatric treatment in the past 6 months,
        - Current or recent abuse of alcohol or recreational drugs by history

- A recent injury to body or limb, muscular disorder, use of any medication, any carcinogenic disease, or other significant medical disorder if that injury, medication, or disease in the judgment of the investigator will affect the completion of the protocol.

Exclusion Criteria: The presence of any of the following is an exclusion for the study:

- Admission for diabetic ketoacidosis in the 12 months prior to enrollment.
- Severe hypoglycemia resulting in seizure or loss of consciousness in the 3 months prior to enrollment.
- Hematocrit less that the lower limit of normal for the assay.
- Pregnancy, breast-feeding, or intention of becoming pregnant over time of study procedures
  - *If female and sexually active, must agree to use a form of contraception to prevent pregnancy while a participant in the study. A negative urine pregnancy test will be required for all premenopausal women who are not surgically sterile. Subjects who become pregnant will be discontinued from the study.*
- Conditions which may increase the risk of induced hypoglycemia such as: known coronary artery disease, congestive heart failure, history of any cardiac arrhythmia (benign premature atrial contractions and premature ventricular contractions allowed), history of seizure disorder, history of cerebrovascular event or transient ischemic attack, hypoglycemia-induced migraine within the last 6 months, or neurological disease.
- Cystic fibrosis
- A known medical condition that in the judgment of the investigator might interfere with the completion of the protocol such as the following examples:
  - Inpatient psychiatric treatment in the past 6 months for either the subject or the subject's diabetes care partner
  - Presence of a known adrenal disorder
  - Abnormal liver function tests (transaminase >3 times the upper limit of normal); testing required for subjects taking medications known to affect liver function or with diseases known to affect liver function
  - Abnormal renal function test results (estimated GFR <60 mL/min/1.73m2); testing required for subjects with diabetes duration of greater than 5 years post onset of puberty
  - Active gastroparesis
  - 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
  - Uncontrolled thyroid disease (TSH undetectable or >10 mIU/L); testing required within 3 months prior to admission for subjects with a goiter, positive antibodies, or who are on thyroid hormone replacement, and within one year otherwise

  - Current or recent abuse of alcohol or recreational drugs by patient history
  - Infectious process not anticipated to resolve prior to study procedures (e.g. meningitis, pneumonia, osteomyelitis)
  - Any skin condition in the area of insertion that prevents safe sensor or pump placement (e.g. bad sunburn, pre-existing dermatitis, intertrigo, psoriasis, extensive scarring, cellulitis)
  - Diagnosed with celiac disease and not currently following a gluten free diet
- A recent injury to body or limb, muscular disorder, use of any medication, any carcinogenic disease, or other significant medical disorder if that injury, medication, or disease in the judgment of the investigator will affect the completion of the protocol
- Current use of any of the following drugs and supplements:
  - Any medication being taken to lower blood glucose, such as Pramlintide, Metformin, GLP-1 Analogs such as Liraglutide, and nutraceuticals intended to lower blood glucose
  - Beta blockers
  - Oral glucocorticoids
  - Pseudoephedrine
  - Any other medication that the investigator believes is a contraindications to the subject's participation

Restrictions on use of other drugs or treatments:

- Acetaminophen will be restricted starting 24 hours prior to CGM use and continuing through the entire study.
- Caffeinated products will be restricted on the day of Visit 3 and Visit 6 until sampling of blood for epinephrine is completed.
- Study procedures will be put on hold if acetaminophen use is medically necessary. A need for repeated doses may result in stopping study participation at the discretion of the investigator.
- The CGM sensor will be removed if MRI is needed. Study procedures will be put on hold and continued subject participation will be at the discretion of the investigator.
- The subject should not donate blood for other purposes while enrolled in this study.
- A medical need for oral or injected glucocorticoids will result in stopping study participation.

G. STUDY TIMELINE

1. Visit 1: Screening 1 Visit

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

- Signed and dated informed consent +/- assent if applicable

- Inclusion and exclusion criteria
- Meter and CGM (if CGM user) download from prior 30 days to assess LBGI and ADRR
- CGM download from prior 4 weeks (if CGM user) to assign subject to one of two pre-study CGM groups:
    - Active user: CGM use ≥5 days/week
    - Non-user: No CGM use
- Clarke Hypoglycemia Perception Awareness survey
- Fear of Hypoglycemia questionnaire
- Demographics (date of birth, gender, race and ethnicity)
- Medical history
- 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 total daily insulin over 7 days, hypoglycemia awareness and adrenergic symptom assessment, history of DKA, history of severe hypoglycemia, and SMBG values)
- Past and current medical conditions
- Surgical history
- Menstrual history (females), sexual activity and contraceptive use agreement
- Allergies
- Medications and supplements
- Social history including drinking, smoking, and drug habits
- Review of systems
- Physical examination
- Weight and height
- Vital signs
- Blood draw for screening labs:
    - HbA1c (results from DCA 2000 or equivalent device within 2 weeks of screening may be accepted)
    - Basic metabolic panel (testing required for subjects with diabetes duration of greater than 5 years post onset of puberty)
    - Liver function tests (testing required for subjects taking medications known to affect liver function or with diseases known to affect liver function)
    - Qualitative serum HCG in women with childbearing potential. If not performed, document reason (i.e. hysterectomy, postmenopausal)
    - Hematocrit

  - TSH (testing required within 3 months prior to screening for subjects with a goiter, positive antibodies, or who are on thyroid hormone replacement, and within one year otherwise)
- Preferred foods for the subject's self-treatment of hypoglycemia will be documented to have available in the monitored research setting.

Subjects travelling from a distance or subjects wishing to be pre-screened for eligibility (e.g. review of meter download, assessment for presence of hypoglycemia unawareness, labs performed locally, etc.) may elect to have the consent +/- assent (50.53) read and explained by study staff by phone. Once all questions have been answered, the signed consent +/- assent will be faxed or mailed to study personnel and the subject may then have pre-screening with labs performed locally (e.g. LabCorp) prior to Visit 1. The consent +/- assent form will be reviewed again with the subject +/- parents at Visit 1.

Once all results of the screening evaluations are available, a decision will be made to determine the subject eligibility for the study. The study physician will have the discretion to repeat screening tests. The repeat screening tests may be conducted locally (e.g. LabCorp). The subject may request a copy of any of the results from the screening evaluation to review with their primary care provider.

- If an exclusionary condition is identified, the study subject will be excluded from participation with follow up and referral 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 an abnormal hematocrit is detected, the patient may have the hematocrit re-tested to exclude the possibility of lab error or hydration effects. If anemia is confirmed on repeat testing, the study subject will be excluded. A copy of the result will be provided and the subject will be advised to discuss the result with the personal physician for further evaluation and treatment.
- Subjects may be re-screened at a later date if their clinical situation changes as determined by the study physician. Subjects that stopped study participation due to need for oral glucocorticoids (e.g. bout of poison ivy) may be re-screened and re-enrolled after there is no further anticipated need for oral glucocorticoids.

The total amount of blood to be withdrawn during the screening visit is up to

25 cc. If a subject meets all the study criteria, s/he will be enrolled in the trial and trained on the study glucometer and Dexcom CGM.

Study Glucometer and Dexcom CGM Training:

- The subject will be trained on the use of the study glucometer and will demonstrate proficiency with a fingerstick test.
- Subjects will be reminded to use the same study glucometer for all finger sticks and calibrations.
- The subject will be trained on Dexcom CGM use and will be supervised during the initial CGM sensor placement.
- If the participant is a Pilot subject, s/he will use the CGM for up to 1 week (unblinded) at home and will be reminded to base all treatment decisions on glucometer results, not CGM data.
- For non-Pilot subjects, once the initial calibration BG is entered and the Dexcom is confirmed to be functional, the CGM will be placed in blinded mode for 1 week use of blinded CGM at home.
- If the participant experiences a sensor failure or issue with the CGM device 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 or device.
- Subjects will be required to perform 4-6 SMBG measurements daily (recommended before meals, about 2 hours after meals and at bedtime), and as needed to calibrate the CGM. Additional fingersticks may be obtained, if desired.
- If a subject is a CGM-wearer at screening, the subject may continue to use the home CGM during blinded study CGM use.

The screening visit and training session will last approximately 3 hours. This may be shorter depending on the amount of pre-screening that was performed and the subject's prior knowledge of study devices.

If the subject cannot schedule Visit 3 within 4 weeks of screening, the inclusion and exclusion criteria will be re-evaluated. The study physician will have the discretion to repeat any test as needed.

2. Visit 2: Screening 2 Visit

After completion of 1 week of baseline blinded CGM use, the subject will return to have the Dexcom CGM and study glucometer downloaded to assess the subject's baseline risk for hypoglycemia and evaluate the reliability of CGM data collection. The meter data will be

assessed for average SMBG/day and randomness of data. Subjects with average SMBG <3.5/day and/or poor randomness of SMBG testing will be reminded of SMBG requirements 4-6 times daily (pre-meal, bedtime, before driving, before exercise, and as indicated).

In order to continue with the trial, the subject must have all of the following:

- Baseline LBGI >1.1 as assessed by the prior 1 week of blinded CGM data
- CGM must have been functional >80% of the time (i.e. >1600 CGM data points/week).

CGM data collection period may be repeated. Eligible subjects will be scheduled for Visit 3 within 3 weeks of Visit 2. Subjects will be randomized to experimental treatment with the AP system+USS Virginia or control treatment with sensor-augmented pump therapy. Groups will be matched for LBGI and pre-study CGM use.

Preparation for Visit 3:

- All subjects will be given written instructions to bring their pump supplies, glucometer supplies, CGM supplies, insulin and all of their current medications (including aspirin or regular analgesics) with them for use during the admission.
- These instructions will also advise the subject to contact the study team in the event of a febrile or vomiting illness within 24 hours of the admission, so that the admission can be rescheduled.
- The subject will be asked to avoid the need for a pump site change during Visit 3.
- The subjects will be asked to arrive at the unit fasting and to not consume caffeine on the morning of admission.
- Subjects will be asked to check a fingerstick BG at 03:00 and 06:00 on the morning of admission for Visit 3 and to aim for a steady BG between 100-150 mg/dL upon arrival to the research unit at 07:00.
- The subject may administer a correction bolus of insulin to stabilize BG or treat hyperglycemia.
- The subject may consume fast acting glucose (glucose tablets, gel or liquid) to stabilize BG or treat BG <100 mg/dL.

