UVA CENTER FOR DIABETES TECHNOLOGY

Safety of the Tandem t:slim X2 with Control-IQ Automated Insulin Delivery System in Preschoolers, age 2-6 Years Old

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NCT04084171

Version Number: v1.3

30-Aug-2019

Key Roles

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Protocol Version History

Version Number	Author(s)	Approver	Effective Date	Revision Description
1.0	Marc Breton	Marc Breton		Original Protocol
1.1	Mary Oliveri	Mary Oliveri	22-Aug-2019	FDA revisions • Exclusion criteria added: use of diluted insulin • A phone with the Dexcom Follow app will be near the child participant during the home study. • Participant Stopping Criteria redefined IRB revisions • Parent/child enrollment required since parent is completing questionnaire; • Questionnaire to occur after home use of equipment; • Added Other Risks: Photographs taken by the study team may be shared at conference; presentations, study brochures, or potential research donors • Revised 'Timing of Event' section; • Revisions throughout document to improve clarity
1.2	Mary Oliveri	Mary Oliveri	29-Aug-2019	FDA revisions • Clarified exclusion criteria • Added SMBG pre-meal on day 1 open-loop & every bedtime during At-Home use • Added caregivers • Physical activity restricted if CGM is below 90 mg/dL
1.3	Mary Oliveri	Mary Oliveri	30-Aug-2019	FDA revisions • If > 1 serious hypoglycemia or > 1 DKA event occurs, the study may be paused to determine a root cause prior to continuation of the study • Transition back to personal insulin pump will be completed under the supervision of a study MD

Site Principal Investigator Statement of Compliance

Protocol Title: Safety of the Tandem t:slim X2 with Control-IQ Automated Insulin Delivery System in Preschoolers, age 2-6 Years Old.

Protocol Version/Date: v1.0/30-Aug-2019

I have read the protocol specified above. In my formal capacity as a Site Principal Investigator, my duties include ensuring the safety of the study participants enrolled under my supervision. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site.

This trial will be carried out in accordance with ICH E6 Good Clinical Practice (GCP) and as required by the following: United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

As the Principal Investigator, I will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), or other approved Ethics Committee, except where necessary to eliminate an immediate hazard(s) to the trial participants.

All key personnel (all individuals responsible for the design and conduct of this trial) have completed Human Participants Protection Training and Good Clinical Practice Training. Further, I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Investigator's Signature _____ Date: _____ / _____ / _____

dd mmm yyyy

Investigator's Name: _____

Site Name: _____

List of Abbreviations

ABBREVIATION	DEFINITION
AP	Artificial Pancreas
BG	Blood Glucose
BT/BTLE	Bluetooth, Bluetooth low energy
CRF	Case Report Form
CGM	Continuous Glucose Monitoring System
CLC	Closed-Loop Control
CSII	Continuous Subcutaneous Insulin Injection
CTR	Control-to-Range
DiAs	Diabetes Assistant
DKA	Diabetic Ketoacidosis
EC	European Commission
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
ID	Identification
iDCL	International Diabetes Closed Loop
IDE	Investigational Device Exemption
IOB	Insulin-on-Board
IQR	Interquartile Range
JDRF	Juvenile Diabetes Research Foundation
LGS	Low Glucose Suspend
PLGS	Predictive Low Glucose Suspend
POC	Point-of-Care
QA	Quality Assurance
QC	Quality Control
RBM	Risk-Based Monitoring
RCT	Randomized Control Trial
SC	Standard of Care group
SD	Standard Deviation
SMBG	Self-Monitoring Blood Glucose
TDD	Total Daily Dose
UI	User Interface

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Protocol Summary

PARTICIPANT AREA	DESCRIPTION
Title	Safety of the Tandem t:slim X2 with Control-IQ Automated Insulin Delivery System in Preschoolers, age 2-6 Years Old.
Investigational Device	Tandem Control-IQ with G6 Continuous Glucose Monitor
Objectives	To assess study the safety profile of the Tandem t:slim X2 with Control-IQ system in children with T1D aged 2-6 years old under free living condition
Study Design	A single-arm, multi-center, clinical study
Number of Sites	3 independent clinical sites – sharing IDE and regulatory documentation only
Endpoint	Number of subjects with less than 6% time below 70 mg/dL and less than 40% time above 180 mg/dL.
Population	**Key Inclusion Criteria** • Age ≥ 2 and < 6 years old at the time of visit 1 • Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least 3 months and using insulin at the time of enrollment • Use of an insulin pump in the past 3 months • Use of Dexcom G6 for at least 11 out of the last 14 days **Key Exclusion Criteria** • Hypoglycemia induced seizure or loss of consciousness in the past 3 months • Concurrent use of any non-insulin glucose-lowering agent • A condition, which in the opinion of the investigator or designee, would put the participant or study at risk.
Sample Size	Up to 15 participants
Participant Duration	About 14 days
Protocol Overview/Synopsis	48 hour hotel stay with 24/7 study team supervision followed by parental remote monitoring for 72 hours of at-home use

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Study Visits and Procedures Schedule

