Efficacy of inControl Advice: A Decision Support System (DSS) for Diabetes

A Randomized Clinical Trial to Assess the Efficacy of CGM+DSS versus CGM to Improve Glucose Control in Subjects with T1DM on MDI Therapy

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Acronym	Abbreviation For
ADA	American Diabetes Association
AP	Artificial Pancreas
ATTD	Advanced Technologies & Treatments for Diabetes
AUC	Area Under the Curve
BG	Blood Glucose
BRM	Basal Rate Modulator
BT	Bluetooth
CRF	Case Report Form
CGM	Continuous Glucose Monitoring
CI	Confidence Interval
CLC	Closed-Loop Control
CSII	Continuous Subcutaneous Insulin Infusion
CTR	Control-to-Range
DSS	Decision Support System
DiAs	Diabetes Assistant
DKA	Diabetic Ketoacidosis
DSMB	Data and Safety Monitoring Board
EC	European Commission
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAS	Hyperglycemia Avoidance Survey
HbA1c	Hemoglobin A1c
HCT	Helmsley Charitable Trust
HFS-II	Hypoglycemia Fear Survey
HMS	Hyperglycemia Mitigation System
ID	Identification
IDE	Investigational Device Exemption
IOB	Insulin-on-Board
IQR	Interquartile Range
JDRF	Juvenile Diabetes Research Foundation
MDI	Multiple Daily Injections
NFC	Near Field Communication
NIH	National Institutes of Health
OS	Operating System
POC	Point-of-Care
QA	Quality Assurance
QC	Quality Control
RCT	Randomized Controlled/Clinical Trial
RMB	Risk-Based Monitoring

Acronym	Abbreviation For
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event
SAP	Sensor-Augmented Pump
SD	Standard Deviation
SFPQ	Six Factor Personality Questionnaire
SH	Severe Hypoglycemia
SI	Insulin Sensitivity
SII	Subcutaneous Insulin Injection
SMBG	Self-Monitoring of Blood Glucose
SSL	Secure Sockets Layer
SSM	Safety Supervision Module
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
UADE	Unanticipated Adverse Device Effect
UI	User Interface
UVA	University of Virginia

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1 INTRODUCTION

1.1 Background

Behavioral Challenges to the Control of Type 1 Diabetes Mellitus (T1DM): Regular meals, exercise, and even a strict daily regiment are interrupted by generally random behavioral events (e.g. insulin overdose, missed food, or excessive exercise [*1*,*2*]). A formal description of the process of self-treatment behavior in T1DM and its potential to generate network challenges is critical for the engineering of any system relying on interaction with human behavior. We have created the Stochastic Model of Self-Regulation Behavior which gives a probabilistic interpretation of the pattern: internal condition → perception/awareness → appraisal → self-regulation decision [*2*,*3*] and approximates behavioral self-regulation of T1DM with a stochastic process quantifying the probability for extreme events, such as severe hypoglycemia or major hyperglycemia. The parameters of this process are specific to each individual. We have shown that such an approach was particularly useful for understanding the causes of severe hypoglycemia [*1*,*4*]; the approach was employed by well-established behavioral interventions, such as BGAT (Blood Glucose Awareness Training) [*5*,*6*].

1.2 Preliminary Studies

The Effects of Automated Decision Support: We have also shown that automated behavioral feedback delivered in the field by a portable device can optimize glycemic control by simultaneously reducing HbA1c and occurrence of severe hypoglycemia [*7*]. This study tested the effect of an automated system providing real-time HbA1c estimates of, glucose variability, and risk for hypoglycemia (Figure 1). For one year, 120 adults with type 1 diabetes, 69/51 female/male, age = 39.1 (±14.3) years, duration of diabetes 20.3 (±12.9) years, HbA1c=8.0 (±1.5) %, performed self-monitoring of blood glucose (SMBG) and received feedback at three increasingly complex levels, each continuing for 3 months: Level 1 - routine SMBG; Level 2 - adding estimated HbA1c, hypoglycemia risk, and glucose variability; Level 3 - adding estimates of symptoms potentially related to hypoglycemia.

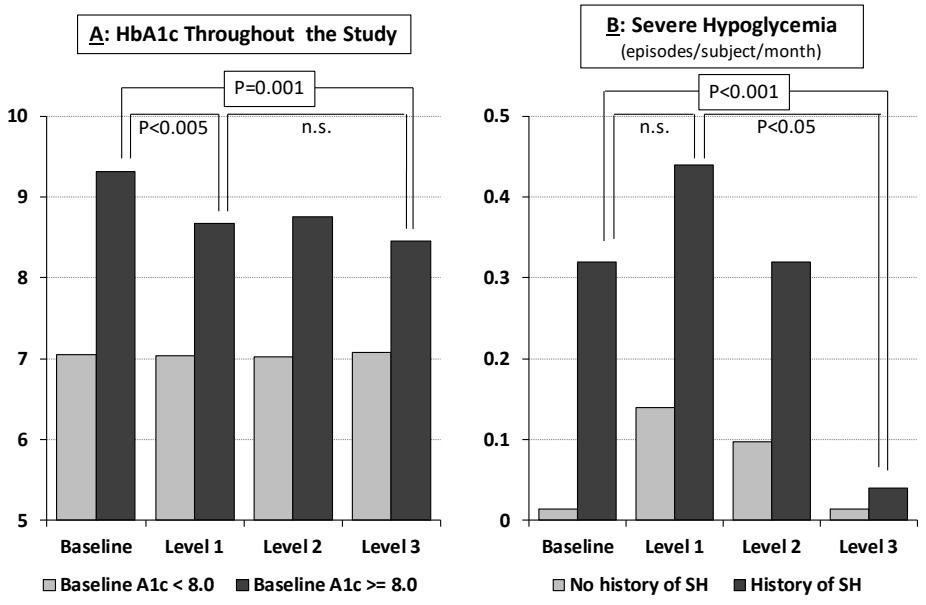

Figure 1: Results from 1-year automated decision-support intervention based on SMBG data, with 3 levels of feedback to the patient: Level 1 – SMBG only; Level 2 – aggregate glycemic characteristics based on SMBG; Level 3 – adding perceived symptom ratings [7]

The subjects were randomized to feedback sequences of either Levels 1-2-3 or Levels 2-3-1. HbA1c, symptomatic hypoglycemia, and blood glucose awareness, were evaluated at baseline and at the end of each level.

For all subjects, this decision-support intervention reduced HbA1c from 8.0 to 7.6 from baseline to the end of study, p=0.001. This effect was confined to subjects with baseline HbA1c above 8.0 (from 9.3 to 8.5, p<0.001). Incidence of symptomatic moderate/severe hypoglycemia was reduced from 5.72 to 3.74 episodes/person per month (p=0.019), more prominently for subjects with history of severe hypoglycemia (from 7.20 to 4.00 episodes, p=0.008) and for those who were hypoglycemia unaware (from 6.44 to 3.71 episodes, p=0.045). The subjects' ratings of the feedback were positive, with up to 89% approval of the provided features. We have therefore concluded that feedback of SMBG data and summary SMBG-based measures resulted in improvement in average glycemic control and reduction in moderate/severe hypoglycemia. As summarized in Figure 1, these effects were most prominent in subjects who were at highest risk at the baseline [*7*]:

The system used in this study was an early prototype of the Decision Support System proposed here; it included advisory modules assessing the risk for hypoglycemia, HbA1c, and BG variability, all estimated from self-monitoring data (see [7]-online appendix).

Closed-Loop Control (CLC): In the past 5 years, our CLC (artificial pancreas, AP) studies have progressed from short-term 2-day trials in controlled outpatient environment to 6-month free-living studies. These studies used the first portable AP platform – the Diabetes Assistant (DiAs) introduced by our UVA group in 2011. DiAs was built using an Android smart phone as a computational hub and included AP user interface (UI) designed for the patient [8-12] and a Cloud-based remote monitoring and automated alert system [11]. The defining characteristic of DiAs is its ability to switch smoothly between different modes of operation, depending on patient preference and signal availability [8,12].

To date, 475 patients with T1DM have tested DiAs for over 230,000 hours of outpatient use. These studies were conducted at several centers in the U.S. and overseas. We can therefore affirm that reliable technology has been developed and sufficient data have been accumulated to warrant the transition of this system to user modes that go beyond closed-loop control - most importantly for this project - *Decision Support for diabetes using closed-loop control technology*.