Visit 2 is anticipated to last approximately 30 minutes.

3. Visit 3: 8 hr Inpatient Assessment of Hypoglycemia Counterregulation and Symptom Awareness

Visit 3 will occur within 4 weeks of the Screening Visit (Visit 1).

Admission Overview:

The subject will be admitted to the research unit by 07:00 for a blinded assessment of hypoglycemia counterregulation and symptom awareness. After a Run-in Period for stabilization of the subject's BG in the ~100-150 mg/dL range, the subject will participate in a previously validated Hypoglycemia Induction (#1) where the home insulin pump therapy will be used to induce an episode of hypoglycemia with goal glucose of <60 mg/dL. After carbohydrate rescue to BG ≥80 mg/dL, the subject will receive a meal and will be monitored for at least an additional hour in the Recovery Period. The subject may then be discharged once the glucose is stable (i.e. at least the prior 2 values) between 100-300 mg/dL and fingerstick ketone level <0.6 mmol/L. The subject will additionally receive training on the Dexcom CGM as needed and will receive supplies and instructions to complete the next portion of the study. The specific details of the ~8 hour inpatient admission are provided below.

Clinical Research Unit (CRU) Procedures:

- A nurse will be at the bedside or on the unit throughout the study.
- Study staff (MD or NP who has experience in diabetes management) will also be immediately available at the bedside or on the unit throughout the entire study.

Blood Sampling and Hypoglycemia Symptom Questionnaires

- The clinical centers will either use reinfusion of blood or will discard blood with each blood draw depending on the standard practice at each center's Clinical Research Unit.
- Subjects and parents (or diabetes care partners) will be blinded to the results of the glucose testing until the Recovery Period in an attempt to eliminate bias when answering questions regarding symptoms of hypoglycemia.
- Once IV access has been established, blood will be sampled for YSI glucose every 5-30 minutes. The frequency of blood draws for YSI sampling is dependent on the value of the previous sample, according to the following ranges:
    - BG >200: every 30 minutes
    - BG >100-200: every 15 minutes
    - BG ≤100 mg/dL: every 5 minutes
- Blood may be sampled for YSI glucose as needed for patient safety or to recheck a suspected erroneous value (e.g. dilute sample).
- Blood will be sampled for epinephrine and glucagon and Hypoglycemia Symptom Questionnaires will be performed during the admission as follows:

- **Run-in Period:**
  - Blood will be sampled for epinephrine at the initial sampling time for YSI glucose after the IV access is established.
  - Once BG is between 100 to 150 mg/dL, baseline Hypoglycemia Symptom Questionnaires will be completed and blood will be sampled for epinephrine and glucagon at the next scheduled sampling time for YSI glucose.
- **Hypoglycemia Induction Period:**
  - Blood will be sampled for epinephrine approximately every 15 minutes once the blood glucose has decreased to ≤90 mg/dL with goal of epinephrine sampling at BGs of 90, 75, 60 and <60 mg/dL.
  - Blood will be sampled for glucagon when the blood glucose is <60 mg/dL, just prior to the administration of hypoglycemia rescue therapy.
  - A Hypoglycemia Symptom Questionnaire will be completed approximately every 15 minutes once the blood glucose has decreased to ≤90 mg/dL (any time blood is sampled for epinephrine) until hypoglycemia BG <60 mg/dL and recovery BG ≥80 mg/dL has been achieved.
- **Recovery Period:**
  - Blood will be sampled for epinephrine every 15 minutes for a total of 4 samples after the nadir blood glucose.

- The actual time (rounded to the nearest minute) of all blood draws and questionnaires per the study clock set to an atomic clock will be documented on the nursing flow sheet.
- There will be about 31 blood draws for glucose sampling during the admission. Approximately 1 cc discard (at discard centers) and 1 cc sample will be taken for each blood draw for glucose. There will additionally be about 11 blood draws for epinephrine in duplicate (2 cc total per epinephrine draw) and 2 blood draws for glucagon in duplicate (2 cc total per glucagon draw). Therefore, the anticipated blood drawn for the entire admission will be about 88 cc at centers using a discard technique and 57 cc at centers using blood-sparing procedures.
- For subjects ≥18 years old, the total blood drawn in the entire study will not exceed 400 cc.
- For subjects <18 years old, the maximum allowed volume will be determined by subject's weight. A maximum of 4 ml/kg may be drawn within 30 days and a maximum of 7 ml/kg may be drawn in an 8 week period.

YSI Instructions

- Once IV access has been established, blood will be sampled for YSI glucose every 5-30 minutes. The frequency of blood draws for YSI sampling is dependent on the value of the previous sample, according to the following ranges:
  - BG >200: every 30 minutes
  - BG >100-200: every 15 minutes
  - BG ≤100 mg/dL: every 5 minutes
- Blood may be sampled for YSI glucose as needed for patient safety or to recheck a suspected erroneous value (e.g. dilute sample).
- In the event of loss of IV access or loss of a functional YSI and need for continued subject monitoring, glucose measurements will be made on capillary whole blood using the study glucometer.

IV Access

- During the CRC portion of the study, intravenous access will be maintained for blood sampling and for the treatment of severe hypoglycemia or hyperglycemia during the study. If an IV fails, a new IV will be inserted.
- If there is failure of intravenous access, the study physician will be available at the bedside to make decisions about appropriate insulin and glucose adjustments. Fingerstick glucose measurements on the study glucometer may be used during times of inadequate IV access and need for glucose monitoring.

Heating Device

- To facilitate IV insertion and blood drawing, and to obtain arterialized blood samples, heat may be applied to the subject's arm using a hospital-approved Gaymar T/pump (Gaymar Industries, Inc., Orchard Park, NY).

β-Hydroxybutyrate Testing

- Subject blood ketones should be evaluated from capillary blood using the ketone meter at the following times:
  - On arrival to and at discharge from the clinic
  - Glucose ≥250 mg/dL every 60 minutes
  - Ketones ≥0.6 mmol/L every 60 minutes
  - Nausea, vomiting or abdominal pain regardless of glucose level
  - A subject will be observed in the clinic until the ketone level is <0.6 mmol/L

Capillary Glucose Testing

- In the event of loss of IV access or loss of functional YSI, glucose measurements may be taken from fingersticks using the study glucometer. Fingersticks will be performed approximately every 30 minutes when the glucose level is >80 mg/dL and approximately every 15 minutes when the glucose level is ≤80 mg/dL. Additional fingersticks may be taken as needed for patient safety.

Inpatient Hypoglycemia Treatment

- Glucose <60 mg/dL will be treated orally with fast acting carbohydrate as needed until a glucose level of ≥80 mg/dL is achieved.
- In the event that there is intravenous access and the subject is at risk for severe hypoglycemia, the subject will be treated with a ~2-3 mL/kg D10 intravenous glucose bolus. Risk for severe hypoglycemia is defined as any of the following situations:
    - Glucose <50 mg/dL
    - The subject is unable to cooperate with oral treatment of hypoglycemia
    - The glucose is dropping at a rate that may not respond adequately to oral treatment
    - The subject experiences symptoms of neuroglycopenia (e.g. lethargy, disorientation, confusion [disordered processing of information or communication], or inappropriate behavior)
    - The subject experiences symptoms of severe hypoglycemia (i.e. hypoglycemic seizure or loss of consciousness)
- In the event that there is NO intravenous access and the subject is at risk for severe hypoglycemia (as defined above), the subject will be treated with 1 mg of glucagon subcutaneously or intramuscularly.
    - The drug will be reconstituted and administered per package insert/instructions.
    - Glucagon may be repeated as needed every 20 minutes to achieve glucose level ≥80 mg/dL. Once the subject is able to consume oral treatment, the subject will be treated orally with fast acting carbohydrate as needed until a glucose level of ≥80 mg/dL is achieved. Orange juice and milk will be avoided after glucagon administration.
    - Attempts will be made to reestablish intravenous access.
- The Hypoglycemia Induction Admission will be stopped if the subject experiences a hypoglycemic seizure or loss of consciousness and only safety procedures will be continued. The study physician or nurse practitioner will take control over glucose sampling decisions in order to stabilize the

subject's glucose between 100-300 mg/dL and determine the appropriate subject disposition (i.e. home or medical facility).

Inpatient Hyperglycemia and Ketone Treatment

- If the subject's glucose is >300 mg/dL or β–hydroxybutyrate level is ≥0.6 mmol/L on admission, the subject will be stabilized per the procedures below. The subject will continue to be monitored until a glucose level between 100-300 mg/dL and β–hydroxybutyrate measurement <0.6 mmol/L has been achieved (or the subject is discharged to an appropriate medical team).
- Subsequently, glucose >300 mg/dL for >2 hours or glucose ≥400 mg/dL at any time will prompt discontinuation of the Hypoglycemia Induction Admission.
- β–hydroxybutyrate will be assessed hourly while the glucose is ≥250 mg/dl or the β–hydroxybutyrate level is ≥0.6 mmol/L.
- If the glucose is >300 mg/dL and β–hydroxybutyrate level is <0.6 mmol/L, corrective action will be taken only after it has been at least 90 minutes from the last subcutaneous insulin dose. Specifically, the subject will be asked to bolus with his/her pump an amount of corrective insulin that will bring him/her to a target glucose of 120 mg/dL.
- If the β–hydroxybutyrate level is ≥0.6 mmol/L, the cause of the elevated ketone level will be investigated (e.g. pump or pump site malfunction). Additional insulin may be administered either via insulin syringe or via a new pump site. The amount of insulin administered will be calculated using the subject's insulin sensitivity factor and a target glucose of 120 mg/dL.
- If the β–hydroxybutyrate level is ≥1.5 mmol/L, the Hypoglycemia Induction Admission will be stopped and the study MD or NP will take control of the subject's insulin dosing. The cause of the elevated ketone level will be investigated (e.g. pump or pump site malfunction). If the subject's home parameters are not felt to be working adequately due to hyperglycemia, ketonemia, or other factors (e.g. intercurrent illness), the study MD or NP will administer corrective insulin either via insulin syringe or via a new pump site using an ISF determined to be appropriate for the setting and a goal glucose of 120 mg/dL. The subject will continue to be monitored until a glucose level between 100-300 mg/dL and β–hydroxybutyrate measurement <0.6 mmol/L has been achieved (or the subject is discharged to an appropriate medical team).