`	SCREENING	OPEN LOOP AT-HOME USE	PRE-ADMISSION CHECK-IN	HOTEL ADMISSION	CLOSED LOOP AT-HOME USE	POST-ADMISSION CHECK-IN
DURATION	**ABOUT 3 HOURS**		**ABOUT 30 MINUTES**	**ABOUT 48 HOURS**	**ABOUT 72 HOURS**	**ABOUT 30 MINUTES**
COMMENT	**SCREEN / ENROLL**		**PHONE, EMAIL, TEXT**	**HOTEL**	**HOME**	**PHONE, EMAIL, TEXT**
Informed Consent	**X**					
Eligibility Assessment	**X**					
Medical History	**X**					
HbA1c	**X**					
Physical Exam	**X**			**X**		
Vital Signs	**X**			**X**		
Equipment Training	**X**			**X**		
Use of Study Equipment		**X**	**X**	**X**	**X**	
Blood Glucose & Ketone Measurement				**X**		
CGM Placement		**X**	**X**			
Review diabetes management and AEs				**X**	**X**	**X**
Review Medical Changes			**X**	**X**		
Questionnaire				**X**		
Return study equipment						**X**

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Chapter 1: BACKGROUND INFORMATION

1.1 Introduction

The Tandem X2 insulin pump with Control-IQ Technology is a third-generation closed-loop control (CLC) system retaining the same control algorithm that was initially tested by UVA's DiAs system and then implemented in the inControl system. DiAs is described in 13 IDEs (see IDEs 1-12 and 14 in the list below) and inControl is described in IDEs G160097, G160181, G150240, G140169/S010. IDE 17-20 below are specific to the implementation proposed here. For complete algorithmic and clinical background, we refer to these IDEs and to a number of scientific publications that describe glycemic control outcomes and clinical impressions from the use of these systems (see list of 25 peer-reviewed papers and scientific presentations under Bibliography). Overall, this control algorithm has been implemented in two mobile platforms (DiAs and inControl) and an embedded system (Tandem t:slim X2 with Control IQ) which have been tested in 35 clinical trials by over 700 adults and children with type 1 diabetes (T1D) for over 1,200,000 hours of use to date in the U.S. and overseas.

As described above, this project is a result of a sequence of clinical trials that have tested extensively. The following 20 IDEs reflect this progress:

1. IDE #G110095: Feasibility study of closed loop control in type 1 diabetes using heart rate monitoring as an exercise marker, approved 10/08/2011;
2. IDE #G120032: Early feasibility (pilot) study of outpatient control-to-range; 3/2/2012;
3. IDE #G120210: Early feasibility study 2 of outpatient control-to-range; 10/12/2012;
4. IDE #G130118: DiAs control-to-range nocturnal closed-loop camp study; 6/19/2013;
5. IDE #G130121: Optimizing closed-loop control of type 1 diabetes mellitus in adolescents; 6/19/2013;
6. IDE# G130142: Closed loop control in adolescents using heart rate as exercise indicator; 7/16/13;
7. IDE #G130143: Early feasibility study of adaptive advisory/automated (AAA) control of type 1 diabetes; 7/19/2013;
8. IDE #G140066: Full day and night closed-loop with DiAs platform; 5/9/14.
9. IDE #G140068: Unified Safety System (USS) Virginia Closed Loop versus sensor augmented pump therapy overnight in type 1 diabetes; 5/14/2014;
10. IDE #G140089: Outpatient control-to-range: Safety and efficacy with day-and-night in-home use; 6/6/2014;
11. IDE #G140169: Unified Safety System (USS) Virginia Closed-Loop versus Sensor Augmented Pump (SAP) therapy for hypoglycemia reduction in type 1 diabetes; 10/3/2014.
12. IDE #G150221: Reducing risks and improving glucose control during extended exercise in youth with T1DM: The AP Ski Camp; 11/09/2015;
13. IDE #G150240: Project Nightlight: Efficacy and system acceptance of dinner/night vs. 24 hr closed loop control; 11/12/2015;

14. IDE #G160047: Closed-loop in school-age children 5-8 years old using DiAs platform; 03/29/2016;
15. IDE #G160097: Clinical Acceptance of the Artificial Pancreas: The International Diabetes Closed-Loop (iDCL) Trial/Research Site Training Protocol; 06/03/16.
16. IDE#G160181: PROTOCOL 1 for "Clinical Acceptance of the Artificial Pancreas: The International Diabetes Closed Loop (iDCL) Trial; 09/21/16
17. IDE#G170267: Real-Time Monitoring and Glucose Control During Winter-Sport Exercise in Youth with Type 1 Diabetes: The AP Ski Camp Continued. 12/01/2017
18. IDE#G180053: Protocol 3: Clinical Acceptance of the Artificial Pancreas (DCLP3)
19. IDE#G180279: Safety and Efficacy of Initializing the Control-IQ Artificial Pancreas System Using Total Daily Insulin, 11/21/2018
20. IDE#G180053/S008: Protocol 5: Clinical Acceptance of the Artificial Pancreas in Pediatrics. A Study of t:slim X2 with Control-IQ Technology, currently enrolling, 12/17/2018

1.2 Study Objective

The closed-loop system, also called Artificial Pancreas (AP), modulates insulin infusion according to computed real-time needs. It has proven to be successful in maintaining blood glucose in euglycemic ranges during the day and even more efficiently during overnight hours where it was shown that the system can keep glycemic values in the euglycemic range (70-180 mg/dL) for 70% to 75% of the time.

The biggest challenges for glycemic control in young children with diabetes are frequent meals and snacks as well as unpredictable activity/exercise routines. Meal variability has the benefit that meals are typically announced and quantified. Glucose control around exercise, on the other hand, is more complicated if the patient doesn't announce a change in activity level.