In addition to a stable, well tested platform, the AP project developed key technologies that are at the core of the proposed DSS, namely: (i) the state estimation and modelling powering the treatment adaptation and insulin sensitivity tracking, and (ii) glycemic forecast modules that now enable the exercise adviser system, the nighttime adviser system, and the hypoglycemia prediction system.

inControl Advice, inControl-AP, Cloud Database, Notifications/Alerts, and Remote Monitoring:

Our DiAs platform [8-12] has now matured into a third-generation system developed by TypeZero Technologies, Inc. (under license from UVA) - the inControl product family (Figure 2), which includes both local (e.g. insulin dosing advice or closed-loop control) and global (e.g. parameter management, notifications, alerts, remote monitoring) functions. The inControl local applications are implemented on a standard Android smartphone and uses Bluetooth (BT) to communicate with a CGM and Near Field Communication (NFC) to communicate with insulin pens. Currently, inControl runs on a modified release of the Android operating system (OS). Modifications of the OS include the removal of unnecessary applications and functions, and fixes to the BT stack to permit communication with peripheral medical devices. The local inControl module is an Android application with a JS/CSS UI.

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inControl-AP: When running closed-loop control, inControl-AP communicates with an insulin pump and modulates insulin delivery automatically to keep blood glucose in a target range. inControl-AP operates on a 5-minute cycle based on the highest frequency of input data. There are three insulin dosing modes (stopped, pump and closed loop) and three operating modes (normal, sleep and

exercise). The combination of insulin dosing mode and operating mode determines what actions inControl-AP will perform and what options are presented to the user.

inControl-Cloud is an external server system that communicates with the Network Service within inControl-AP over a secure SSL to:

- Allow the patient to log in with their inControl-Cloud ID;
- Deliver user biometric data (height, weight, date of birth etc.) and therapy profile information (basal rate, carbohydrate to insulin ratio, correction factor).

inControl Advice: In this protocol, we now intend to use inControl-Advice, which is designed to provide advice to users, instead of directly controlling the insulin delivery system. inControl Advice shares many of the features of inControl-AP described above, but does not implement automated insulin delivery and receives data from an insulin pen. Instead of automated 5-min adjustments to the insulin delivery, the system provides a series of real-time alerts and on-demand advice, for both dosing of insulin and ingestion of carbohydrates, based on data collected from T1DM patients (i.e. carbohydrate consumption, insulin injected, CGM) and inConrol Cloud analytics. inControl Advice includes 6 modules:

1. Retrospective analysis of the past few weeks, based on replay simulation technologies which optimizes the patient's functional insulin therapy parameters (basal doses, insulin sensitivity (ISF) factors, and carbohydrate ratios);
2. A CGM-based bolus calculator that enhances usual computations (bolus=CHO/CR+(SMBG-target)/ISF –IOB) by replacing the SMBG value with a short term (30 minutes) glucose prediction;
3. A Hypoglycemia alert system capable of predicting hypoglycemic events within the next 3 hours;
4. A long-term tracker of average glycemia using CGM to estimate changes in HbA1c;
5. A nighttime adviser, minimizing the risk of overnight exposure to hypoglycemia by proposing adequate bedtime carbohydrate intake which is optimized to minimize the exposure to hyperglycemia;
6. A physical activity adviser, allowing for safe physical activity without hypoglycemia and without increasing the risk of rebound hyperglycemia.

The feasibility and safety of a prototype DSS is currently being tested in 30 adults with T1DM, both insulin pump and MDI users. This single-site clinical trial follows a non-blinded randomized crossover design, with two 48-hour observation periods where patients are exposed to a variety of meal and physical activities to challenge the patients' own control strategies and the advisory system. Preliminary analysis of the first 11 patients showed a clear trend towards increased time spent in good control (between 70-180mg/dL, which was associated with a reduction in both hyperglycemia and hypoglycemia exposure (See Figure 3). The effect size was above 0.5. Use of the decision support system also reduced glucose variability, as shown by the Low BG Index [13] and by the Average Daily Risk Range [14], with effect size of 0.4. Our previous decision-support trial [7] and these preliminary data were used in the power calculations for this study.

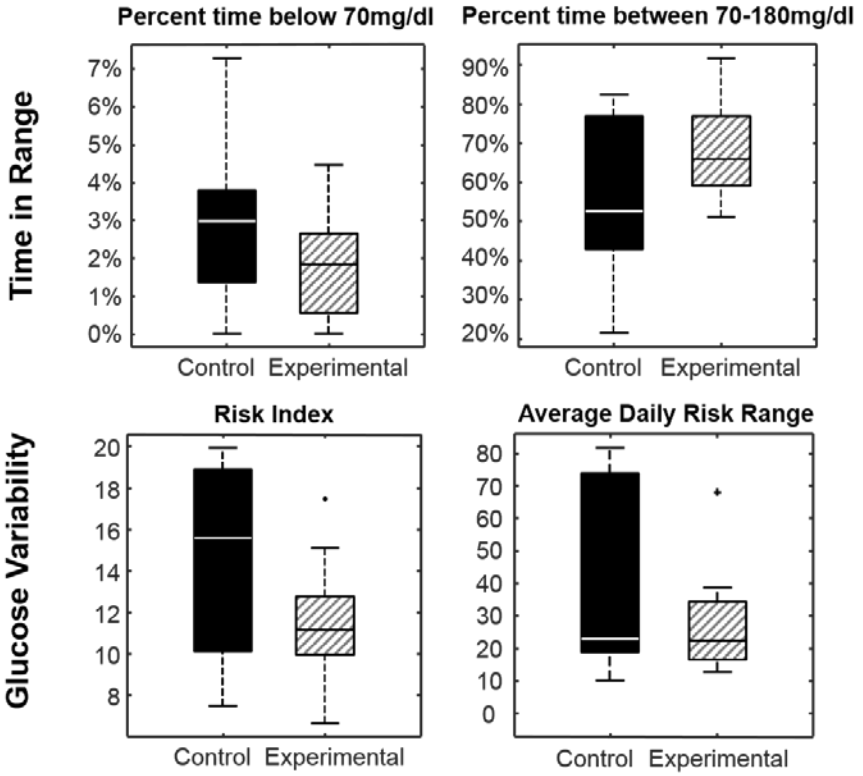

Figure 3: Results from pilot-feasibility testing of Decision Support System

1.3 Synopsis of Study Protocol

1.3.1 Study Objective

The objective of the study is to assess the efficacy of CGM+DSS versus CGM alone to improve glucose control in T1DM patients using multiple daily injections (MDI). The system will be deployed on a portable medical application platform (inControl Advice) and will include the following elements:

1. An MDI treatment parameters optimization routine, using a month of collected Continuous Glucose Monitoring (CGM)/insulin/meal data
2. A smart bolus calculator based on CGM glucose measurements and glycemic prediction.
3. A hypoglycemia detector with accompanying warning system and recommendation for BG monitoring and treatment.
4. A long-term average glycemia tracker
5. A bedtime button that is activated by the user before bedtime that assesses risk for overnight hypoglycemia and recommends a bedtime snack if hypoglycemia risk is elevated.
6. An exercise risk warning system, capable of predicting hypoglycemia at the onset of physical activity and advising on mitigating treatments such as carbohydrate consumption.

1.3.2 Study Design

Prior to outpatient use of substantially changed or updated DSS system components (as deemed by the FDA), there will be pilot testing in 2-5 subjects for approximately 48 hours each in a monitored transitional setting. Pilot testing may occur at multiple times during the study, dependent on whether significant changes are made to the DSS that requires testing prior to home use. Upon successful completion of pilot testing (assessed as no device anomalies or malfunctions and no device-related adverse events), the tested DSS system may be deployed in the main protocol home setting.

The main protocol is a 12-week parallel group multi-center randomized trial designed to compare CGM+DSS with CGM alone.

1.3.3 Major Eligibility Criteria

- Willingness to provide informed consent.
- Clinical diagnosis of type 1 diabetes, treated with insulin for at least 1 year
- Using basal and meal insulin (NovoLog® [insulin aspart], Humalog® [insulin lispro] or Apidra® [insulin glulisine]) for Intensive Insulin Therapy including carbohydrate counting and use of pre-defined parameters for glucose goal, carbohydrate ratio, and insulin sensitivity factor for at least 1 month.
    -
- Age ≥15 years old
- Willingness to use the study basal insulin (Tresiba® [insulin degludec]) and meal insulin (NovoLog® [insulin aspart]) for the duration of the study.
- Willingness to use the home or DSS-optimized carbohydrate counting parameters for all meal dosing and enter the information into the inControl APP.

1.3.4 Sample Size

For pilot testing of new DSS system components, up to 30 subjects may be recruited in total across the study sites. Pilot subjects may additionally participate in the main study.

We plan on 132 subjects completing the study at three clinical sites. Based on our experience with similar studies, we estimate an expected 17.5% screen failures, dropouts or withdrawal due to the data collection and eligibility requirements. Therefore, up to 160 subjects may sign consent for the main study. Every effort will be made to recruit a broad range of ages into the study.

1.3.5 Main Study Treatment Groups

Following the initial 2 weeks of baseline blinded CGM data, subjects will be randomized in a 2:1 ratio to either CGM+DSS or CGM alone.