Acceptable Medications

- The subject may continue any home medications including his/her home

over-the-counter or prescribed analgesics as long as the medication is not on the list of restricted drugs and the subject brought his/her own supply. The patient may use his/her own ibuprofen or aspirin per package labeling.

Inpatient Admission Detail (~6.5-9.5 hours)

1. Admission at approximately 07:00
2. Run-in Period for glucose stabilization at approximately 07:30-08:00
3. (Optional extension of the Run-in Period for glucose stabilization until 11:00)
4. Hypoglycemia Induction Period to achieve hypoglycemia to goal glucose <60 mg/dL from ~08:00 – 12:00)
5. Recovery Period with meal and glucose stabilization from ~12:00-13:00
6. Discharge Preparation Period ~13:00-13:30
7. Discharge at ~13:30. Discharge may be as late as 16:30 if the Run-in Period is extended.

Admission Day:

- **Pre-Admission Set-up:**
  - At approximately 06:30 the CRU study equipment (YSI, Precision Xtra Blood Glucose and Ketone Monitoring System, and study glucometer) will be calibrated and the appropriate Quality Controls will be run per the manufacturer's guidelines.
  - The times on all study devices (i.e. study clocks, YSI(s), glucometers, and Precision Xtra β-ketone monitor) will be synchronized to the Official US Time using www.time.gov or to an equivalent atomic clock.
  - All of the medications required for the treatment of hypoglycemia, hyperglycemia or hypotension including glucose tablets, glucose gel/liquid, D10W, glucagon 1 mg emergency kit, and 1 L normal saline bags will be placed at the subject's bedside.
  - The CRC code cart will be in close proximity to the subject's room.

- **Subject Admission Readiness Assessment:**
  - The subject will meet the study team at the Clinical Research Unit by approximately 07:00 and the subject will be assessed for admission readiness.
  - The subject will be asked about any adverse events since the last study visit.
  - The subject will continue to use his/her individual insulin pump for insulin dosing throughout the admission.
  - The study team will confirm that the subject brought his/her personal

insulin and insulin pump supplies and regular medications.
- The study team will confirm the absence of a febrile or vomiting illness within 24 hours of the admission.
- Female subjects of childbearing capacity 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.
- Vital signs (blood pressure, pulse, temperature) will be performed and documented. The subject must have T <99.5ºF (<37.5ºC) for admission.
- The study nurse will perform a fingerstick glucose with the study glucometer and fingerstick β-hydroxybutyrate with the study Precision Xtra meter. The subject must have an admission glucose ≤300 mg/dL and β-hydroxybutyrate <0.6 mmol/L to continue with the inpatient admission.
  - If glucose is >300 mg/dl or β-hydroxybutyrate is ≥0.6 mmol/L, the subject will be rescheduled and stabilized per the procedures above (Inpatient Hyperglycemia and Ketone Treatment).
  - The subject will continue to be monitored until a glucose level between 100-300 mg/dL and β–hydroxybutyrate measurement <0.6 mmol/L has been achieved (or the subject is discharged to an appropriate medical team).
- If all admission readiness criteria are not met, the subject will be rescheduled. If all of the admission readiness conditions are met, the subject will be admitted to the Clinical Research Unit.

- **Procedures Upon Admission:**
  - Heat may be applied to the sites of IV insertion with a hospital-approved Gaymar T/pump heating pad.
  - Intravenous access appropriate for blood drawing and potential intravenous DW10 rescue will be established.
  - The subject's current pump parameters will be reviewed by the study physician and documented. Any insulin boluses administered on the day of admission will be recorded.
  - Aside from administered meals and carbohydrate rescue, the subject will remain fasting on the unit except for ad lib water and glucose-free beverages. Caffeine will be restricted until blood sampling for epinephrine is completed.
  - Strenuous activity is restricted until blood sampling for epinephrine is

completed.
- Subjects and parents (or diabetes care partners) will be blinded to the results of the glucose testing until the Recovery Period in an attempt to eliminate bias when answering questions regarding symptoms of hypoglycemia.

- **Procedures Related to the Run-in Period:**
  - The Run-in Period will nominally occur from 07:30-08:00.
  - The goal of the Run-in Period is to reach a target glucose of 100-150 mg/dL.
  - Once IV access has been established, blood will be sampled for YSI glucose every 5-30 minutes per the Blood Sampling guidelines above.
  - Blood will be sampled for epinephrine at the initial sampling time for YSI glucose.
  - Fast acting carbohydrates may be used to stabilize the glucose or treat BG <100 mg/dL at any time during the Run-in Period.
  - For glucose >150 mg/dL, correction boluses may be administered with the home pump up to every 90 minutes for a maximum of 2 correction boluses. The amount of insulin administered will be calculated using the subject's insulin sensitivity factor and a target glucose of 120 mg/dL.
  - Once BG is between 100 to 150 mg/dL, baseline Hypoglycemia Symptom Questionnaires will be completed and blood will be sampled for epinephrine and glucagon at the next scheduled sampling time for YSI glucose.
  - The Run-in Period may be extended until 11:00 to ensure that it has been at least 90 minutes since the last correction bolus, at least 60 minutes since the last glucose <70 mg/dL, and at least 30 minutes since the last carbohydrate treatment. The subject may enter the Hypoglycemia Induction Period once these criteria are met and glucose is 100-150 mg/dL. If these criteria are not attained by 11:00, the subject will be rescheduled. The subject MD or NP will take control of the glucose sampling and insulin management and the subject will continue to be monitored until a glucose level of 100-300 mg/dL is attained prior to discharge.

- **Procedures Related to Hypoglycemia Induction Period:**
  - The Hypoglycemia Induction Period is anticipated to last approximately 2-4 hours (~08:00-12:00). If the subject has not reached the endpoint (<60 mg/dL) within ~4 hours, the subject will

proceed to the Preparation for Discharge Period at the discretion of the investigator.

- At the start of the hypoglycemia induction, the basal insulin rate will be increased by approximately 25-50% to provide a gradual decline in blood glucose (~1 mg/dL/min). A small priming bolus dose of insulin equal to approximately one hour of the subject's usual basal dose +/- correction dose with goal 120 mg/dL may also be given at the discretion of the investigator (e.g. trend upward) in addition to the 25-50% increase in the basal insulin.
- The basal insulin rate may be increased approximately hourly and additional bolus insulin doses may be given as described above at the discretion of the investigator in order to get a gradual decline in the glucose concentration (decline rate of ~1 mg/dL/min).
- Blood will be sampled for YSI glucose every 5-30 minutes per the Blood Sampling guidelines above.
- Blood will be sampled for epinephrine approximately every 15 minutes once the blood glucose has decreased to ≤90 mg/dL with goal of epinephrine sampling at BGs of 90, 75, 60 and <60 mg/dL.
- Blood will be sampled for glucagon when BG <60 mg/dL, just prior to hypoglycemia rescue therapy.
- A Hypoglycemia Symptom Questionnaire will be completed approximately every 15 minutes once the blood glucose has decreased to ≤90 mg/dL (any time blood is sampled for epinephrine) and until hypoglycemia BG <60 mg/dL and recovery BG ≥80 mg/dL has been achieved.
- Once the study endpoint is reached (the first time YSI glucose is <60 mg/dL), the pump will be stopped and the subject will be treated with oral fast acting carbohydrates (preferred), a 2-3 mL/kg D10 intravenous glucose bolus (for BG <50 or risk of severe hypoglycemia with IV access), or a glucagon emergency kit (for severe hypoglycemia with NO IV access) per the Inpatient Hypoglycemia Treatment guidelines above to achieve a recovery glucose ≥80 mg/dL.
- Once a recovery glucose of ≥80 mg/dL is achieved, the subject will resume pump therapy with the normal basal rate and will proceed to the Recovery Period.

- **Procedures Related to the Recovery Period:**
  - Once the procedures related to the Hypoglycemia Induction Period are complete and the subject's glucose is ≥80 mg/dl, the subject will

be served a regular meal and will be monitored for a 1 hour Recovery Period.

- The meal carbohydrates will be estimated by the subject and the meal will be covered with insulin via the subject's pump based on the subject's individual carbohydrate ratio and insulin sensitivity factor parameters and a glucose goal of 120 mg/dL or the subject's home glucose goal, whichever is higher. The subject may use the YSI glucose information and the insulin dosing chosen will be discussed with the study physician prior to administration. The amount of insulin given and time of administration will be documented.
- During the 1-hour Recovery Period, blood will be sampled for YSI glucose every 5-30 minutes per the Blood Sampling guidelines above.
- Blood will also be sampled for epinephrine every 15 minutes x 4 samples after the nadir blood glucose.
- Subjects will then enter the Discharge Preparation Period.