Over the last 5 years, our teams have developed and tested different version of closed-loop systems and remote monitoring systems conducting clinical trials in summer and winter camp settings demonstrating significantly improved glycemic control and hypoglycemia avoidance in young adult and pediatric patients with T1D.

There is a new wearable version of a closed-loop control system that is proposed to be tested in this clinical trial. The Closed-Loop Control System contained in t-slim X2 with Control-IQ Technology that is described in Master File MAF-2032/A003. Control-IQ Technology is derived from inControl previously described in IDE# G160097, G160181, G150240 and G140169/S010. The CLC is an "artificial pancreas" (AP) application that uses advanced closed loop control algorithms to automatically manage blood glucose levels for people with Type 1 Diabetes. The system modulates insulin to keep blood glucose in a targeted range. The system components include the t:slim X2 with Control-IQ Technology and the Dexcom CGM G6 (Figure 1).

Figure 1: t:slim X2 with Control-IQ and DexCom G6 system

This clinical trial aims to demonstrate the safety of the Closed-Loop Control (CLC), also known as Artificial Pancreas (AP) named t:slim X2 with Control-IQ Technology and assess usability in a supervised setting for the treatment of type 1 diabetes (T1D) in young children (2-6 years old). It is important to note that the system under study has been shown safe in efficacious in a large (N=168) RCT clinical trial in subjects 14 and up (results presented at ADA 2019), which Compared the system with sensor-augmented pump therapy, CLC system (Control-IQ) use for 6 months improved:

- Time in target range 70-180 mg/dL (+11%; p<0.0001)
- HbA1c (-0.33%; p=0.0014)
- Mean Glucose by CGM (-13 mg/dL; p<0.0001)
- Hyperglycemia >180 mg/dL (-10%; p<0.0001)
- Hypoglycemia <70 mg/dL (-0.88%; p<0.0001)
- Hypoglycemia <54 mg/dL (-0.10%; p=0.02)

The same system is also currently the subject of a similar trial down to 6 years old (IDE#20 above).

Finally, preliminary analysis of a clinical trial in France using the same system in prepubertal children (6-10 yo) comparing 24/7 vs overnight use has shown very promising performances as well (Table 1).

Table 1: Interim analysis of FREELIFEKIDS AP (N=30 for 3 months)

	Overall					
	CLC at night		CLC 24/7		Stats	
	baseline	CLC	baseline	CLC	base vs Tx	Night vs 24/7
% time below 50mg/dL	0.4 ± 0.3%	0.3 ± 0.2%	0.5 ± 0.7%	0.3 ± 0.2%	ns	ns
% time below 54mg/dL	0.7 ± 0.6%	0.6 ± 0.3%	0.9 ± 1%	0.5 ± 0.4%	0.081	ns

% time below 60mg/dL	1.5 ± 1%	1.1 ± 0.5%	1.7 ± 1.6%	1.1 ± 0.8%	**0.041**	ns
% time below 70 mg/dL	4.1 ± 1.9%	2.8 ± 1%	3.9 ± 2.8%	2.8 ± 1.9%	**0.006**	ns
% time between 70-140mg/dL	42 ± 8.6%	45.6 ± 7.4%	37.9 ± 8.2%	49.3 ± 4.9%	**<0.001**	**0.009**
% time between 70-180mg/dL	63.2 ± 9.1%	67.5 ± 6.5%	59.7 ± 8.4%	71.8 ± 4%	**<0.001**	**0.009**
% time above 180mg/dL	32.8 ± 9.2%	29.6 ± 6.7%	36.4 ± 9.5%	25.4 ± 4.8%	**<0.001**	**0.010**
% time above 250mg/dL	9.6 ± 4.3%	8.6 ± 3.7%	11.8 ± 5.6%	6.1 ± 2.2%	**0.001**	**0.010**
% time above 300mg/dL	2.8 ± 1.7%	2.7 ± 1.8%	3.9 ± 3.7%	1.7 ± 1%	**0.030**	**0.046**
Average CGM [mg/dL]	158.1 ± 13.6	156.7 ± 10.5	165.4 ± 15.8	150.2 ± 7.4	**0.001**	**0.006**

We propose to use the Control-IQ System during a supervised 48 hours hotel stay with planned activities and meals; in addition, child participants will continue to use the system for another 3 days at home under the parent/guardian(s) supervision.

1.3 Primary Specific Aim

Study the safety profile of the Tandem t:slim X2 with Control-IQ System in children with type 1 diabetes aged 2-6 years old.

1.4 Secondary Specific Aims

- Assess the safety profile of the system at home under parental/legal guardian(s) supervision
- Compare system performance to normative data from a 6-12 years old cohort

1.5 Study Design

1.5.1 Purpose/Objectives of Clinical Study

The purpose of this study is to demonstrate the safety and efficacy the Artificial Pancreas system (Tandem t:slim X2 with Control IQ Technology) in T1D participants, aged 2-6 y.o.

1.5.2 Study Participants

Approximately 15 participants with Type 1 Diabetes Mellitus, currently managed with insulin pump therapy, will participate in the trial for approximately 14 days. The study will be performed at the University of Virginia, Stanford University, and the Barbara Davis Center at the University of Colorado. Children and a parent/guardian(s) will use the system at home in Open Loop until the start of the Hotel Admission. The child participant will then use the Control-IQ System during a ~48 hours study hotel/house admission. The child participant will then use the Control-IQ System at home for 72 hours under parental supervision and remote monitoring by the study team.