1.3.6 Main Study Visit and Phone Contact Schedule

Subjects will have a Screening Visit with a baseline central HbA1c. They will then complete a 2-week period of blinded study CGM and glucometer use to characterize baseline glycemic control. During this time, they will use their home insulins dosed according to their pre-defined home parameters for carbohydrate counting.

Eligible subjects will complete baseline questionnaires and be randomized to either CGM+DSS or CGM alone for the remainder of the study. All subjects will continue to use the study CGM (unblinded) and study glucometer and will be transitioned to the study basal insulin pens (Tresiba® [insulin degludec] 100 U/mL) per product guidelines. For meal insulin, subjects with average total

daily insulin (TDI) <60 U/day will use NovoLog® (insulin aspart) pens capable of 0.5U increment dosing and subjects with average TDI ≥60 U/day will use NovoLog® (insulin aspart) pens capable of 1.0U increment dosing. All subjects will receive insulin pen training including pen differentiation training. The differences between the pen for Tresiba® (insulin degludec) and for NovoLog® (insulin aspart) will be emphasized to the patient. The training will include the explanation of the user interfaces of both the insulin pens and inControl Advice and how the equipment interacts with the other.

- Participants in the CGM+DSS group will be trained on the inControl Advice APP and will use it for insulin dose calculations for the remainder of the study.
- Participants in the CGM alone group will use their pre-defined home carbohydrate counting parameters for insulin dose calculations for the remainder of the study.

All participants have the same post-randomization clinic visit and phone contact schedule, with the possible exception of additional phone contacts based on DSS-requested optimization of insulin parameters for the CGM+DSS group.

- Phone contacts after: 2 weeks, 4 weeks, 6 weeks, 8 weeks, and 10 weeks for collection of CGM downloads
- Alternately, emails may be used to contact study subjects.

The Study Conclusion will be a clinic visit for central HbA1c and post-intervention questionnaires.

Figure 4: Study Flow Diagram

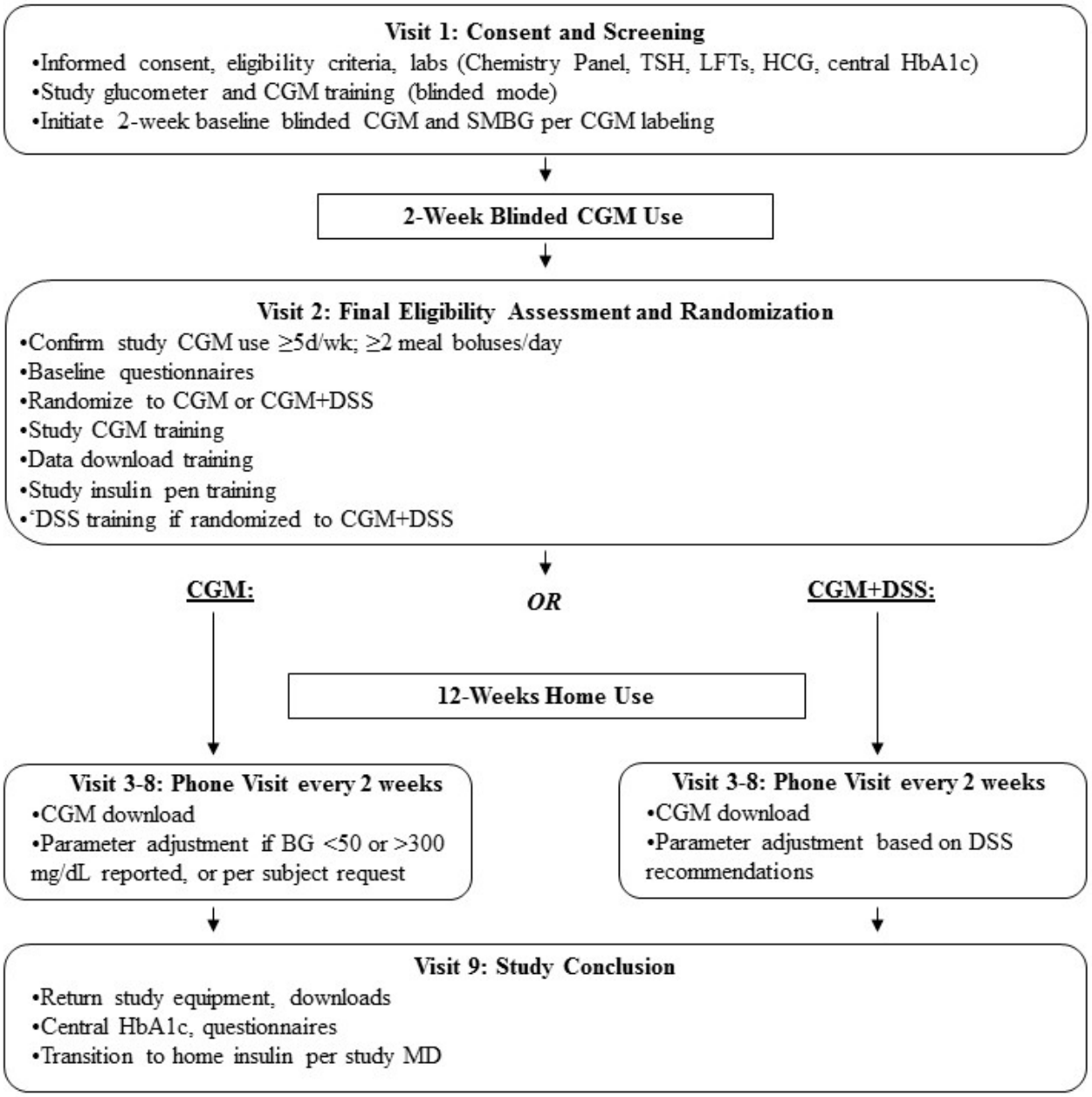

Table 1: Schedule of Study Visits/Phone Contacts and Examination Procedures During 12 week RCT Phase (Randomization at Week 0)

	Pre	0	2w	4w	6w	8w	10w	12w
Visit or Phone	V	V	P	P	P	P	P	V, P
Comment	Screen/Enroll, Blinded CGM run-in	Rand						Conc
Eligibility Assessment	X	X						
Blinded CGM (2 weeks)	X							
HbA1c (Central lab)	X							X
Blood draw for screening labs (chemistry panel, liver function tests, and TSH)	X							
Urine or serum pregnancy test (premenopausal females not surgically sterile)	X	X						
CGM Data download		X	X	X	X	X	X	X
Assessment for BGs <50 or >300 and AEs		X	X	X	X	X	X	X
Clarke Hypoglycemia Awareness Scale, Hyperglycemia Avoidance Scale, Fear of Hypoglycemia Survey, Diabetes Distress Scale, Diabetes Specific Personality Questionnaire, and Technology Expectations Survey (CGM+DSS group)		X						
Clarke Hypoglycemia Awareness Scale, Hyperglycemia Avoidance Scale, Fear of Hypoglycemia Survey, Diabetes Distress Scale, and Technology Acceptance Survey (CGM+DSS group)								X

1.3.7 Endpoints

Primary Efficacy Outcome:
The primary efficacy outcome is increased % time within target range defined as CGM readings of 70-180 mg/dL during the day and 80-140 mg/dL overnight.

Secondary Efficacy Endpoints:
Secondary efficacy endpoints include

1. Optimized metabolic control for the entire study population defined as:
    a. Reduced risk for hypoglycemia, and
    b. Reduced postprandial blood glucose variability defined by the postprandial High Blood Glucose Index and by area under the postprandial CGM glucose curve;
2. Selective improvements for specific sub-populations defined as follows:
    a. Reduced HbA1c without increasing risk for hypoglycemia (measured by the Low Blood Glucose Index), particularly for those who were poorly controlled at the baseline (baseline A1c > 8%);
    b. Reduced incidence and risk for hypoglycemia without deterioration in HbA1c for those with an A1c <8%;
3. Improved psycho-behavioral markers and acceptance of the system feedback by patients, including:
    a. Improved patient/parent diabetes quality of life scores;
    b. Improved hypoglycemia perception/awareness and reduced patient/parent fear of hypoglycemia in those with hypoglycemia unawareness and/or history of severe hypoglycemia at the baseline.

Main Safety Endpoints:

- Episodes of severe hypoglycemia
- Episodes of diabetic ketoacidosis (DKA)
- Other serious adverse events

Interim Analysis:
All CGM-related study endpoints and data collected will be analyzed for the first 6 weeks of study intervention in the first 40 subjects.

1.4 General Considerations

The study is being conducted in compliance with the policies described in the study policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice (GCP). (www.wma.net/en/30publications/10policies/b3/.)

Data will be directly collected in case report forms, which will be considered the source data.

There is no restriction on the number of subjects to be enrolled by each site towards the overall recruitment goal.