- **Procedures Related to the Discharge Preparation Period:**
  - A fingerstick β-hydroxybutyrate test will be performed.
  - Blood will be sampled for YSI glucose every 5-30 minutes per the Blood Sampling guidelines above.
  - Once plasma glucose is 100-300 mg/dL, and β–hydroxybutyrate is ≤0.6 mmol/L, blood sampling will be discontinued and the subject will be prepared for discharge.
  - If plasma glucose is <100 mg/dL, carbohydrates will be given to raise the glucose to ≥100 mg/dL.
  - If plasma glucose is >300 mg/dL, or fingerstick β–hydroxybutyrate is >0.6 mmol/L, the Inpatient Hyperglycemia and Ketone Treatment guidelines will be followed.
  - Additional inpatient time for BG stabilization will not be considered an adverse event.
  - A final set of vital signs (temperature, blood pressure and pulse) will be performed and documented.
  - The subject will be provided with a Precision Xtra ketone meter (if the subject does not have one) and blood ketone test strips and instructed on their use to monitor for ketones. Patients will be instructed to check ketones as follows:
    - Hourly if the glucose is >300 mg/dL for >2 hours until glucose is <300 mg/dL and ketones <0.6 mmol/L
    - If symptoms of nausea, vomiting, or abdominal pain occur.
  - The subject will be given instructions on how to contact study staff 24

hours a day to report any study-related problems.
- The subject will be instructed to contact the study staff for prolonged hyperglycemia >300 mg/dL, ketones ≥1.5 mmol/L, or if s/he experiences nausea, vomiting, or abdominal pain within 48 hours after discharge.
- The IVs will be removed and the IV sites will be observed and the condition will be documented along with any AEs.
- The subject will be instructed to contact the study staff for any problems related to IV insertion sites, including fever, pain, redness, itching, discharge or swelling at the IV insertion sites.
- Any existing protocol-related problems will be followed-up after discharge until resolution.
- The subject will be informed of possible fluctuations in their glucose control during the next 72 hours.
- The study subject will be contacted within 48-72 hours after discharge.

Study Glucometer and Dexcom CGM Training (1 hour):

CGM training may occur at any time that the subject is not hypoglycemic during Visit 3.

- Subjects will be provided with a study blood glucose meter, test strips, and standard control solution to perform quality control (QC) testing at home per manufacturer guidelines.
- Study staff will answer any questions the subject has about the study glucometer and the subject will demonstrate proficiency with a fingerstick test.
- Subjects will be reminded to use the same study glucometer for all finger sticks and calibrations and to only use SMBG values (not CGM values) to guide treatment decisions.
- Subjects will be required to perform 4-6 SMBG measurements daily (recommended before meals, about 2 hours after meals and at bedtime), and as needed to calibrate the CGM. Additional fingersticks may be obtained, if desired.
- Subjects will be given additional training on the Dexcom Share AP CGM to be proficient with its use during the experimental or control treatment.
- The subject will be taught how to calibrate the CGM per manufacturer's guidelines with the study glucometer. For this study, the subject will be asked to perform calibrations before meals and at bedtime, and as prompted by the CGM receiver. Only BG values taken within 5 minutes of the intended calibration should be used for calibration. The antenna symbol needs to be present on the Dexcom receiver before a blood glucose value is entered for

calibration.

- If the subject is in the control group, s/he will be given appropriate supplies to complete 5 weeks of sensor augmented pump therapy at home.
    - The low glucose alert will be set per patient preference, but may not be lower than 70 mg/dL.
    - The subject may determine the settings for any of the other alerts.
    - The subject will be contacted daily by study staff for the first 5 days, then weekly. CGM downloads will occur at week 2 and week 5.
    - An appointment will be made for Visit 6 to be scheduled within 8 weeks of Visit 3 and within 1 week of completing the intervention.
- If the subject is in the experimental group, s/he will be given appropriate supplies for CGM use until Visit 4.
    - The low glucose alert will be set per patient preference, but may not be lower than 70 mg/dL.
    - The subject may determine the settings for any of the other alerts.

4. Visit 4: Study Pump and AP system Training

Subjects in the experimental group will participate in a training session in a monitored outpatient setting during which the subject and diabetes care companion will be trained to use the study pump, the AP system controlling the study pump, and the Dexcom receiver to display CGM values on the system. Visit 4 may start on the same day as Visit 3.

Monitored Outpatient Setting Procedures:

- More than one subject and diabetes care partner may be admitted at a time.
- The subject and diabetes care partner will meet the study team and check into the monitored outpatient setting at the agreed upon time.
- The subject will be asked to perform a fingerstick glucose using the study glucometer shortly after arrival.
- The study team will confirm that the subject brought his/her insulin, insulin pump supplies, and regular medications including the home glucagon emergency kit (if available).
- The study team will also confirm the absence of a febrile or vomiting illness and absence of acetaminophen use. The subject may be rescheduled if these criteria are not met.

- 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.
- The subject and care partner will be trained as needed on the Outpatient Hypoglycemia, Hyperglycemia and Ketone Treatment Instructions that will be followed during the visit and any time a study pump is in use (APPENDIX A-12).
- If the subject requires glucagon while at the research facility, it will be administered by qualified study staff. The diabetes care partner will be educated as needed on the use of glucagon per the package instructions in the event the subject requires glucagon for severe hypoglycemia outside of the research facility.
- The subject and care partner will be trained as needed on the use of the study ketone meter and the subject will be asked to check fingerstick ketone levels per the Outpatient Hypoglycemia, Hyperglycemia and Ketone Treatment Instructions.
- The subject will continue to perform 4-6 SMBG measurements daily (recommended before meals, about 2 hours after meals and at bedtime), and as needed to calibrate the CGM or follow the Outpatient Hypoglycemia, Hyperglycemia and Ketone Treatment Instructions. Additional fingersticks may be obtained, if desired.
- The subject will be instructed to enter each SMBG result in The AP system .
- The subject will continue to use the study CGM.
- The research facility 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 at all sites.
- The research facility at all sites will be located within 4 miles of an emergency department and will have an automated external defibrillator (AED) and Ambu bag for ventilation.
- Hypoglycemic treatments can occur at any time per the subject's request.
- The subject will have access to ad lib beverages.
- All meals will be provided by the study and the study staff will try to accommodate patient preferences.
- The subject may also administer snacks or correction boluses per their usual regimen.
- The subjects will be encouraged to follow a regular sleep pattern between 11PM and 7AM.

Visit 4 Study Pump Training Procedures:

- The subject and the care partner will be fully instructed on the study insulin pump. 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 and correction boluses. Additional topics not limited to but may include: site initiation, cartridge/priming procedures, setting up the pump, changing batteries, navigation through menus, bolus procedures including stopping a bolus, pairing procedures with the meter remote, etc.
- The study team will assist the subject in study pump infusion site initiation and will start the subject on the study pump. The study pump will be programmed with the subject's usual basal rates and pump parameters. The subject's personal pump will be removed.
- The subject will be supervised with the study pump during at least one meal bolus to ensure subject understanding of the pump features.
- The subject may eat meals and snacks and bolus for the meals and snacks using the study pump per the home routine.
- The subject and diabetes care partner will be encouraged to review the literature provided with the pump, infusion sets, and meter remote after the training is completed.
- Once the subject is adequately trained on the study pump, study staff will meet with the subject and diabetes care partner for training on the use of the AP system with the study pump and study CGM.

Visit 4 AP System Training Procedures:

- Prior to initial use, the AP system will be initialized by a study team member with the subject's individual parameters, including carbohydrate ratio, correction factor, and basal rate pattern. The settings will be confirmed by the study physician or NP.
- The subject and care partner may be taught how to unpair the study pump from the meter remote and how to turn off the meter Bluetooth. The meter remote will continue to be used as a glucometer for the remainder of the study. (When there is no Bluetooth connection to the meter remote, the subject's basal rate pattern is still administered according to the preprogrammed basal rates on the study pump.)
- All study equipment including the AP system cell phone, insulin pump, and CGM receiver will be set using an atomic clock as a reference.
- The subject will be taught how to initiate Pump mode. Once Pump mode is activated, the system will take control of the insulin pump and will direct the administration of insulin according to the subject's usual basal rate pattern.
- The meal screen on the system will be introduced and the subject will be

supervised during at least one meal bolus.

- The subject and care partner will be trained to use the AP interface and the pertinent portions of the User Manual will be reviewed; the training will continue until all questions are answered. The User Manual is included in APPENDIX A-13.
- Study team members will train the subject and diabetes care companion in performing specific tasks including the following:
    - How to switch the system between Pump mode (with the AP system in control of delivering preprogrammed basal insulin) and Stopped mode (with the study insulin pump in control of delivering preprogrammed basal insulin) depending on circumstances. Stopped mode is used when a cartridge/infusion set needs to be changed or when disconnecting from the pump as for showering. Stopped mode is also used when switching from the study pump to an alternative form of insulin administration.
    - How to start a new sensor and connect the AP system with the CGM receiver.
    - How to calibrate the CGM unit as usual via the CGM receiver unit.
    - How to access the CGM trace and insulin delivery plot on the AP user interface.
    - How to perform a pump site change when using the system.
    - How to activate the meal screen of the system any time insulin will be given with a meal or snack or any time additional correction insulin is desired.
    - How the Hypoglycemia and Hyperglycemia color coding functions in Pump mode. The coding will activate per the safety system, and audible alerts will be sounded.
    - How to inform the system of hypoglycemia treatment via the hypoglycemia treatment button on the AP user interface.
    - How to assess whether remote monitoring is working.
    - The subject and diabetes care partner will be assessed for understanding of the system interface and how the to react to any messages on the AP system.
    - The subject and diabetes care partner will be given a printed User Manual as a reference.
- Once all questions are answered, the subject will then be primarily responsible for using the system, with the study team serving as back-up when needed.
- The subject and diabetes care partner will be re-educated as needed until they are able to complete all system-related tasks on the AP Training (APPENDIX

A-15).

The subject may be discharged after all training and monitoring is successfully completed. The subject must be able to complete system-related tasks independently to be eligible to continue in the study.