1.5.3 Clinical Sites

Each clinical site will perform the trial independently, seeking their own local IRB approval.

- The University of Virginia-Center for Diabetes Technology
- 560 Ray Hunt Drive, Charlottesville VA 22903

- Stanford University
- 300 Pasteur Drive, # S302, Palo Alto, CA 94304

- Barbara Davis Center for Diabetes, University of Colorado Anschutz Medical Campus:
- 1775 Aurora Court, Aurora, CO 80045

1.5.4 Study Diagram

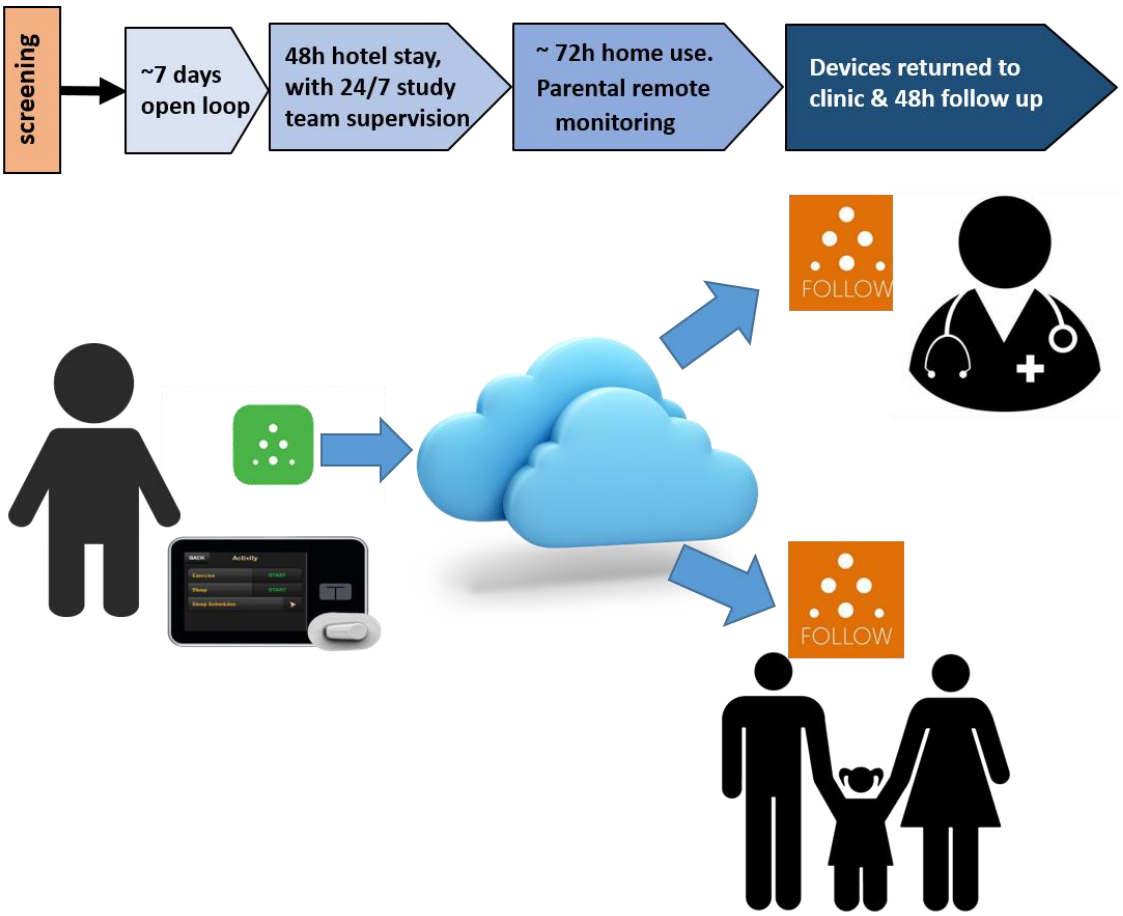

Figure 2: Study Diagram

Chapter 2: STUDY ENROLLMENT AND SCREENING

2.1 Participant Recruitment and Enrollment

Enrollment will proceed with the goal of completing 15 participants in this trial, approximately 5 participants per clinical site.

Enrollment at the University of Virginia will be defined as a parent/child dyad as the parent is completing the questionnaire at the conclusion of the study.

Up to 25 participants may sign the consent form.

2.2 Informed Consent and Authorization Procedures

Consenting procedures and documentation is defined in section 15.3.

2.3 Participant Inclusion Criteria

Child participants must meet all of the following inclusion criteria in order to be eligible to participate in the study.

1. Age ≥ 2 and < 6 years old at the time of consent
2. Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least 3 months and using insulin at the time of enrollment
3. Use of an insulin pump in the past 3 months
4. Use of Dexcom G6 for at least 11 out of the last 14 days
5. Parent/guardian(s) have familiarity with and use of carbohydrate ratios for meal boluses
6. Living with one or more parent/guardian knowledgeable about emergency procedures for severe hypoglycemia and able to contact emergency services and study staff
7. At least one parent/guardian is willing to stay with the child during the hotel/house portion of the study on the dates selected by the study team
8. Investigator has confidence that the parent/guardian(s) can successfully operate all study devices and is capable of adhering to the protocol
9. Willingness to switch to lispro (Humalog) or aspart (Novolog) if not already, and to use no other insulin besides lispro (Humalog) or aspart (Novolog) during the study
10. Total daily insulin dose (TDD) of at least 5 U/day
11. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial
12. Child participant and parent/guardian(s) willingness to participate in all training sessions as directed by study staff
13. Willingness to discontinue non-Tandem t:slim insulin pumps during the entire study
14. Willingness to wear a Dexcom G6 sensor during the entire study
15. An understanding and willingness to follow the protocol and sign informed consent

2.4 Participant Exclusion Criteria

Individuals meeting any of the following exclusion criteria at baseline will be excluded from study participation.