The protocol is considered a significant risk device study, due to the fact that the inControl Advice system is experimental. Therefore, an investigational device exemption (IDE) from the U.S. Food and Drug Administration (FDA) is required to conduct the study.

This study is supported by third party collaborators for the provision of study drugs, devices, and software. Current study collaborators are:

- Novo Nordisk (Bagsværd, Denmark)
- TypeZero Technologies Inc., (Charlottesville, VA)

2 SUBJECT SCREENING AND ENROLLMENT

2.1 Study Population

Up to 30 pilot subjects may be enrolled for pilot DSS system testing. These subjects will sign a separate Pilot Subject consent form. Pilot subjects may also participate in the main study.

Enrollment for the main study will proceed with the goal of at least 132 subjects ≥15 years old completing the trial. A maximum of 160 subjects may be enrolled in the study in order to achieve that goal.

2.2 Eligibility and Exclusion Criteria

2.2.1 Eligibility

To be eligible for the pilot and main study, a subject must meet the following criteria:

1. Willingness to provide informed consent
2. Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year and using insulin for at least 1 year
3. Using basal and meal insulin (NovoLog® [insulin aspart], Humalog® [insulin lispro] or Apidra® [insulin glulisine]) for Intensive Insulin Therapy including carbohydrate counting and use of pre-defined parameters for glucose goal, carbohydrate ratio, and insulin sensitivity factor for at least 1 months.
4. Age ≥15.0 years old
5. Willingness to use the study basal insulin (Tresiba® [insulin degludec]) and meal insulin (NovoLog® [insulin aspart]) for the duration of the study.
6. Willingness to use the home or DSS-optimized carbohydrate counting parameters for all meal dosing and enter the information into the inControl APP (for CGM+DSS group).
7. For females, not currently known to be pregnant
8. If female and sexually active, must agree to use a highly effective form of contraception to prevent pregnancy while a participant in the study. A negative serum or 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. Also, subjects who during the study develop and express the intention to become pregnant within the timespan of the study will be discontinued.
9. Ability to access the Internet to provide data to the clinical team or to travel to the research center so that the study equipment can be downloaded.
10. Ability to have 3G or Wi-Fi to be able to use the DSS smart bolus calculator and advice given (i.e. sleep, exercise).
11. Demonstration of proper mental status and cognition for the study
12. Investigator has confidence that the subject can successfully operate all study devices and is capable of adhering to the protocol
13. If on a non-insulin hyperglycemic therapy, stability on that therapy for the prior 3 months and willingness not to alter the therapy for the study duration.

2.2.2 Exclusion

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

1. Medical need for chronic acetaminophen

2. Use of any medication that at the discretion of the clinical protocol chair is deemed to interfere with the trial.
3. Current treatment of a seizure disorder.
4. Coronary artery disease or heart failure, unless written clearance is received from a cardiologist.
5. Hemophilia or any other bleeding disorder
6. A known medical condition, which in the opinion of the investigator or designee, would put the participant or study at risk such as the following examples:
    a. Inpatient psychiatric treatment in the past 6 months
    b. Presence of a known adrenal disorder
    c. Abnormal liver function test results (Transaminase >3 times the upper limit of normal)
    d. Abnormal renal function test results (calculated GFR <60 mL/min/1.73m2).
    e. Active gastroparesis requiring medical therapy
    f. Uncontrolled thyroid disease (TSH undetectable or >10 mlU/L).
    g. Abuse of alcohol or recreational drugs
    h. Infectious process not anticipated to be resolved prior to study procedures (e.g. meningitis, pneumonia, osteomyelitis, deep tissue infection).
    i. Uncontrolled arterial hypertension (Resting diastolic blood pressure >100 mmHg and/or systolic blood pressure >180 mmHg).
    j. Uncontrolled microvascular complications such as current active proliferative diabetic retinopathy defined as proliferative retinopathy requiring treatment (e.g. laser therapy or VEGF inhibitor injections) in the past 12 months.
7. 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.
8. Current use of the following drugs and supplements:
    k. Regular acetaminophen user, or not willing to suspend acetaminophen 24 hours before and during the entire length of the trial
    l. Oral steroids
    m. Any other medication that the investigator believes is a contraindication to the subject's participation
9. Participation in another pharmaceutical or device trial at the time of enrollment or during the study

2.3 Authorization Procedures

Written informed consent must be obtained prior to performing any study specific procedures with the subject that are not part of the subject's routine care.

For eligible subjects 18 years of age or older, the study will be discussed with the subject and the subject will be provided with an Informed Consent Form to read and will be given the opportunity to ask questions. If the subject agrees to participate, the Informed Consent Form will be signed. A copy of the consent form will be provided to the subject and another copy will be added to the subject's clinic chart.

For eligible subjects under 18 years of age, a parent/legal guardian (referred to subsequently as "parent") will be provided with an Informed Consent Form to read and will be given the opportunity to ask questions. Each subject will be given a Child Assent Form to read and discuss with parents and study personnel. If the parent and child agree to participate, the Informed Consent Form and Child Assent Form will be signed. A copy of the consent forms will be provided to the subject and his/her parent and another copy will be added to the subject's clinic chart.

Separate Informed Consent Forms will be used for the pilot study and the main study.

2.4 Screening and Enrollment Visit Logistics

Potential subjects will be evaluated for study eligibility through the elicitation of a medical history, performance of a physical examination by study personnel and local laboratory testing to screen for exclusionary medical conditions. Subject exclusion will be at the discretion of the investigator based on study inclusion/exclusion criteria.

Subjects travelling from a distance or subjects wishing to be pre-screened for eligibility may elect to have the consent +/- assent 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. Screening procedures do not need to be repeated for a subject participating in both the pilot and main study if the subject proceeds to the main study within 8 weeks of the original screening visit. After 8 weeks, the medical history will be updated, labs repeated, and eligibility criteria reevaluated. 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.
- 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.

Subjects may begin the Blinded CGM phase of the study before laboratory results return if the study physician believes that the laboratory results are unlikely to reveal an exclusionary condition.

2.4.1 Data Collection and Testing

A standard physical exam (including vital signs and height and weight measurements) will be performed by the study investigator or designee (a physician, fellow, nurse practitioner or a physician assistant).

The following procedures will be performed/data collected/eligibility criteria checked and documented:

- Subject, and where indicated parent/guardian fully informed about the study and informed consent form/assent form signed according to IRB requirements
- Inclusion and exclusion criteria assessed
- Demographics (date of birth, gender, race and ethnicity)
- Diabetic history
- Medical history
- Substance use history (drinking, smoking, and drug habits)
- Concomitant medications
- Physical examination to include:
    - Weight, height
    - Vital signs including measurement of blood pressure and pulse
- A blood sample will be drawn to send to the central laboratory for baseline HbA1c determination to be used in endpoint analyses and for local assessment of a chemistry panel, liver function tests and TSH.
- Urine or serum pregnancy test for all premenopausal women who are not surgically sterile

Screening procedures will last approximately 1-2 hours.

3 PILOT TESTING OF DSS

3.1 Pilot Testing Overview

Prior to outpatient use of substantially changed or updated DSS system components (as deemed by the FDA), we will conduct a pilot study of 2-5 subjects using CGM+DSS under supervision. These subjects will have an approximately 48-hour visit to an outpatient transitional setting such as a hotel. The subjects will be monitored continuously with remote monitoring and will be supervised by study staff with medical personnel (e.g. nurse, EMT, physician) available during the entire visit. Subjects will eat at restaurants or take-out meals and participate in at least 45 minutes of activities such as walking or shopping each day. If there are no device anomalies or malfunctions and no device-related adverse events during the pilot testing, the DSS may be deployed for home use. Pilot testing may be repeated as needed after addressing software or device anomalies until successful pilot testing occurs.

4 2-WEEK BLINDED CGM

4.1 2-Week Blinded CGM Overview

Prior to randomization, the subject will initiate 2 weeks of home use of blinded CGM for characterization of baseline glycemic control and collection of baseline CGM data.
The subject will use carbohydrate counting per their usual routine with their usual home insulins during this time.

The subject will receive supplies for blood glucose and ketone testing during this period:

- Blood glucose testing
    - 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.
    - All study blood glucose meters will be QC tested during all office visits. 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 be instructed to contact study staff for a replacement of the meter, test strips, and control solution if a meter fails QC testing at home.
    - The blood glucose meter training will include instructions to follow labeling instructions with regards to the glucose meter and test strips.
    - Subjects will be reminded to use the study blood glucose meter for all fingerstick blood glucose measurements during the trial.
    - Subjects will be given guidelines for treatment of low or high blood glucose
    - Subjects will be asked to perform fingerstick BG testing according to the CGM manufacturer guidelines and as needed to follow study guidelines for the treatment of low or high blood glucose.
- Blood ketone testing
    - Subjects will be provided with a study blood ketone meter and test strips. All study blood ketone meters will be QC tested at the start of the study with at least two different concentrations of control solution if available. 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.
    - All study blood ketone meters will be QC tested during all office visits. 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 be instructed to contact study staff for a replacement of the meter, test strips, and control solution if a meter fails QC testing at home.
    - Subjects will be instructed to perform blood ketone testing as described in Section 7.1.2.2.
    - Subjects will be given guidelines for treatment of elevated blood ketones
- Subjects will be required to have a home glucagon emergency kit. Subjects who currently do not have one will be given a prescription for the glucagon emergency kit.