Eligible subjects will be provided with the following:

- Subjects will receive sufficient device supplies to use the AP system at home for one week with the study pump and study CGM.
- Subjects will also receive a study emergency kit for the treatment of low or high blood glucose (contents described in APPENDIX A-19).
- Subjects will also be provided with a study blood ketone meter and test strips. All study blood ketone meters will be QC tested with at least two different concentrations of control solution prior to use. A tested meter will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling.
- The subject will continue to perform 4-6 SMBG measurements daily (recommended before meals, about 2 hours after meals and at bedtime), and as needed to calibrate the CGM or follow the Outpatient Hypoglycemia, Hyperglycemia and Ketone Treatment Instructions. Additional fingersticks may be obtained, if desired.
- The subject will be asked to check fingerstick ketone levels per the Outpatient Hypoglycemia, Hyperglycemia and Ketone Treatment Instructions.

5. Home Use with the AP system in Pump Mode

Eligible subjects will then use the AP system at home in Pump mode, connected to the study CGM and study pump.

- Remote monitoring will be available during this period for the purposes of data collection and assessment of system performance by study clinicians or engineers.
- Study staff will contact the subject daily to answer any questions and enquire about any device complaints, adverse events, and whether the adverse event was related to system use.
- Study staff will also check the number of SMBG tests entered on the AP system via remote monitoring and will remind the subject to perform 4-6 SMBG daily.
- If a study device malfunctions, it may be replaced.
- CGM will be downloaded after one week at home.
- The ability of the AP system to be remotely monitored in the subject's daily

environment will also be assessed with daily checks of the remote monitoring site.

- After completion of 1 week of AP use Pump mode at home, study staff will determine whether additional training and practice is needed and whether the subject will repeat all or portions of Visit 4 and 1 week of home use (up to 1 time if needed) or proceed to Visit 5.
- Subjects who failed to use the system for more than 80% of the time during this phase will be ineligible to continue in the study.
- Subject's that cannot be adequately monitored at least 75% of the time in their local environment by the final day of home use will be ineligible to continue in the study.

6. Visit 5: USS Virginia Training

Eligible subjects in the experimental group will participate in a training session in a monitored outpatient setting during which the subject and diabetes care partner will be trained to use the AP system +USS Virginia. The training will include an initial the AP system Closed Loop mode training followed by independent use. The study team will be in a different room during the independent use time, but immediately available as needed.

Monitored Outpatient Setting Procedures: Identical to Visit 4.

Visit 5 AP System Training Procedures:

- Any questions regarding the study equipment will be answered.
- The subject may eat meals and snacks and bolus for the meals and snack using the AP system and study pump per the home routine.
- Study staff will meet with the subject and diabetes care partner for training on the use of the AP system +USS Virginia with the study pump and study CGM.
  The system will be reconfigured to allow Closed Loop operation.
- The study MD or NP will confirm that the subject's home pump parameters including carbohydrate ratios, correction factors, and basal rate pattern are reproduced in the AP settings.
- The subject and care partner will be trained to use the AP system interface in Closed Loop mode and the pertinent portions of the User Manual will be reviewed; the training will continue until all questions are answered.
- Study team members will train the subject and diabetes care companion in performing specific tasks including the following:
  - How to switch the system between Pump mode and Closed Loop

mode
- How to start a new sensor when connected to the AP system in Closed Loop mode.
- How to calibrate the CGM unit as usual via the CGM receiver unit.
- How to perform a pump site change when using the AP system in Closed Loop mode.
- How to activate the meal screen with the AP system in Closed Loop mode any time insulin will be given with a meal or snack or any time additional correction insulin is desired.
- How the Hypoglycemia and Hyperglycemia color code functions in Closed Loop mode and how to respond to Red alerts.
- How to inform the system of hypoglycemia treatment via the hypoglycemia treatment button on the AP system user interface.
- How to switch to Exercise mode for activities such as exercise, driving, or operating heavy machinery.
- The subject and diabetes care partner will be assessed for understanding of the system interface and how the to react to any messages on the system.
- The subject and diabetes care partner will be given a printed User Guide as a reference.

- Once all questions are answered, the subject will then be primarily responsible for using the system, with the study team serving as back-up when needed.
- During the first part of the training session, the subject and diabetes care partner will be re-educated as needed until they are able to complete all system-related tasks on the AP Training (APPENDIX A-15) and study staff will be immediately present for training and to respond to system issues.
- During the second part of the admission, study staff will be nearby and available, but will not immediately assist the subject in completing the described training tasks or responding to system issues (unless the study is stopped due to a problem that is unable to be resolved by the subject). Nursing staff will monitor the subjects during the entire admission, report fingerstick BG values to the medical team, and ensure that Outpatient Hypoglycemia, Hyperglycemia and Ketone Treatment Instructions are followed by the subject.

The subject may be discharged after all of the of training and monitoring is successfully completed. The subject must be able to complete system-related tasks independently to be eligible to continue in the study.

Eligible subjects will be provided with the following:

- Subjects will receive sufficient device supplies to use the AP system at home for four weeks with the study pump and study CGM.
- Subjects will also have any supplies replenished as needed for the Study Emergency Kit for the treatment of low or high blood glucose.
- The subject will continue to perform 4-6 SMBG measurements daily (recommended before meals, about 2 hours after meals and at bedtime), and as needed to calibrate the CGM or follow the Outpatient Hypoglycemia, Hyperglycemia and Ketone Treatment Instructions. Additional fingersticks may be obtained, if desired.
- The subject will be instructed to enter each SMBG in the AP system.
- The subject will be asked to check fingerstick ketone levels per the Outpatient Hypoglycemia, Hyperglycemia and Ketone Treatment Instructions.

7. Closed Loop Mode Home Use Trial Period

After a successful training of Closed Loop mode in Visit 5, eligible subjects will then initiate a 3-5 day trial period of the AP system at home in Closed Loop mode, connected to the study CGM and study pump. Remote monitoring will be in place and designated study medical and technical staff will receive automated notifications when alert conditions are met.

- The subject will be instructed to use the system in a Closed Loop mode except when no calibrated CGM sensor is available. Pump mode may be used during times of no active CGM.
- The subject will be instructed to perform a fingerstick and switch the system to Exercise Mode prior to exercising or engaging in potentially dangerous activities such as driving or operating heavy machinery.
- When exercising, the subject will be instructed to limit activity to no more than one hour at no more than a moderate level of intensity.
- While using the AP system +USS Virginia system, the subject will be instructed to avoid deviating from his/her regular daily routine in regards to diet and exercise, aside from potentially limiting exercise duration and intensity as described above.
- The subject will specifically be asked to avoid consuming more than 3 alcoholic drinks in any one day.
- The subject will also be instructed to avoid use of Closed-Loop mode during periods of illness with an elevated temperature >101.5 degrees Fahrenheit, periods of significant illness, or during periods of use of medications such as epinephrine (e.g. for the emergency treatment of a severe allergic reactions or asthma attack) and oral or injectable glucocorticoids.

After each day of system use, clinical staff will contact the subject and assess the subject's system use via a review of the subject's data from the previous day. Study staff will also check the number of SMBG tests entered on The AP system and will remind the subject to perform 4-6 SMBG daily. The study team will determine whether the subject used the system in the appropriate mode at least 80% of the time during the day and night and whether remote monitoring was functional at least 75% of the time. Subjects who meet the success criteria on three days in a period of up to five days are eligible, at the discretion of the investigator, to continue to the next phase of the study.

Subjects who do not meet the success criteria on three nights in a period of up to five days may, at the discretion of the investigator, repeat part or all of the Visit 5 USS Virginia Training and then repeat the 3-5 day Closed Loop Mode Home Use Trial Period one time.

8. Four-Week USS Virginia Closed Loop Home Use Period

Eligible subjects will continue to use the AP system at home in Closed Loop configuration for a total of four weeks.

- Study staff will continue to contact the subject daily for the first 5 days, then weekly to answer any questions and enquire about any device complaints, adverse events, and whether the adverse event was related to the AP system use. Study staff will also check the number of SMBG tests entered on the AP system and will remind the subject to perform 4-6 SMBG daily.
- Study staff will check the number of SMBG entered on the AP system daily via remote monitoring and contact the subject is <4 SMBG are observed on any day.
- CGM downloads will occur at week 2 and week 4.
- If an alert is triggered, the staff that received the alert will log onto the remote monitoring system to evaluate the problem and follow it until a reasonable resolution has occurred. In some instances, this may require a call to the subject to resolve the condition. For example, if no data was received from the AP system and a technical alert was issued, the technical staff on call may determine that a call is needed to find out why the system was not communicating with remote monitoring. Attempts to contact the subject would be made multiple times for up to 30 minutes. If the subject is not able to be contacted within 30 minutes, the care partner would be contacted in a similar manner. We would have additional contact information provided by the subject at enrollment (e.g. home number, work number, other family members, etc.) that would also be tried. If a subject is unreachable for more

than 2 hours with these attempts on more than 2 occasions, s/he may be dropped from the study per investigator discretion. Other alerts may be triggered that resolve without the need for subject contact. For example, a hypoglycemia red light occurs and the medical staff gets a notification. If the medical staff observes on remote monitoring that the subject has acknowledge the alert, checked a BG and administered appropriate treatment, the medical staff may decide to observe that event via remote monitoring until the event is resolved.

9. Visit 6: 8 hr Inpatient Assessment of Hypoglycemia Counterregulation and Symptom Awareness

Within one week of completing either USS Virginia or sensor-augmented pump therapy at home, the subjects will undergo a final hypoglycemia induction using the home pump therapy with frequently sampled YSI glucose levels. Additionally, if a subject completes more than 1 week of either USS Virginia or sensor-augmented pump therapy and subsequently withdraws from the study intervention, they will be asked to complete Visit 6 within one week of discontinuing the intervention.

Procedures for this visit are identical to the Visit 3 inpatient procedures with the exception of no additional study glucometer and CGM training.

The subject will have a post-intervention HbA1c assessed at the time of one of the scheduled blood sampling times and will complete the hypoglycemia questionnaires (Clarke Hypoglycemia Perception Awareness, Fear of Hypoglycemia II and a DiAs Usability questionnaire (DiAs users only) (APPENDIX A-5)).

The subject will return all study equipment and unused supplies.