1. Hypoglycemia induced seizure or loss of consciousness in the past 3 months
2. Diabetes Ketoacidosis in the past 3 months
3. Use of diluted insulin
4. Concurrent use of any non-insulin glucose-lowering agent
5. Hemophilia or any other bleeding disorder
6. A condition, which in the opinion of the investigator or designee, would put the participant or study at risk. These conditions may include:
   - Acute illness at the time of the enrollment visit (fever of 101 or higher, vomiting, diarrhea)
   - Addison's disease
   - Diagnosed at less than 1 year of age without positive antibodies
   - Decreased renal function
   - Cystic fibrosis
   - Other chronic conditions, such as an underlying seizure disorder
7. Participation in another pharmaceutical or device trial at the time of enrollment or during the study.
8. Having a family member(s) employed by Tandem Diabetes Care, Inc. or having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial.

2.5 Eligibility Screening Procedures

After informed consent has been signed, the child participant will be evaluated for study inclusion and exclusion eligibility and documented:

1. Demographics (date of birth, gender, race and ethnicity)
2. Medical history
3. Details of the diabetes history: duration of disease (number of years), diagnosis details, current insulin pump model, history of CGM use, current treatment (including basal rates, carbohydrate ratios, insulin sensitivity factors, target glucose, average daily insulin, history of diabetic ketoacidosis, history of severe hypoglycemia, history of seizures or loss of consciousness, and average number of blood tests performed daily).
4. Surgical history
5. Allergies
6. Medications and supplements
7. Short Physical examination – A historical history and physical report within 52 weeks of screening appointment may be used
8. Weight and height
9. Vital signs
10. Hemoglobin HbA1c assessment (blood draw or point of care per study physician discretion) – A historical lab value dated within the last 30 days from screening date may be used
11. Use of Dexcom G6 for at least 11 out of the last 14 days

Once all results of the screening evaluations are available, a decision will be made to determine the subject's eligibility for the study or if one or more parts of the screening will have to be repeated. If at the first screening or repeat screening an exclusionary condition is identified, the study subject will be excluded from participation in the study. The participants will be referred to their primary care physician as needed. Subjects may be re-screened at a later date if their clinical situation changes at the discretion of the study physician during an acceptable timeline.

Parent/guardian(s) will be instructed to contact the study team in the event of a febrile illness anytime during the study.

Chapter 3: STUDY DEVICES

3.1 Insulin Pump

The study system will include the Tandem t:slim X2 with Control-IQ technology.

3.2 Continuous Glucose Monitoring

The study CGM will include Dexcom G6 transmitter and sensors. The CGM sensor is viable for 10 days.

3.3 Blood Glucose Meter and Strips

Blood glucose levels will be measured using the Accu-Chek Guide blood glucose meter (glucometer). The CGM device will be calibrated, if needed, using the study glucometer and strips in accordance with the manufacturer's labeling.

3.4 Ketone Meter and Strips

Blood ketone levels will be measured using the Abbott Precision Xtra meter and strips in accordance with the manufacturer's labeling. The blood glucose meter component of the Precision Xtra device will not be used.

3.5 Study Device Accountability Procedures

Device serial numbers will be recorded and use of equipment will be tracked.

Chapter 4: STUDY EQUIPMENT TRAINING

Equipment training may begin immediately after screening eligibility has been met or may be deferred for a maximum of 14 days but should not be less than 48 hours prior to the start of the study to allow for a CGM warmup period. The purpose of this training is to introduce the study insulin pump and study CGM to the parent/guardian(s) and child participant.

The subject's insulin parameters will be programmed into their Tandem t:slim X2 with Control-IQ pump by two research staff. Subjects will then switch to the study insulin pump. The subject's personal pump and infusion site will be removed.

At the conclusion of the study equipment training session, the child participant will use the system in pump only (open loop) configuration where no closed loop algorithms are activated until the start of the Hotel Admission.

Child participants will have the insulin pump and sensor on them at all times. Parent/guardian(s) will monitor their child using the Dexcom App. Parent/guardian(s) will also be required to carry the study glucometer and ketone meter with them at all times and must be within BLE connection distance of their child (same room) or equip the child with a Clarity enabled cellphone. Study supplied phones will be available upon request.