Blinded CGM Use

At the screening visit, a CGM sensor will be placed. For subjects not currently using a CGM, the study CGM receiver will be blinded so that the participant is not able to see the CGM glucose values. The participant will be instructed on sensor use including insertion of a new sensor as recommended by the manufacturer (or sooner if the sensor comes out). Additional sensors will be provided. Subjects that currently use a CGM may use the study CGM in the unblinded mode to maintain usual care.

Participants will be informed that in order to be eligible for the randomized trial, the study CGM must be used on a minimum of 10 out of 14 days.

4.1.1 Blinded CGM Use Assessment

Enrolled participants will return approximately 19 ± 5 days after screening to assess the blinded CGM wear. The purpose of the visit will include the following:

- Assessment of compliance with the use of the CGM
- Assessment of skin reaction in areas where a CGM sensor was worn
-
- CGM download.
- Collection and assessment of adverse events, adverse device effects, and device issues
- Assessment of occurrence of BG <50 or >300 mg/dL. (If BG <50 or >300 mg/dL occurred during the blinded CGM use, the Dexcom data will be reviewed by the study physician to evaluate whether an insulin parameter adjustment is needed. Adjustments will be made prior to randomization to the CGM+DSS or CGM alone group.

The CGM data will be downloaded and reviewed to assess whether the participant has used the CGM on at least 10 out of 14 days.

Participants who are unable to meet the CGM compliance requirement will be withdrawn from the study, unless the investigator believes that there were extenuating circumstances that prevented successful completion. In such cases, the subject may be asked to repeat this portion of the study.

5 Randomized Trial

5.1 Randomization Visit

The Randomization Visit will occur concurrently with the Blinded CGM Use Assessment.

A urine pregnancy test will be repeated for all premenopausal women who are not surgically sterile. The test must be negative to be eligible for continuation in the study.

Subjects will complete the following baseline questionnaires:

- Fear of Hypoglycemia Survey (HFS-II)
- Hyperglycemia Avoidance Scale
- Diabetes Distress Scale
- Clarke's Hypoglycemia Awareness scale
- Diabetes Specific Personality Questionnaire

The home insulin regimen will be reviewed and the subject will be transitioned to the study insulins consisting of Tresiba® (insulin degludec) (100 U/mL) for basal insulin dosing and NovoLog® (insulin aspart) (100 U/mL) for meal and correction insulin dosing. The investigators making the basal insulin recommendations will be physicians knowledgeable in insulin titration. The starting dose of Tresiba will be the same unit dose as the total daily long acting unit dose, as per the product manufacturer guidelines for adults already on insulin therapy.

To mitigate the risk of hypoglycemia when transitioning from the home basal insulin to Tresiba, subjects will be asked to perform fingerstick blood glucose measurements a minimum of four times daily for the first 2 weeks of Tresiba use (premeal and bedtime, for CGM calibrations, to confirm low or high CGM alarms, and for symptoms of low or high blood sugar). The subjects will have the additional protection of wearing a CGM system, approved for non-adjunct use (Dexcom G5), with the low alarm set to 70 mg/dL and the high alarm set to 300 mg/dL. These alerts will allow the subject to time the required fingersticks to when the risk to the subject is highest. During the first 2 weeks of Tresiba use, subjects will be instructed to verify that their CGM functions before bedtime, and strongly advised to measure their blood glucose around 3am using the study provided blood glucose meter.

The study insulin degludec (Tresiba®) will be available in a PenFill® cartridge which is inserted into a NovoPen® 5 Plus pen. The study insulin aspart (NovoLog®) will be available in a PenFill® cartridge which is inserted into a NovoPen Echo® Plus or NovoPen® 5 Plus pen. The individual PenFill® is labelled with the drug type. The differences between the pen for Tresiba® (insulin degludec) and for NovoLog® (insulin aspart) will be emphasized to the patient. The insulin delivery device containing NovoLog® (insulin aspart) PenFill® will deliver in 0.5 U increments for subjects with average total daily insulin <60 U/day and in 1 U increments for subjects with average total daily insulin ≥60 U/day. Pen needles will also be provided. The Instruction for Use for the pens will be reviewed with the subject and the subject will demonstrate proper insulin pen priming, injection technique and the ability to change the insulin cartridge to the training staff. If the subject receives a prandial insulin recommendation that is not capable of being delivered by the pen, the subject will be asked to round to the next closest number per the clinical scenario (e.g. if CGM arrow flat or downward, round down; if CGM

arrow upward, round up). Storage and in use conditions for the insulins will be per the trial product label. Initial once daily doses of Tresiba® (insulin degludec) will be determined per the product guidelines.

Subjects will be advised that they may experience more high or low blood sugars when switching from the home insulins to the study insulins. Subjects will be provided with study staff contact information and will be instructed to contact study staff for any concerns regarding an increase in high or low blood sugars.

Subjects will be provided with study supplies and will be asked to perform fingerstick blood glucose measurements a minimum of four times daily for the first 2 weeks of using the study insulins (premeal and bedtime, for CGM calibrations, to confirm low or high CGM alarms, and for symptoms of low or high blood sugar). Thereafter, subjects will be asked to perform fingersticks in accordance with the labeling of the study CGM device and as needed to follow study guidelines for the treatment of low or high blood glucose. Subjects will continue to use the study basal and meal insulin pens for the remainder of the study.

5.1.1 CGM Training

The participant will be provided with sensors and instructed to use the CGM daily for the remainder of the trial. Depending on the subject's prior CGM experience, the subject will have approximately 1 hour of training on how to use CGM for daily diabetes management using the manufacturer's training materials. Product labeling for the Dexcom G5 mobile system states that it is indicated for the management of diabetes in persons age 2 years and older. It is designed to replace fingerstick blood glucose testing for diabetes treatment decisions. Per the product guidelines, fingersticks are required for calibration, or if symptoms or expectations do not match readings, or when taking medications containing acetaminophen.

During the CGM training session, subjects will view the interactive Dexcom G5 mobile training tutorial that is available on the Dexcom website: (https://s3-us-west-2.amazonaws.com/dexcommisc/tutorial/story_html5.html). Of relevance, proper calibration timing and technique is described in the training tutorial. This training session also covers but is not limited to the following topics:

- Dexcom G5 mobile components
- Display device options
- Setting high/low alerts
- Inserting sensor
- Starting sensor session
- Entering BG meter value
- Ending sensor session

5.1.2 Randomization

Eligible subjects will be randomly assigned to one of two treatment groups:

1. CGM+DSS Group
2. CGM alone Group

Subjects randomized to CGM+DSS will complete an additional baseline questionnaire:

- Technology Expectations Survey

5.1.3 CGM Data Downloads

Subjects in both groups will be provided with the software needed to download the study CGM and transmit the data to study personnel and will be asked to do so prior to scheduled phone contacts for the remainder of the study.

5.2 Procedures for the CGM+DSS Group

5.2.1 DSS Training

Subjects randomized to the CGM+DSS group will receive DSS training.

The subject will be trained by qualified study staff to use the DSS (inControl Advice) APP to calculate insulin doses for meals and corrections. Prior to initial use, the inControl system will be initialized by a study team member with each subject's individual insulin dosing parameters, including carbohydrate ratio, insulin sensitivity factor and basal insulin dose.

Study team members will train the subject in performing specific tasks including the following:

- The study team will confirm the carbohydrate counting parameters entered in the system with the study physician.
- How to activate the "meal" screen of the inControl system any time insulin will be given with a meal and the "add correction" screen any time additional correction insulin is desired
- How to use the NFC communication on the insulin pens to inform and confirm on the inControl system that an insulin dose was injected.
- How to inform the system of hypoglycemia treatment via a "hypoglycemia treatment" button on the inControl user interface after glucose is consumed that is not accompanied by an insulin bolus
- What to do when exercising while using the system and how to react to the exercise advice given
- How to react to the hypoglycemia risk alarm.
- How to access the bedtime button and react to the possible advice for a bedtime snack.

The subject will also be instructed to contact study staff during periods of illness with an elevated temperature >101.5 degrees Fahrenheit (38.6 degrees Celsius), periods of significant illness, or during periods of use of medications such as epinephrine (e.g. for the emergency treatment of a severe allergic reaction or asthma attack) or oral or injectable glucocorticoids to determine if study procedures should be temporarily discontinued.