If during the trial it becomes evident that the pump parameters of a subject may benefit from adjustment, the study physician will discuss this with the subject. This is possible because the USS is initialized with each subject's established pump parameters and then works as add-on to normal pump therapy manipulating insulin delivery around the subject's normal insulin rate. For example, overnight the basal rate module can attenuate basal rate smoothly to prevent hypoglycemia. If this happens systematically, this would suggest that the normal basal rate of the subject may be too high during certain periods. The study physician would therefore discuss such an observation with the subject upon discharge.

H. SAFETY MONITORING / RISK ANALYSIS

- Glucose Monitoring Risk:

The YSI method for glucose monitoring will be employed during the inpatient Visits 3 and 6 in order to have the most accurate method available during the Hypoglycemia Induction procedures.

During outpatient procedures the Accu-Chek Aviva glucometer will be used. It is an FDA approved 510K Class II Medical Device (510K number K101299). Subjects and diabetes care partners will be trained on the use of the glucometer.

- Hypoglycemic/Hyperglycemic and Ketone Risk:

To decrease the risk of severe hypoglycemia or hyperglycemia, the following schedule for monitoring blood glucose concentrations during the inpatient procedures will be adhered to

- Once IV access has been established, blood will be sampled for YSI glucose every 5-30 minutes. The frequency of blood draws for YSI sampling is dependent on the value of the previous sample, according to the following ranges:
  - BG >200: every 30 minutes
  - BG >100-200: every 15 minutes
  - BG ≤100 mg/dL: every 5 minutes
- Blood may be sampled for YSI glucose as needed for patient safety or to recheck a suspected erroneous value (e.g. dilute sample).
- In the event of loss of IV access or loss of a functional YSI and need for continued subject monitoring, glucose measurements will be made on capillary whole blood using the study glucometer.

The Inpatient Hypoglycemia Treatment and Inpatient Hyperglycemia and Ketone Treatment instructions (below) will be followed during the inpatient portions of the study at Visit 3 and Visit 6.

Inpatient Hypoglycemia Treatment

- Glucose <60 mg/dL will be treated orally with fast acting carbohydrate as needed until a glucose level of ≥80 mg/dL is achieved.
- In the event that there is intravenous access and the subject is at risk for severe hypoglycemia, the subject will be treated with a ~2-3 mL/kg D10 intravenous glucose bolus. Risk for severe hypoglycemia is defined as any of the following situations:

- Glucose <50 mg/dL
- The subject is unable to cooperate with oral treatment of hypoglycemia
- The glucose is dropping at a rate that may not respond adequately to oral treatment
- The subject experiences symptoms of neuroglycopenia (e.g. lethargy, disorientation, confusion [disordered processing of information or communication], or inappropriate behavior)
- The subject experiences symptoms of severe hypoglycemia (i.e. hypoglycemic seizure or loss of consciousness)

- In the event that there is NO intravenous access and the subject is at risk for severe hypoglycemia (as defined above), the subject will be treated with 1 mg of glucagon subcutaneously or intramuscularly.
  - The drug will be reconstituted and administered per package insert/instructions.
  - Glucagon may be repeated as needed every 20 minutes to achieve glucose level ≥80 mg/dL. Once the subject is able to consume oral treatment, the subject will be treated orally with fast acting carbohydrate as needed until a glucose level of ≥80 mg/dL is achieved. Orange juice and milk will be avoided after glucagon administration.
  - Attempts will be made to reestablish intravenous access.
- The Hypoglycemia Induction Admission will be stopped if the subject experiences a hypoglycemic seizure or loss of consciousness and only safety procedures will be continued. The study physician or nurse practitioner will take control over glucose sampling decisions in order to stabilize the subject's glucose between 100-300 mg/dL and determine the appropriate subject disposition (i.e. home or medical facility).

Inpatient Hyperglycemia and Ketone Treatment

- If the subject's glucose is >300 mg/dL or β–hydroxybutyrate level is ≥0.6 mmol/L on admission, the subject will be stabilized per the procedures below. The subject will continue to be monitored until a glucose level between 100-300 mg/dL and β–hydroxybutyrate measurement <0.6 mmol/L has been achieved (or the subject is discharged to an appropriate medical team).
- Subsequently, glucose >300 mg/dL for >2 hours or glucose ≥400 mg/dL at any time will prompt discontinuation of the Hypoglycemia Induction Admission.
- β–hydroxybutyrate will be assessed hourly while the glucose is ≥250 mg/dl

or the β–hydroxybutyrate level is ≥0.6 mmol/L.

- If the glucose is >300 mg/dL and β–hydroxybutyrate level is <0.6 mmol/L, corrective action will be taken only after it has been at least 90 minutes from the last subcutaneous insulin dose. Specifically, the subject will be asked to bolus with his/her pump an amount of corrective insulin that will bring him/her to a target glucose of 120 mg/dL.
- If the β–hydroxybutyrate level is ≥0.6 mmol/L, the cause of the elevated ketone level will be investigated (e.g. pump or pump site malfunction). Additional insulin may be administered either via insulin syringe or via a new pump site. The amount of insulin administered will be calculated using the subject's insulin sensitivity factor and a target glucose of 120 mg/dL.
- If the β–hydroxybutyrate level is ≥1.5 mmol/L, the Hypoglycemia Induction Admission will be stopped and the study MD or NP will take control of the subject's insulin dosing. The cause of the elevated ketone level will be investigated (e.g. pump or pump site malfunction). If the subject's home parameters are not felt to be working adequately due to hyperglycemia, ketonemia, or other factors (e.g. intercurrent illness), the study MD or NP will administer corrective insulin either via insulin syringe or via a new pump site using an ISF determined to be appropriate for the setting and a goal glucose of 120 mg/dL. The subject will continue to be monitored until a glucose level between 100-300 mg/dL and β–hydroxybutyrate measurement <0.6 mmol/L has been achieved (or the subject is discharged to an appropriate medical team).

The Outpatient Hypoglycemia, Hyperglycemia and Ketone Treatment instructions will be followed during Visit 4 and 5 and at any time that the study pump is in use. The treatment guidelines are attached in APPENDIX A-12.

- Calibration of CGM Risk:

During the portions of the study when CGM is used, subjects should calibrate the CGM with fingerstick values before meals and at bedtime and no less than every 12 hours.

- 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 Dexcom Professional Cleaning Instructions 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.

Dexcom CGM Cleaning Procedure: Healthcare professionals must clean and disinfect the transmitter before providing to each user. Use caution when handling products worn or handled by another person. Wear personal protective equipment as appropriate (gloves, protective goggles, lab coat, etc.). **Clean the transmitter before disinfecting. Cleaning the transmitter removes dirt from the surface of the transmitter, but it does not kill bacteria or viruses.**

Products:

1. Clorox Healthcare Bleach Germicidal Cleaner (EPA registration number 56392-7) – spray bottle and pourable gallon size.
2. Dispatch Hospital Cleaner Disinfectant Towels with Bleach (EPA registration number 56392-8).
3. Nylon bristled brush
4. Low-lint wipes

Cleaning Instructions:

1. Prepare a soaking container by adding enough Clorox Healthcare Bleach Germicidal Cleaner solution to submerge a transmitter.
2. Place the transmitter with the contact (metal circles) side down on an absorbent wipe or clean surface.
3. Hold the Clorox Healthcare Bleach Germicidal Cleaner spray bottle 6-8 inches from unit and dispense two sprays on surface.
4. Flip the transmitter to expose the contacts (metal circles).
5. Hold Clorox cleaner spray bottle 6-8 inches from unit and dispense two sprays on surface.
6. Using nylon brush, scrub the transmitter on all sides for 30 seconds.
7. Submerge transmitter into prepared Clorox Healthcare Bleach Germicidal Cleaner for one minute.
8. Remove transmitter and rinse under flowing tap water for ten seconds.
9. Wipe transmitter with a cloth until completely dry.

Disinfecting Instructions:

1. Prepare a soaking container by adding enough Clorox Healthcare Bleach Germicidal Cleaner solution to submerge a transmitter. *(DO NOT USE SOLUTION USED IN CLEANING PROCEDURE.)*
2. Place the transmitter with the contact (metal circles) side down on an absorbent wipe or clean surface.
3. Remove a pre-saturated Dispatch Hospital Cleaner Disinfectant Towel with Bleach from its packaging.
4. Fold the Dispatch Towel into 2x2 inch square.
5. Wipe all surfaces of the transmitter by passing over the transmitter by passing over the transmitter surface in one direction and then back in the opposite direction (back and forth means two passes).
6. Turn over the Dispatch Towel to use a clean side for a second back and forth wipe.
7. Refold the Dispatch Towel to use a clean side for a third back and forth wipe
8. Turn over the Dispatch Towel to use a clean side for a fourth back and forth wipe.
9. Keep track to be sure you wiped four times back and forth for a total of eight passes and that the transmitter surfaces are covered with disinfectant.
10. Place the transmitter on a clean non-porous surface and allow the disinfectant to contact it for one minute.
11. Place the transmitter into prepared Clorox Healthcare Bleach Germicidal Cleaner for one minute.
12. Remove transmitter and rinse under flowing tap water for ten seconds.
13. Wipe transmitter with a low lint, absorbent cloth until completely dry.

The Accu-Chek Combo System is labeled for single-patient use. The Accu-Chek Combo system is comprised of the Accu-Chek Spirit Insulin Pump and the Aviva Combo Device. The Aviva Combo device when used as a glucometer will be single patient use at all times. The Accu-Chek Spirit Insulin Pump itself is handheld and is not a glucometer. The subject interactions are primarily with the AP system interface and the Aviva Combo device, not with the Accu-Chek Spirit Insulin Pump menu interface itself. The Accu-Chek Spirit Insulin Pump handheld device will be reused after cleaning with Super Sani-Cloth (EPA registration number 9480-4). Do not clean/disinfect the pump when the reservoir and infusion set are connected to the insulin pump. All infusion set equipment will be single patient use only (infusion set insertion kits, tubing, cartridges etc.) Equipment will

be stored in a clean zipped bag.