4.1 Insulin Pump Training

Insulin pump training will include:

- The parent/guardian(s) will be fully instructed on the study insulin pump. A qualified system trainer 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: infusion site initiation, cartridge/priming procedures, setting up the pump, charging the pump, navigation through menus, bolus procedures including stopping a bolus, etc.
- The study team will assist the parent/guardian(s) in study pump infusion site initiation and will start the participant on the study pump. The study pump will be programmed with the child participant's usual basal rates and pump parameters. The child participant's personal pump will be removed.
- The parent/guardian(s) will be supervised with the study pump during at least one meal or snack bolus to ensure participant understanding of the pump features.
- The parent/guardian(s) will be encouraged to review the literature provided with the pump and infusion sets after the training is completed. Infusion sets manufactured by Tandem will be provided to the study subject and a sample list is below and may be provided in different cannula lengths (e.g. 6mm or 9mm) and tubing lengths (e.g. 23 or 43 inch):
    - ❖ Tandem Autosoft Line (e.g. Autosoft 30, Autosoft 90, Autosoft XC)
    - ❖ Tandem Varisoft
    - ❖ Tandem TruSteel

Insulin pump training specific to the Control-IQ Technology functions will include:

- How to turn on and off Control-IQ technology
- How to understand when Control-IQ is increasing or decreasing basal rates
- How to administer a meal or correction bolus on the t:slim X2 with Control-IQ system
- How to enable the sleep function and set the sleep schedule
- The participant will be assessed for understanding of the system interface and how to react to safety/alert messages
- The participant will be given a User Guide as a reference

4.1.1 Closed Loop Training

The parent/guardian(s) will be instructed to how to use the system if insulin is delivered by any means other than the study pump (e.g. injection of subcutaneous insulin via syringe in the event of infusion site failure). If insulin is delivered by any means other than the study pump, the parent/guardian(s) will be instructed to turn off Control-IQ for approximately four hours.

The parent/guardian(s) will be provided with contact information and will be asked to call the study clinical 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 for the emergency treatment of a severe allergic reaction or asthma attack in addition to use of oral or injectable glucocorticoids to determine if closed-loop use should be temporarily discontinued.

The parent/guardian(s) will also be asked to call the study clinical staff for technical issues with t:slim X2 with Control-IQ. The study pump without Control-IQ activated and study CGM (open loop mode) during periods of component disconnections or technical difficulties. Study staff contact information will be provided to parent/guardian(s) to ask any questions they may have during the study.

Upon completion of the t:slim X2 with Control-IQ training, study staff will document, using a checklist, that the participant is familiar with the function/feature and/or capable of performing each of the tasks specified.

Parents/legal guardian(s) will be provided Glycemic Treatment Guidelines (section 7.2) to use at home.

4.2 CGM Training

A study CGM will be provided to all child participants at the training session. The parent/guardian(s) will be provided with CGM equipment and instructed to use the study CGM on a daily basis. Child participants have prior use of the CGM so re-training will be specific to the individual. Training may include review of study CGM in real-time to make management decisions and how to review the data after an upload (if needed) for retrospective review.

The child's personal CGM will be discontinued. The parent/guardian(s) will be observed placing the sensor and will learn/review how to access the CGM trace via the t:slim X2 with Control-IQ user interface. The parent/guardian(s) will be instructed to perform a fingerstick blood glucose measurement prior to meal time for the first open-loop day. The parent/guardian(s) will be asked to perform fingerstick blood glucose measurements (if needed) in accordance with the labeling of the study CGM device.

The study CGM user's guide will be provided for the parent/guardian(s) to take home. The study team will be sure that the parent/guardian(s) will leave the clinic knowing how to use proper use the CGM. The study team will be available for any questions.

The use of Dexcom Apps on personal devices to monitor the child participant's CGM values and alerts in real-time may be used.

Participants will have the option of using their personal smartphone or receive a study smartphone to use in order to collect the data from the devices.

4.3 Blood Glucose and Ketone Testing

4.3.1 Blood glucose testing

Parent/guardian(s) will be provided with a study blood glucose meter and test strips to be used at home per manufacturer guidelines.

All study blood glucose meters will be QC tested by study staff 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.

Parent/guardian(s) will be reminded to use the study blood glucose meter for all fingerstick BGs during the study.

4.3.2 Blood ketone testing

Parent/guardian(s) will be provided with a study blood ketone meter and test strips to be used at home per manufacturer guidelines.

All study blood ketone meters will be QC tested by study staff 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.

Parents/legal guardian(s) will be instructed to perform blood ketone testing as described in Glycemic Treatment Guidelines (section 7.2). A home glucagon emergency kit will be required. Participants who currently do not have one will be given a prescription for the glucagon emergency kit.

4.4 Optimization of Insulin Pump Settings

Data-driven optimization of pump settings can occur any time during the study, particularly if the parent/guardian(s) contacts the study physician due to concerns about their pump settings due to recurring hypo- or hyperglycemia.

Chapter 5: HOTEL ADMISSION PROCEDURES

5.1 General Admission Instructions

The Hotel Admission will take place in a hotel or research house for approximately 48 hours. Alternately, the clinical trial may occur at a house.

The CGM used in the study is FDA-approved for the non-adjunctive measurement of blood glucose (i.e. the CGM reading can be used for insulin dosing decisions). The CGM readings will be the primary source of blood glucose levels. There are no protocol fingerstick blood glucose measurements other than at times of CGM calibration (if necessary) and if directed by the study team. Glycemic Treatment Guidelines to be used during the hotel admission are defined in section 7.1.

5.2 Hotel Staffing Qualifications

There will be at least one physician, advanced practice provider, registered nurse, and/or other medical personnel who are specifically trained in diabetes management and trained technicians supervising the Hotel Admission. Certification of their skill is supervised by the clinical site PI. All medical personnel who will have direct contact with the child participants will have current certification in Basic Life Support including CPR. Study personnel, trained in the use and maintenance of the Tandem t:slim X2 with Control-IQ Technology, will be monitoring the system during the entire trial.