Subjects will be given the inControl Advice device and will be provided with sufficient supplies to last until the final clinic visit.

5.3 Procedures for the CGM Group

Subjects in the CGM Group will continue to use the study CGM and will be provided with sufficient supplies to last until the final clinic visit.

The subject will also be instructed to contact study staff during periods of illness with an elevated temperature >101.5 degrees Fahrenheit (38.6 degrees Celsius), periods of significant illness, or during periods of use of medications such as epinephrine (e.g. for the emergency treatment of a severe allergic reaction or asthma attack) or oral or injectable glucocorticoids to determine if study procedures should be temporarily discontinued.

5.4 Follow-up Phone Contacts for Both Groups

The schedule for remaining follow-up visits and phone contacts is the same for both treatment groups. A primary purpose of the contacts will be to collect the CGM downloads and to assess for BGs <50 or >300 and any AEs.

5.4.1 Phone Contacts

A phone call will be made at the following times:

- 2 weeks (±3 days)
- 4 weeks (±1 week)
- 6 weeks (±1 week)
- 8 weeks (±1 week)
- 10 weeks (±1 week)

The following procedures will be performed in both groups during each phone contact, unless otherwise specified:

- Assessment of compliance with study device use
- Assessment of occurrence of BG <50 or >300 mg/dL.
- CGM download.
- Collection and assessment of adverse events, adverse device effects, and device issues

5.4.2 Study Conclusion Visit

The following procedures will be performed in both groups at the study conclusion visit:

- All study devices will be returned and downloaded
- Blood will be drawn for central HbA1c assessment.

Subjects will complete the following post-intervention questionnaires:

- Fear of Hypoglycemia Survey (HFS-II)
- Hyperglycemia Avoidance Scale
- Diabetes Distress Scale
- Clarke's Hypoglycemia Awareness scale
- Technology Acceptance Survey (CGM+DSS group)

Study participants will meet with the study physician and the Dexcom data will be reviewed. The subject will be instructed on how to transition back to the home insulins and the doses to be used. Subjects will be informed that there may be a risk of severe hypoglycemia and/or severe hyperglycemia during the transition back to the subject's usual home basal insulin from the study basal insulin (Tresiba). They will be asked to perform fingerstick BGs before meals, at bedtime, and at 3AM for the first 3 days on the home insulin.

5.5 Follow-up Phone Contacts for Both Groups: Post-study

A follow-up safety call will be made with the subject within 3-7 days to assess for any problems transitioning to the home insulin, including any episodes of BG 300 mg/dL.

6 QUESTIONNAIRES

6.1 Introduction

The following questionnaires will be completed at the randomization visit:

- Diabetes Specific Personality Questionnaire
- Clarke Hypoglycemia Awareness Scale
- Fear of Hypoglycemia Survey (HFS-II)
- Hyperglycemia Avoidance Scale
- Diabetes Distress Scale
- Technology Expectations Survey (CGM+DSS group only)

The following questionnaires will be completed at the final visit at week 12:

- Clarke's Hypoglycemia Awareness Scale
- Fear of Hypoglycemia Survey (HFS-II)
- Hyperglycemia Avoidance Scale
- Diabetes Distress Scale
- Technology Acceptance Survey (CGM+DSS group only)

Each questionnaire is described briefly below. The procedures for administration are described in the study procedures manual.

6.2 Diabetes Specific Personality Questionnaire

The Diabetes Specific Personality Questionnaire (24) is based on the original Six Factor Personality Questionnaire (25), a well-validated measure that was adapted for the diabetes-specific version of the questionnaire. The SFPQ is a measure of six personality dimensions each consisting of three facet scales, measured by 108 Likert items. The SFPQ facet scales are organized in terms of six factor scales.

Administration time is approximately 15 minutes.

6.3 Clarke's Hypoglycemia Awareness Scale

The scale (26) comprises eight questions characterizing the participant's exposure to episodes of moderate and severe hypoglycemia. It also examines the glycemic threshold for, and symptomatic responses to, hypoglycemia. A score of four or more on a scale of 0 to 8 implies impaired awareness of hypoglycemia.

Administration time is approximately 5 minutes.

6.4 Hypoglycemia Fear Survey (HFS-II) / Low Blood Sugar Survey

The Hypoglycemia Fear Survey-II (27) was developed to measure behaviors and worries related to fear of hypoglycemia in adults with type 1 diabetes. It is composed of 2 subscales, the Behavior (HFS-B) and Worry (HFS-W). HFS-B items describe behaviors in which patients may engage to avoid hypoglycemic episodes and/or their negative consequences (e.g., keeping blood glucose levels above 150 mg/dL, making sure other people are around, and limiting exercise or physical activity). HFS-W items describe specific concerns that patients may have about their hypoglycemic episodes (e.g., being alone, episodes occurring during sleep, or having an accident).

Administration time is approximately 10 minutes.

6.5 Hyperglycemia Avoidance Survey (HAS) / High Blood Sugar Survey

The HAS (28) reliably quantifies affective and behavioral aspects of hyperglycemia avoidance and is used to assess the extent of potentially problematic avoidant attitudes and behaviors regarding hyperglycemia in people with Type 1 diabetes mellitus (T1DM).
Administration time is approximately 10 minutes.

6.6 Diabetes Distress Scale

The Diabetes Distress Scale (29) is a measure of diabetes-related emotional distress and consists of a scale of 28 items. These include 7 items from each of four domains central to diabetes-related emotional distress. Patients rate the degree to which each item is currently problematic for them on a 6-point Likert scale, from 1 (no problem) to 6 (serious problem).

Administration time is approximately 10 minutes.

6.7 Technology Expectation and Technology Acceptance Surveys

The Technology Expectation and Technology Acceptance Surveys were developed for a Bionic Pancreas camp study (30). The 38 items in the Questionnaire were based on interviews conducted with individuals who had participated in previous Bionic Pancreas trials about their experience regarding the Bionic Pancreas. It was subsequently adapted to assess these same measures for the inControl Advice system. It assesses both positive and negative experiences with inControl, including blood glucose management, device burden, and overall satisfaction. Items are rated on a 5-point scale.

Administration time is approximately 10 minutes.

7 SAFETY MEASURES

7.1 Safety Measures

7.1.1 CGM Calibration

Throughout the study, subjects will be instructed to calibrate the study CGM in accordance with manufacturer labelling.

7.1.2 Safety Measures

7.1.2.1 Hypoglycemia Safety Protocol

All subjects will be required to set the CGM hypoglycemia threshold alarm to a value no less than 70 mg/dL.

If a subject receives a CGM hypoglycemia threshold alarm or notes that the CGM glucose is <70 mg/dL, confirmatory fingerstick testing will be recommended and the subject will be instructed to treat hypoglycemia with ~16 grams of fast-acting oral glucose.

7.1.2.2 Hyperglycemia Safety Protocol

Subjects will be required to set the CGM hyperglycemia threshold alarm to a value no greater than 300 mg/dL.

If a subject receives a CGM hyperglycemia threshold alarm or notes that the CGM glucose is ≥300 mg/dL, confirmatory fingerstick testing will be recommended.

If a subject's CGM reading is ≥300 mg/dL for over 1 hour, or ≥400 mg/dL at any point, the subject will be instructed to take the following steps:

- Perform a blood ketone measurement with the study ketone meter. Subjects will also be encouraged to check ketones if they are clinically concerned.
- Correction insulin may be taken per the subject's usual routine (CGM group) or per the inControl Advice recommendation (CGM+DSS group).
- Subjects will be instructed to administer correction insulin per the subject's usual routine (CGM group) or per the inControl Advice recommendation (CGM+DSS group) for ketones ≥0.6 mmol/L and to additionally notify study staff for ketones ≥3.0 mmol/L.

7.1.2.3 Study System Failure

If the inControl Advice APP stops working, subjects will be instructed to resume their regular home insulin therapy until he/she can contact study staff for confirmation of the current carbohydrate counting parameters or until the study system can be repaired or replaced.

8 ADVERSE EVENTS, DEVICE ISSUES, POTENTIAL RISKS, AND STOPPING RULES

8.1 Adverse Event Definition

A reportable adverse event for this protocol includes any untoward medical occurrence that meets criteria for a serious adverse event or any unanticipated medical occurrence in a study subject that is study- or device-related, including severe hypoglycemia as defined below and severe hyperglycemia/diabetic ketoacidosis (DKA) as defined below. Skin reactions from sensor placement are only reportable if severe and/or required treatment.

Hypoglycemic events are recorded as Adverse Events (severe hypoglycemic event) if the event required assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the participant was impaired cognitively to the point that he/she was unable to treat himself/herself, was unable to verbalize his/ her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Hyperglycemic events are recorded as Adverse Events (severe hyperglycemic event) if the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below, or in the absence of DKA if evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia with ketosis.