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. 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 Accu-Chek Aviva Combo will be used throughout the study as the study glucometer. Subjects will be trained on that device. At the training session, 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 or with an alcohol swap and allowed to dry 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 Accu-Chek Spirit Insulin Pump is part of the Visit 4 training visit and will occur with a qualified clinical member of the study team.

Visit 4 Study Pump Training Procedures:

- The subject and the care partner will be fully instructed on the study insulin pump. 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 and correction boluses. Additional topics not limited to but may include: site initiation, cartridge/priming procedures, setting up the pump, changing batteries, navigation through menus, bolus procedures including stopping a bolus, pairing procedures with the meter remote, etc.
- The study team will assist the subject in study pump infusion site initiation and will start the subject on the study pump. The study pump will be programmed with the subject's usual basal rates and pump parameters. The subject's personal pump will be removed.
- The subject will be supervised with the study pump during at least one meal bolus to ensure subject understanding of the pump features.
- The subject may eat meals and bolus for the meals using the study pump per the home routine.
- The subject and diabetes care partner will be encouraged to review the literature provided with the pump, infusion sets, and meter remote after the training is completed.
- Once the subject is adequately trained on the study pump, study staff will meet with the subject and diabetes care partner for training on the use of the AP system with the study pump and study CGM.

AP system <u>training:</u>
The AP system training occurs during both the Visit 4 and Visit 5 training sessions with a qualified clinical member of the study team and with the User Manual in hand (APPENDIX A-13).

Visit 4 AP System Training Procedures:

- Prior to initial use, the system will be initialized by a study team member with the subject's individual parameters, including carbohydrate ratio, correction factor, and basal rate pattern. The settings will be confirmed by the study physician or NP.
- The subject and care partner will be taught how to unpair the study pump from the meter remote and how to turn off the meter Bluetooth. The meter remote will continue to be used as a glucometer for the remainder of the study. (When there is no Bluetooth connection to the meter remote, the subject's basal rate pattern is still administered according to the preprogrammed basal rates on the study pump.)
- All study equipment including the AP system cell phone, insulin pump, and

CGM receiver will be set using an atomic clock as a reference.

- The subject will be taught how to initiate Pump mode on the AP. Once Pump mode is activated, the system will take control of the insulin pump and will direct the administration of insulin according to the subject's usual basal rate pattern.
- The meal screen on the AP will be introduced and the subject will be supervised during at least one meal bolus.
- The subject and care partner will be trained to use the AP interface and the pertinent portions of the User Manual will be reviewed; the training will continue until all questions are answered.
- Study team members will train the subject and diabetes care companion in performing specific tasks including the following:
    - How to switch the system between Pump mode (with the AP system in control of delivering preprogrammed basal insulin) and Stopped mode (with the study insulin pump in control of delivering preprogrammed basal insulin) depending on circumstances. Stopped mode is used when a cartridge/infusion set needs to be changed or when disconnecting from the pump as for showering. Stopped mode is also used when switching from the study pump to an alternative form of insulin administration.
    - How to start a new sensor and connect the AP system with the CGM receiver.
    - How to calibrate the CGM unit as usual via the CGM receiver unit.
    - How to access the CGM trace and insulin delivery plot via the Plots button on the AP user interface.
    - How to perform a pump site change when using the AP system.
    - How to activate the meal screen of the system any time insulin will be given with a meal or snack or any time additional correction insulin is desired.
    - How the Hypoglycemia and Hyperglycemia color code functions in Pump mode. The colors will activate per the safety system, and audible alerts will be sounded.
    - How to inform the system of hypoglycemia treatment via the hypoglycemia treatment button on the AP user interface.
    - How to assess whether remote monitoring is working.
    - The subject and diabetes care partner will be assessed for understanding of the system interface and how the to react to any messages on the AP system.
    - The subject and diabetes care partner will be given a printed User Manual as a reference.

- Once all questions are answered, the subject will then be primarily responsible for using the system, with the study team serving as back-up when needed.
- Subjects will be provide a copy of the AP system manual.
- The subject and diabetes care partner will be re-educated as needed until they are able to complete all system-related tasks on the AP Training (APPENDIX A-15).

Visit 5 AP system Training Procedures:

- Any questions regarding the study equipment will be answered.
- The subject may eat meals and snacks and bolus for the meals and snack using the AP system and study pump per the home routine.
- Study staff will meet with the subject and diabetes care partner for training on the use of the AP system+USS Virginia with the study pump and study CGM.
  The system will be reconfigured to allow Closed Loop operation.
- The study MD or NP will confirm that the subject's home pump parameters including carbohydrate ratios, correction factors, and basal rate pattern are reproduced in the settings.
- The subject and care partner will be trained to use the AP interface in Closed Loop mode and the pertinent portions of the User Manual will be reviewed; the training will continue until all questions are answered.
- Study team members will train the subject and diabetes care companion in performing specific tasks including the following:
  - How to switch the system between Pump mode and Closed Loop mode depending on circumstances.
  - How to start a new sensor when connected to the AP system in Closed Loop mode.
  - How to calibrate the CGM unit as usual via the CGM receiver unit.
  - How to perform a pump site change when using the AP system in Closed Loop mode.
  - How to activate the meal screen with the AP system in Closed Loop mode any time insulin will be given with a meal or snack or any time additional correction insulin is desired.
  - How the Hypoglycemia and Hyperglycemia color code functions in Closed Loop mode and how to respond to Red alerts.
  - How to inform the system of hypoglycemia treatment via the hypoglycemia treatment button on the AP user interface.
  - How to switch to Exercise mode for activities such as exercise, driving, or operating heavy machinery.

- The subject and diabetes care partner will be assessed for understanding of the system interface and how the to react to any messages on the system.
- The subject and diabetes care partner will be given a printed User Guide as a reference.

- Once all questions are answered, the subject will then be primarily responsible for using the system, with the study team serving as back-up when needed.
- During the first half of the training session, the subject and diabetes care partner will be re-educated as needed until they are able to complete all system-related tasks on the AP Training Checklist and study staff will be immediately present for training and to respond to system issues.
- During the last half of the admission, study staff will be nearby and available, but will not immediately assist the subject in completing the described training tasks or responding to system issues (unless the study is stopped due to a problem that is unable to be resolved by the subject). Nursing staff will monitor the subjects during the entire admission, report fingerstick BG values to the medical team, and ensure that Outpatient Hypoglycemia, Hyperglycemia and Ketone Treatment Instructions are followed by the subject.

  The subject may be discharged after all of training and monitoring is successfully completed. The subject must be able to complete system-related tasks independently to be eligible to continue in the study.

- 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 at All Study Sites

All study nurses will be currently licensed RNs or Nurse Practitioners. 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 team. 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 inpatient procedures and outpatient training sessions during the trial. A designated MD or NP will be on call to receive automated alerts when remote monitoring is in place.

I. STOPPING RULES

Stopping Rules for Subjects during the Visit 3 and Visit 6 Inpatient Assessment of Hypoglycemia Counterregulation and Symptom Awareness (that may result in stopping the entire study):

- Hypoglycemic seizure
- Loss of consciousness
- Diabetic ketoacidosis (DKA)

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 inpatient session.

Stopping Rules for Subjects during the Visit 3 and Visit 6 Inpatient Assessment of Hypoglycemia Counterregulation and Symptom Awareness (that will not result in stopping the entire study):

- Presence of a febrile or vomiting illness within 24 hours of the admission
- Positive urine pregnancy test
- Temperature ≥99.5ºF (≥37.5ºC)
- Fingerstick glucose >300 mg/dL or fingerstick ketone level ≥0.6 mmol/L during Admission Readiness Assessment
- Glucose >300 mg/dL for >2 hours
- Glucose ≥400 mg/dL at any time
- Fingerstick β–hydroxybutyrate level ≥1.5 mmol/L

Reason Inpatient 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

Stopping Rules for Subjects during the outpatient portions of the study (that may result in stopping of the entire study):

- Hypoglycemic seizure
- Loss of consciousness due to hypoglycemia
- Glucagon is required to treat hypoglycemia
- Confirmed diabetic ketoacidosis per review of the medical record
- Subject had a serious adverse event deemed related to the study.

Stopping Rules for Subjects during the outpatient portions of the study (that will not result in stopping of the entire study):

- Medical need for repeated doses of Tylenol / acetaminophen
- Medical need for oral or injected glucocorticoids
- Positive pregnancy test
- At Visit 2 review of the blinded CGM shows that the CGM was functional ≤80% of the time or LBGI ≤1.1
- If after completion of 1 week of the AP system Pump mode home use, the investigator determines that the subject cannot be adequately monitored at least 75% of the time in their local environment.
- If after the Visit 4 Study Pump and the AP system Training, the subject is unable to complete system-related tasks independently.
- If during Home Use with the AP system in Pump Mode the subject failed to use the system for more than 80% of the time during this phase or the subject could not be adequately monitored at least 75% of the time in their local environment by the final day of home use.
- If after the Visit 5 USS Virginia Training, the subject is unable to complete system-related tasks independently.
- If during a second Closed Loop Mode Home Use Trial Period the subject used the system in the appropriate mode <80% of the time during the day and night or the remote monitoring was functional <75% of the time.
- If study staff are persistently unable to contact the subject or the care partner in a timely manner during the course of the study.

Study Procedures will be put on hold during the outpatient portions of the study if:

- Fingerstick β–hydroxybutyrate level ≥3.0 mmol/L
- Abdominal pain
- Vomiting illness
- Unable to eat or drink

- Fever ≥101.5 ºF
- Clinical need for Tylenol / acetaminophen
- Significant illness
- Use of epinephrine to treat a severe allergic reaction or asthma

Stopping Rules for the Entire study:

The study will be stopped if three similar AE's occur that result in individual subjects stopping the study (except those identified above that will not stop the entire study) or if there are system communication failures, which may trigger revision of the system software. Additionally, the Principal Investigator, IRB-HSR, the Data Safety Monitoring Board (DSMB), 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 and DSMB if the study is temporarily stopped. The pertinent regulatory authorities will be informed according to national regulations. The DSMB will meet to determine if changes to the protocol or system are needed prior to restarting the study and whether the study may be restarted.