There will be a team of at least 3 experienced study personnel in attendance during the day (7 p.m. -7 a.m.) and one study staff member during the overnight hours of 7 p.m. – 7 a.m. during the hotel admission. These staff members will be proficient with devices, the study protocol and its procedures, including the glycemic safety protocols.

Glucagon for the emergency treatment of hypoglycemia will be available on-site.

5.3 Pre-Admission Check-in Visit

The parent/guardian(s) will be contacted by the study team approximately 48-72 hours prior to the hotel admission to verify the following information:

- Inquire about any changes to the child participant's health (e.g. illness, medications, etc…)
- Inquire about current use of the study equipment
- Remind parent/guardian(s) to bring all current medications for use during the study.
- Determine what pump profile(s) the subject uses on certain days
- Verify that a new CGM sensor will be placed approximately 48 hours prior to the admission for proper warm up
- Verify with the subject that the goal CGM reading at time of arrival is less than 250 mg/dL

Should any concerns regarding medical history, pump information, or unforeseen issues arise, the admission may be cancelled for that participant at the discretion of the investigator.

Additional phone contact(s) can occur at the study team's discretion.

5.4 Admission Check-In (times are approximate)

On day 1 of the admission, parent/guardian(s) and child participants will arrive to the hotel at approximately 3-5 pm. The study team will perform vital signs and inquire about any changes to the participant's medical history. The study team will confirm that the child participant has brought his/her insulin and regular medications. Any changes to medical history will be communicated to the medical physician to ensure continued eligibility and participation. The study team will ensure the proper function of the CGM and insulin pump. Insulin parameters will be reviewed by the study medical team

A SMBG and a ketone value will be collected on the study equipment. In the event that the child participant's CGM reading is not between 80 – 300 mg/dL or ketone concentration is ≤0.6 mmol/L prior to the Control-IQ initiation, the study physician may recommend corrective action as outlined in the Hotel Admission Glycemic Guidelines (section 7.1). Study physician may elect to cancel participant's participation in the hotel admission if concerned about their medical safety.

Data from subjects' insulin pumps will be reviewed and/or downloaded for a review of pump settings and average of daily insulin delivery.

5.5 Study Procedures

Parent/guardian(s) will be retrained on the study equipment as needed. During system use, subjects will be remotely monitored and will have immediate access to medical personnel and technical personnel. Child participants will be accompanied by at least one parent/guardian during the supervised stay and trained on the Control-IQ System. A trained parent/caregiver or study team member must remain in the immediate vicinity of the subjects as long as the AP system is active.

The parent/guardian(s) will be primarily responsible for using the system at this time, with the study team serving as a back-up when needed. Re-education will be provided as needed. Study staff will be available at all times to assure proper use of all study equipment.

CGM sensors last up to 10 days; therefore, there should be no need to change CGM sensors. All sensor changes during camp will be handled by the study team, but caregivers of subjects will be trained on how to change sensors in case of sensor failure during the 72 hours home use.

5.6 Hotel Admission Schedule (times are approximate)

Parent/guardian(s) and child participants will be provided dinner at approximately 6 – 7 p.m. Parent/guardian(s) and child participants will be permitted to retire to their personal rooms after dinner, if desired. Bedtime for the child participant is encouraged to be no later than 9 p.m. Devices should be charged overnight while subjects are sleeping.

On day 2 of the admission, breakfast will be provided at approximately 7 – 8 a.m. Group activities will occur from approximately 9 – 11 a.m. An optional snack will be available at approximately 10 a.m.

Lunch will be provided at approximately 11:30 – 12:30 p.m. Parent/guardian(s) and child participants will retire to their personal rooms for quiet time. An optional snack will be available at approximately 3 p.m. Group activities will occur from approximately 3:30 – 5:30 p.m.

Parent/guardian(s) and child participants will be provided dinner at approximately 6-7 p.m. Parent/guardian(s) and child participants will be permitted to retire to their personal rooms after dinner, if desired. Bedtime for the child participant is encouraged to be no later than 9 p.m. Devices should be charged overnight while subjects are sleeping.

On day 3 of the admission, breakfast will be provided at approximately 7 – 8 a.m. Group activities will occur from approximately 9 – 11 a.m. An optional snack will be available at approximately 10 a.m. Lunch will be provided at approximately 11:30 – 12:30 p.m.

Discharge will occur after lunch.

5.7 Bolus Treatment

Use of a temporary basal rate will be permitted during the hotel admission.

5.8 Meal Boluses

The time and size of the meal bolus will be determined by parent/guardian(s) and will be supervised by the study team.

5.9 Group Activities

Planned group activities may be managed by the study team or a specialized service provider (e.g. preschool professionals) with study staff supervision. These activities may include transporting parent/guardian(s) and child participants to off-site locations (e.g. museums, amusement parks, etc…). One medical personnel per car will be required. Parents and their children are expected to participate in all activities of the supervised phase, unless excused by the study team.

5.10 Procedures Related to Discharge

Parent/guardian(s) will show proficiency of using the system before leaving for the home portion of the trial.

Parent/guardian(s) will show proficiency on how to change CGM before leaving for the home use portion of the trial.