Hyperglycemic events are classified as DKA if the following are present:

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Serum ketones >1.5 mmol/L or large/moderate urine ketones;
- Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15; and
- Treatment provided in a health care facility

8.2 Recording of Adverse Events

Throughout the course of the study, all efforts will be made to remain alert to possible adverse events or untoward findings. The first concern will be the safety of the study participant, and appropriate medical intervention will be made.

All reportable adverse events whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported on an adverse event form online. Each adverse event form is reviewed by the Medical Monitor at the Coordinating Center to verify the coding and the reporting that is required.

The study investigator will assess the relationship of any adverse event to be related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by the study intervention.

To ensure consistency of adverse event causality assessments, investigators should apply the following general guideline when determining whether an adverse event is related:

Yes
There is a plausible temporal relationship between the onset of the adverse event and the study intervention, and the adverse event cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study intervention; and/or the adverse event abates or resolves upon discontinuation of the study intervention or dose reduction and, if applicable, reappears upon re-challenge.

No
Evidence exists that the adverse event has an etiology other than the study intervention (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to study intervention.

The intensity of adverse events will be rated on a three-point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity: thus, a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

Adverse events will be coded using the MedDRA dictionary.

All adverse events including adverse events that continue after the study participant's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

8.3 Reporting Serious Adverse Events, Unexpected Adverse Device Effects, Serious Adverse Reactions (SAR) and Serious Adverse Drug Reaction (SARD)

Any untoward occurrence that:

- Results in death.
- Results in transmission of a bloodborne pathogen.
- Is life-threatening; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital anomaly or birth defect
- Is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the endpoints listed above).

An Unanticipated Adverse Device Effect is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)). Reporting timelines are noted in Table 2.

Subjects will be instructed to notify the study team immediately if they become pregnant during the trial. Pregnancies will be reported to third party collaborators within 15 calendar days of the study team being notified of the event. However, pregnancy will not be considered an adverse event in this trial. Pregnancy complications will be recorded as adverse event(s).

Each principal investigator is responsible for reporting serious study-related adverse events and abiding by any other reporting requirements specific to his/her Institutional Review Board and third party collaborators.

Type of Event	To whom will it be reported:	Time Frame for Reporting	How reported?
Any event resulting in death that is deemed DEFINITELY related to (caused by) study participation	IRB Third party collaborators	Within 24 hours	IRB Online and phone call
Serious Adverse Event, Unexpected Adverse Event, Serious Adverse Reactions (SAR), Serious Adverse Drug Reaction (SARD)	IRB Third party collaborators	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
Unanticipated Problems that are not adverse events or protocol violations. This would include a Data Breach.	IRB Third party collaborators	Within 10 day calendar days of the study team receiving knowledge of the event	IRB Online
Protocol Violations/ Noncompliance The IRB only requires that MAJOR violation be reported, unless otherwise required by the sponsor **OR** **Enrollment Exceptions**	IRB	Within 7 calendar days from the time, the study team received knowledge of the event.	Unanticipated Problem report form.
Data Breach	IRB	Within 7 calendar days from the time, the study team received knowledge of the event.	Protocol Violation, Noncompliance and Enrollment Exception Reporting Form

OUTSIDE SPONSOR	The UVa Corporate Compliance and Privacy Office, a ITC: if breach involves electronic data- Police if breach includes items that are stolen: Stolen on UVA Grounds OR Stolen off UVa Grounds- contact police department of jurisdiction of last known location of PHI	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 UVa Police- Phone- (434) 924-7166
UVA PI IDE			
Life-threatening and/or fatal unexpected events related or possibly related to the use of the investigational device.	FDA Third party collaborators	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 Third party collaborators	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 Third party collaborators	Within 10 working days of the study team receiving knowledge of the event	Form FDA 3500A (MedWatch) or narrative
All adverse events	FDA	Annually	IDE annual report

Table 2: Adverse Event Reporting Table

8.4 Device Issues

Device malfunctions (failure of device to perform as intended) will be reported, irrespective of whether associated with an adverse event. However, CGM sensors lasting less than 7 days will not be reported unless associated with an adverse event. Additionally, inControl CGM disconnections will not be reported unless associated with an adverse event.

8.5 Potential Risks and Side Effects

Loss of confidentiality is a potential risk; however, data are handled to minimize this risk. Hyperglycemia and ketone formation and hypoglycemia are always a risk in subjects with type 1 diabetes and subjects will be closely monitored for this. When wearing sensors and insulin infusion

sets there is always a risk of skin rashes, allergic reactions to the tape, or infections at the insertion site. There is always a risk for a small piece of a sensor remaining under the skin or a sensor or infusion set breaking off under the skin.

8.5.1 Venipuncture Risks

A hollow needle/plastic tube will be placed in the arm for taking blood samples. Blood draws can cause some common reactions like pain, bruising, or redness at the sampling site. Less common reactions include bleeding from the sampling site, formation of a small blood clot or swelling of the vein and surrounding tissues, and fainting.

8.5.2 Fingerstick Risks

About 1 drop of blood will be removed by fingerstick for measuring blood sugars and sometimes HbA1c or other tests. This is a standard method used to obtain blood for routine hospital laboratory tests. Pain is common at the time of lancing. In about 1 in 10 cases, a small amount of bleeding under the skin will produce a bruise. A small scar may persist for several weeks. The risk of local infection is less than 1 in 1000. This should not be a significant contributor to risks in this study as fingersticks are part of the usual care for people with diabetes.

8.5.3 Subcutaneous Catheter Risks (CGM)

Subjects using the CGM will be at low risk for developing a local skin infection at the site of the sensor needle placement. If a catheter is left under the skin for more than 24 hours it is possible to get an infection where it goes into the skin, with swelling, redness and pain. There may be bleeding where the catheter is put in and bleeding under the skin causes a bruise (1 in 10 risk).

Study staff should verbally alert the subject that on rare occasions, the CGM may break and leave a small portion of the sensor under the skin that may cause redness, swelling or pain at the insertion site. The subject should be further instructed to notify the study coordinator immediately if this occurs.

8.5.4 Risk of Hypoglycemia

As with any person having type 1 diabetes and using insulin, there is always a risk of having a low blood sugar (hypoglycemia). The frequency of hypoglycemia should be no more and possibly less than it would be as part of daily living. Symptoms of hypoglycemia can include sweating, jitteriness, and not feeling well. Just as at home, there is the possibility of fainting or seizures (convulsions) and that for a few days the subject may not be as aware of symptoms of hypoglycemia. A CGM functioning poorly and significantly over-reading glucose values could lead to inappropriate insulin delivery. Inadvertent mix-ups of short-acting and long-acting insulins could contribute to the risk of hypoglycemia.

8.5.5 Risk of Hyperglycemia

Hyperglycemia and ketonemia could occur if insulin delivery is attenuated or suspended for an extended period. A CGM functioning poorly and significantly under-reading glucose values could lead to an inappropriate insulin recommendation. Inadvertent mix-ups of short-acting and long-acting insulins could contribute to the risk of hyperglycemia.

8.5.6 Risk of Device Reuse

The study CGM system is labeled for single-patient use only. The sensor (the component of the system that enters the skin) will be single-patient use only. The transmitter and receiver may be reused during the study after cleaning the device using a hospital-approved cleaning procedure. The transmitter is

attached to the sensor but does not enter the skin and the receiver is a hand held device. Subjects will be informed that FDA or relevant national authorities have approved these devices for single use and that by using them among multiple patients, bloodborne pathogens (i.e. Hepatitis B) may be spread by multiple users.

8.5.7 Psychosocial Questionnaires

As part of the study, participants will complete psychosocial questionnaires which include questions about their private attitudes, feelings and behavior related to diabetes. It is possible that some people may find these questionnaires to be mildly upsetting. Similar questionnaires have been used in previous research and these types of reactions have been uncommon.

8.5.8 Other Risks

Some subjects may develop skin irritation or allergic reactions to the adhesives used to secure the CGM. If these reactions occur, different adhesives or "under-taping" (such as with IV 3000, Tegaderm, etc.) will be tried, sites will be rotated frequently, and a mild topical steroid cream or other medication may be required.

Whenever the skin is broken there is the possibility of an infection. The CGM sensors are inserted under the skin. It is possible that any part that is inserted under the skin may cause an infection. These occur very infrequently, but, if an infection was to occur, oral and/or topical antibiotics can be used. The risk of skin problems could be greater if you use a sensor for longer than it is supposed to be used. Therefore, participants will be carefully instructed about proper use of the sensor.

Data downloaded from the CGM and blood glucose and ketone meters will be collected for the study as measures of diabetes self-management behaviors. Some people may be uncomfortable with the researchers' having such detailed information about their daily diabetes habits.