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 at least 1 week of the study intervention may be replaced. 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 DSMB must determine if the UADE presents an unreasonable risk to subjects. If so, the DSMB 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 DSMB 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 and DSMB will be notified if the study is stopped, and permission to resume will be obtained from the FDA, DSMB and IRB prior to restarting.

CATASTROPHIC EVENT PLAN

The Outpatient Emergency Plan will go into effect should a catastrophic event occur during any monitored outpatient setting (Visit 4 or Visit 5). 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
Cardiac Arrest	1) Tell Tech to call 911 2) Begin Basic Life Support	Refer to Study Physician
Severe Hypoglycemic Event as defined by hypoglycemia accompanied by unconsciousness or seizure	1) Tell Tech to call 911 2) Administer glucagon IM (described in Outpatient Hypoglycemia, Hyperglycemia and Ketone Treatment Instructions APPENDIX A-12) 3) Remove study pump	Refer to Study Physician
Severe Hyperglycemic Event as defined by β-ketone level ≥3.0 mmol/L	1) Discuss correction dose of insulin to administer s.c. via syringe with study M.D. 2) Encourage p.o. water intake 3) Remove study pump and start home insulin pump 4) Go to nearest medical facility for evaluation and treatment.	Refer to Study Physician

Table 2: Outpatient Emergency Plan

In the unlikely event of a disruption in 911 phone service, the sites will contact their local non-emergency number (e.g. 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.

DATA AND SAFETY MONITORING PLAN

Adverse Events, Unanticipated Problems, Protocol Violations and Data Breaches Reporting Table

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 to (caused by) study participation (Note: An internal event is one that occurs in a subject enrolled in a UVa protocol.)	IRB-HSR, DSMB	Within 24 hours	IRB Online and phone call www.irb.virginia.edu/
Internal, Serious, Unexpected adverse event.	IRB-HSR, DSMB	Within 7 calendar days from the time the study team received knowledge of the event. *Timeline includes submission of signed hardcopy of AE form.*	IRB Online www.irb.virginia.edu/
For Device Studies: Unanticipated adverse device effects (internal)	IRB-HSR, DSMB	Within 10 day calendar days of the study team receiving knowledge of the event	IRB Online www.irb.virginia.edu/
Unanticipated Problems that are not adverse events or protocol violations This would include a Data Breach.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. *http://www.virginia.edu/vprgs/irb/HSR_docs/Forms/Reporting_Requirements-Unanticipated_Problems.doc)*
Protocol Violations The IRB-HSR only requires that MAJOR violation be reported, unless otherwise required by the sponsor	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Violation and Enrollment Exception Reporting Form *http://www.virginia.edu/vprgs/irb/hsr_forms.html* *Go to 3rd bullet from the bottom*

Data Breach	The UVa Corporate Compliance and Privacy Office, a ITC: if breach involves electronic data- UVa Police if breach includes such things as stolen computers.	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY.	UVa Corporate Compliance and Privacy Office- Phone 924-9741 ITC: Information Security Incident Reporting procedure, http://www.itc.virginia.edu/security/reporting.html Phone- (434) 924-7166
UVA PI- IDE			
Life-threatening and/or fatal unexpected events related or possibly related to the use of the investigational agent.	FDA, DSMB	Within 7 calendar days of the study team learning of the event	Form FDA 3500A (MedWatch) or narrative
Serious, unexpected and related or possibly related adverse events	FDA, DSMB	Within 15 calendar days after the study team receives knowledge of the event	Form FDA 3500A (MedWatch) or narrative
For Device Studies: Unanticipated adverse device effects (internal or external)	FDA, DSMB	Within 10 working days of the study team receiving knowledge of the event	Form FDA 3500A (MedWatch) or narrative
All adverse events	FDA, DSMB	Annually	IDE annual report
UVA PI of MULTI-SITE TRIAL			
Serious, unexpected and related or possibly related adverse events	All Research Sites	Within 15 days after the Overall PI receives knowledge	IND/IDE Safety Report (Cover letter, copy of MedWatch/narrative)

		of the event.	
For Device Studies: Unanticipated adverse device effects (internal or external)	All Research Sites	Within 15 calendar days from the time the Overall PI receives knowledge of the event.	Letter to Participating PIs, Copy of MedWatch or narrative
Unanticipated Problem	All Research Sites	Within 15 calendar days from the time the Overall PI receives knowledge of the event.	Letter to Participating PIs, Copy of MedWatch or narrative

J. ENDPOINTS

This study is a randomized, controlled trial involving subjects with type 1 diabetes to test the effectiveness of the Unified Safety System (USS) Virginia closed-loop in preventing hypoglycemia compared with sensor-augmented pump (SAP) therapy. We will also evaluate the effectiveness of the control system (USS Virginia) at improving hypoglycemia counterregulation, hypoglycemia awareness, and overall glycemic control compared with versus SAP. To achieve this goal, we will conduct pre- and post-intervention inpatient assessments of hypoglycemia counterregulation and symptom awareness. For the interventions, subjects randomized to USS Virginia will participate in two training visits at a monitored outpatient setting for the step-wise deployment of the AP system at home in Pump mode followed by 4 weeks using AP at home in Closed Loop mode running USS Virginia. Subjects randomized to sensor-augmented pump therapy will complete 5 weeks of CGM with the home pump.

The *basic unit for analyses of hypoglycemia risk and occurrence 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 endpoint of reduction in hypoglycemia will be assessed by:

1. LBGI from CGM during 1 week of blinded use versus during the last week of

intervention

The secondary endpoints of improvement in counterregulatory response to hypoglycemia and hypoglycemia awareness at baseline versus follow-up will be assessed by:

1. Peak epinephrine
2. Epinephrine AUC
3. Epinephrine increase over baseline
4. Hypoglycemia symptom ratings
5. Clarke Hypoglycemia Perception Awareness score
6. Fear of hypoglycemia scores

Additional secondary endpoints of reduction in hypoglycemia will be assessed by:

1. CGM time <70 mg/dL and <50 mg/dL by retrofitted CGM and SMBG trace from 1 week of blinded use versus the last week of intervention
    a. During 24 hours, and
    b. Overnight (11PM – 7AM)

Additional secondary endpoints of improvement in glycemic control at baseline versus the last week of intervention will be assessed by:

1. Time within target (70-180 mg/dL) over a 24 hour period
2. Time within target range of 80-140 mg/dL overnight (11PM – 7AM), and
3. Distribution of wake-up glucose levels at 7AM

K. SUCCESS CRITERIA / **GOAL**

As a general rule, a subject's data will be considered useful for data analysis if the subject completes at least 1 week of study intervention with USS Virginia+AP system or SAP.

L. STATISTICAL ANALYSIS PLAN

Sample size determination is based on literature data (#3) and on results from our previous studies of hypoglycemia unawareness (#4)(#5). We estimate, conservatively, that the effect size of using the AP system+USS Virginia vs. CGM in terms of restoration of epinephrine response will be moderate ~0.35. Power calculations assuming α=0.05, and power of 80% yield a required sample size of N=36 (using G*Power 3 software [#5]). With this sample size, the power for finding significant effects on frequency and extent of hypoglycemia (Low BG Index [#6]) exceeds 0.9. Assuming a proportion of noncompliance R=20% for Intention-to-Treat (ITT) analysis (#7), 44 completed subjects will adequately address the specific aims of this study. Per-protocol analysis will also be performed. In order to achieve 44 completed subjects, up to 70

subjects may sign consent given an expected screen failure, withdrawal and drop-out rate of ~40% due to the rigorous exclusion criteria and requirements imposed for the AP system use in the subject's local environment.

REFERENCES

#1 Diabetes Research in Children Network (DirecNet) Study Group, Tsalikian E, Tamborlane W, Xing D, Becker DM, Mauras N, Fiallo-Scharer R, Buckingham B, Weinzimer S, Steffes M, Singh R, Beck R, Ruedy K, Kollman C. Blunted counterregulatory hormone responses to hypoglycemia in young children and adolescents with well-controlled type 1 diabetes. *Diabetes Care,* 32 (11):1954-1959, 2009.

#2 Kovatchev BP, Cox DJ, Kumar A, Gonder-Frederick LA and WL Clarke. Algorithmic evaluation of metabolic control and risk of severe hypoglycemia in type 1 and type 2 diabetes using self-monitoring blood glucose (SMBG) data. *Diabetes Technol Ther*, 5: 817-828, 2003.

#3 Ly TT, Hewitt J, Davey RJ, Lim EM, Davis EA, Jones TW. Improving epinephrine responses in hypoglycemia unawareness with real-time continuous glucose monitoring in adolescents with type 1 diabetes. *Diabetes Care*, 34:50-2, 2011

#4 Cox DJ, Gonder-Frederick LA, Polonsky W, Schlundt D, Julian D, Kovatchev BP, Clarke WL. Blood Glucose Awareness Training (BGAT-II): Long term benefits. *Diabetes Care*, 24: 637-642, 2001.

#5 Faul F, Erdfelder E, Lang A-G, & Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, 39, 175-191, 2007.

#6 Kovatchev BP, Cox DJ, Gonder-Frederick LA Young-Hyman D, Schlundt D, Clarke WL. Assessment of risk for severe hypoglycemia among adults with IDDM: Validation of the Low Blood Glucose Index. *Diabetes Care* 21: 1870-1875, 1998.

#7 Lachin JM. Statistical considerations in the intent-to-treat principle. *Control Clin Trials,* 21:167-89, 2000.

#8 Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care*, 18:517-22, 1995

#9 Kovatchev BP, Otto E, Cox DJ, Gonder-Frederick LA, Clarke WL. Evaluation of a New Measure of Blood Glucose Variability in Diabetes. *Diabetes Care*, 29: 2433-2438, 2006.