8.6 Study Stopping Criteria

8.6.1 Subject Discontinuation of Study Treatment

Rules for discontinuing inControl Advice (if randomized to CGM+DSS group) or study CGM use (if randomized to the CGM group) are as follows:

1. One episode of severe hypoglycemia, or of hyperglycemia/DKA as defined in Section 8.1
2. One serious adverse event related to device malfunction.
3. The subject requests that the treatment be stopped
4. Subject pregnancy

8.6.2 Criteria for Suspending/Stopping Overall Study

In the case of inControl Advice resulting in a severe hypoglycemia or severe hyperglycemia event (as defined in Section 8.1) that is thought to be advice-related (due to excess insulin administration) and occurs more than three times, the overall study will be suspended while the problem is diagnosed. 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 overall study will be stopped in the event of three serious adverse events related to device malfunction.

9 MISCELLANEOUS CONSIDERATIONS

9.1 Benefits

One purpose of this research is to reduce the frequency of hypoglycemia and severe hypoglycemic events. Hypoglycemia is the number one fear of many individuals and families with someone who has type 1 diabetes and this fear often prevents optimal glycemic control.

It is expected that this protocol will yield increased knowledge about using a decision support system to help control the glucose level. In addition, it is the belief of the investigators that this study also presents prospect of direct benefit to the subjects and general benefit to others with diabetes.

9.2 Subject Compensation

Pilot subjects completing the 48-hour transitional setting admission will be compensated $200.

Subjects will be compensated $50 for each clinic visit during the study.

9.3 Subject Withdrawal

Participation in the study is voluntary, and a subject may withdraw at any time. For subjects who withdraw, their data will be used up until the time of withdrawal.

9.4 Confidentiality

For security and confidentiality purposes, subjects will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the third party collaborators. De-identified subject information may also be provided to research sites involved in the study.

9.5 Drug Accountability and Storage

Insulin will be provided by a third party collaborator and delivered to the Investigational Pharmacy. The clinical investigator will be responsible for maintaining adequate records of the disposition of the drug. The clinical investigator will also ensure proper security and storage of the investigational drug.

Documentation: The site will document drug receipt, subject dispensing and return, returns of used and unused supplies to a third party collaborator (or on-site destruction), and will maintain a current accounting of all supplies in inventory—that is, a balance-on-hand log. The balance-on-hand, or dispensing, log will contain the protocol number, the investigative site(s), the drug name, and the medication units—such as cartridge). The site will document receipt of each drug shipment in the balance-on-hand log, noting the date, amount, and lot, batch, or ID numbers. When dispensing drug to a subject, site personnel will record the date, subject number, and amount dispensed. When a subject returns a drug, the amount used and unused will be documented, and an explanation for any inadvertent loss or destruction of supplies will also be recorded.

Ensuring compliance and reconciliation: Site personnel will assess dosing regimen compliance and drug reconciliation in an ongoing manner. At each subject visit, subject compliance will be evaluated and documented, including calculating the expected amount of consumed drug given the regimen and amount of time between visits. This figure will be compared with the amount dispensed minus the amount the subject returned. Site personnel will question the subject regarding any discrepancies in these amounts and document the explanation.

Insulin Storage: Insulin will be stored per product labeling as follows:

Insulin	Temperature	Use up to
In use (opened)	Room temperature: up to 86°F	28 days
Not in use (unopened)	Room temperature: up to 86°F	28 days
Not in use (unopened)	Refrigerated: 36°F to 46°F	Expiration date

10 STATISTICAL CONSIDERATIONS

The approaches to sample size and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized prior to the completion of the study.

10.1 Sample Size

We plan on 132 subjects finishing the study, leading to a potential enrollment of 160, with up to 17.5% attrition. We base our analysis on our previous decision-support trial [7] which recruited N=120 subjects and concluded with N=96 yielding effect size of 0.2 on key parameters, and on the feasibility and safety study described in the background. In this study, 11 T1DM pump users tested a prototype of the DSS leading to an estimated moderate effect size of 0.5 (Cohen D method). Assuming a substantial reduction of effect size due to (i) the focus on MDI patients, (ii) the presence of CGM in both the experimental and the control groups, and (iii) the translation of the effect to an uncontrolled environment similar to the environment of our previous trial [7], we assume a small to medium effect size. Using the statistical analysis presented below, a 0.15 effect size, with 2 groups randomized in a ratio of 2:1 (experimental-control), and 3 repeated measures (inter measure correlation of 0.5) leads to a required sample size of N=132 (expected power of 95.6%) [15].

10.2 Primary Endpoints Analyses

The primary analysis will follow the intention-to-treat principle [16]. It will include all subjects and the data will be analyzed in the group to which the subjects were assigned through randomization. Percent in range (70-180 during the day and 80-140 at night) will be computed over each month of data and entered in a Repeated Measure ANOVA, where the within-between interaction (group x period) will be studied.

10.3 Secondary Efficacy Analyses

In addition to the primary endpoint we will study:

- HbA1c: estimated effect size of 0.15; repeated measures ANOVA, 2 groups, 2 measures, results in power of 90% with current enrollment;
- Exposure to hypoglycemia, as measured by the percent of time spent below 70mg/dL and by the Low BG Index [13]; estimated effect size 0.25; power for repeated measures ANOVA 2x3 >99%;
- Exposure to hyperglycemia, as measured by the percent of time spent above 300mg/dL; estimated effect size 0.2; power for repeated measure ANOVA 2x3 = 99%;
- Glucose variability as measured by the Average Daily Risk Range [14] (over 2-week period); estimated effect size 0.15; power for repeated measure ANOVA 2x6 = 95%.

10.4 Questionnaires

The following questionnaires will be completed at the randomization visit:

- Diabetes Specific Personality Questionnaire
- Clarke Hypoglycemia Awareness Scale [17]
- Fear of Hypoglycemia Survey (HFS-II) [18]
- Low Blood Sugar Survey
- High Blood Sugar Survey
- Diabetes Distress Scale
- Technology Expectations Survey (CGM+DSS group)

The following questionnaires will be completed at the final visit at week 12:

- Clarke's Hypoglycemia Awareness Scale
- Fear of Hypoglycemia Survey (HFS-II)
- Low Blood Sugar Survey
- High Blood Sugar Survey
- Diabetes Distress Scale
- Technology Acceptance Survey (CGM+DSS group)

For each questionnaire, mean ± SD values or percentiles appropriate to the distribution will be given by randomization group for the total score and each subscale. For questionnaires administered to both randomization groups comparisons will be made using similar ANCOVA models as described above for the primary endpoints. No formal adjustment will be made for multiple comparisons.

10.5 Primary Safety Analyses

All subjects will be included in these analyses.

The circumstances of all reportable cases of the following will be summarized and tabulated by treatment group:

- Severe hypoglycemia (as defined in Section 8.1)
- Diabetic ketoacidosis (as defined in Section 8.1)
- Other serious adverse events (SAE) and serious adverse device events (SADE)
- Unanticipated adverse device effects (UADE)

The total number of SH or DKA events per subject will be compared using robust Poisson regression and the percentage of subjects with at least one event will be compared using Fisher's exact test.

10.6 Additional Tabulations

The following tabulations will be performed without statistical testing:

- baseline demographics and clinical characteristics
- flow chart accounting for all subjects for all visits
- visit completion rates for each follow-up visit
- hours of sensor use
- days of sensor use per week
- phone contact completion rates for each follow-up visit
- protocol deviations
- number and reasons for unscheduled visits and phone calls
- device malfunctions requiring study team contact and other reported device issues
- In addition, performance metrics will be tabulated, describing the inControl Advice system and its components.

10.7 Interim Analysis

All CGM-related study endpoints will be analyzed for the first 6 weeks of study intervention in the first 40 subjects. The purpose of the interim analysis is to support regulatory submissions for the CGM+DSS system.

11 DATA COLLECTION AND MONITORING

11.1 Case Report Forms and Device Data

The main study data are collected through a combination of case report forms (CRFs) and electronic device data files obtained from the study software and individual hardware components. These electronic device files and electronic CRFs from the study website are considered the primary source documentation.

11.2 Document Storage and Retention

The Investigator of each clinical site will retain all records and documents pertaining to this study. They will be available for inspection by the appropriate regulatory agencies. In addition, the Investigator will retain the source documents from which the information entered on the CRFs was derived. These records are to be retained in a secure storage facility maintained by the investigational center until 3 years (or longer/shorter if local laws require) after approval of the above-listed study devices or termination of the study, whichever is longer. The investigator should take measures to prevent accidental or early destruction of the clinical study related materials.

12 Publication Policy

The contents of this protocol, the manuals pertaining to this study and the results of the investigation are confidential and may not be published or disclosed without the written consent of University of Virginia. The identity of the subjects may not be disclosed, unless required by law, to any persons not immediately involved in the study or the study procedures. The results of the clinical study will be submitted for publication in a peer-reviewed scientific journal upon study completion.

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