The child participant's SMBG value needs to be between 70-300 mg/dL and ketone concentration is ≤ 0.6 mmol/L prior to discharge. The parent/guardian(s) and child will be offered a snack prior to discharge. The study team will verify that parent/guardian(s) have study team's contact information.

Chapter 6: CONTROL-IQ AT HOME

6.1 At-Home Use

Child participants will continue to use the Control-IQ System for another 72 hours at home under parental/legal guardian(s) supervision. The study team will continue remote monitoring as described in section 8.2. Study staff will be available 24/7 by phone to answer any questions or concerns or to help resolve any technical problems.

At the conclusion of 72 hours, the parent/guardian(s) will remove the study equipment under the supervision of a study physician which may occur at home or in the presence of study staff. Participants who discontinue use of the study devices at home will return study devices by standard shipping (e.g. FedEx) provided by the research team.

Parent/guardian(s) will be asked to download the child participant's personal pump to ensure the child's personal equipment is working properly.

6.2 Meal Bolus

Child participants may consume meals and snacks of their own choice with no restrictions. Meal size will be estimated by the parent/guardian(s). The timing of the bolus will be per each child participant's typical dosing routine.

6.3 Blood Glucose Checks

Parent/guardian(s) will be advised to obtain their child's fingerstick blood glucose value prior to bedtime each night of at-home use.

6.4 Activity

The child should refrain from activity (e.g. sports) if their CGM value is below 90 mg/dL.

6.5 Caregivers

In the event that the child is in the care of someone other than the parent/guardian(s), the child must be routinely cared for by this individual (i.e. more than once per week for more than one month). This individual must be trained on the use of the study devices and safety guidelines by study staff prior to the child using the device at home.

6.6 Post-Study Check-in Visit

Approximately 48 hours after the home use of the equipment, the study team will contact the parent/guardian(s) via phone/email/text to assess:

- adverse events, adverse device effects, and device issues
- blood glucose values <60 mg/dL and >300 mg/dL
- verify collection of ketone measurement data
- answer any questions related to device use

- unscheduled calls during the study period may be recommended for additional device training or other unanticipated needs

6.7 Questionnaire

Parent/Guardian(s) will be asked to complete a Technology Acceptance Questionnaire (Parent Version) asking them their perceptions and feeling about the technology used during the Hotel Admission.

Chapter 7: GLYCEMIC TREATMENT GUIDELINES

7.1 Hotel Admission Glycemic Guidelines

Upon arrival, the subject will be asked to check the CGM reading and ketone concentration using the study ketone meter. If CGM is <70 mg/dL or >300 mg/dL, or ketone test is >0.6 mmol/L, the study physician will suggest appropriate treatment. The study team may request fingersticks as needed. The study subject may continue participation in the trial once CGM is between 70-300 mg /dL and ketone concentration is ≤0.6 mmol/L.

If CGM < 80 mg/dL during the day, the patient will be treated until CGM reads >80 mg/dL. If CGM < 70 mg/dL during the night, hypoglycemia treatment will be provided until CGM reads > 80 mg/dL. SMBG may be performed if the MD on-call deems it necessary.

If CGM >300 mg/dL for more than 60 minutes, SMBG will be performed every 60 minutes. If SMBG >300 mg/dL, the Glycemic Treatment Guidelines will be applied.

If CGM <80 mg/dL at any time, subjects will be given approximately 16 grams of fast-acting rescue carbohydrates. Study team will monitor CGM rise and will consider treating again if CGM <80 mg/dL after approximately 20 minutes. Hypoglycemic treatments can occur at any time per study physician request.

Parent/guardian(s) will be asked to respond to both hypoglycemia and hyperglycemia alarms during the Hotel Admission. If they do not respond to the alarms within 10 minutes, study personnel will assist as per the Glycemic Treatment Guidelines.

Medical personnel and emergency supplies (e.g. glucagon) will be available on site.

7.2 At-Home Glycemic Guidelines

7.2.1 CGM Measurements

CGM values are updated every 5 minutes and parents will be able to see it on the pump and Dexcom App.

CGM alarms on the study team controlled Dexcom App will be set at 70 mg/dl for 30 minutes and 300 mg/dl for 60 minutes.

If CGM < 80 mg/dL during the day, the patient will be treated until CGM reads >80 mg/dL. If CGM < 70 mg/dL during the night. Hypoglycemia treatment will be provided until CGM reads > 80 mg/dL. SMBG may be performed if the MD on-call deems it necessary.

If CGM >300 mg/dL for more than 60 minutes, SMBG will be performed every 60 minutes. If SMBG >300 mg/dL, the Glycemic Treatment Guidelines will be applied.

A study team member will contact the family if either of the above conditions is triggered and confirm treatment per provided guidelines.

7.2.2 Ketone Measurements

Parent/guardian(s) will be advised to test for ketones any time the CGM is above 300 mg/dL for more than 2 hours.

If ketones are 0.6-3.0 mmol/L, the following guidelines should be followed until SMBG < 250 mg/dL.

- Notify MD as soon as possible
- Consider taking correction dose of insulin by syringe or pen
- Change insulin in reservoir and tubing and change pump site
- Drink sugar-free beverages
- Once BG is 100-250 mg/dL, restart pump treatment in appropriate mode. Record the amount of insulin that was given when prompted

If ketones are >3.0 mmol/L, the following guidelines should occur:

- The participant will stop the study
- Notify MD as soon as possible
- Disconnect the STUDY insulin pump and start HOME insulin pump once instructed by MD
- Take correction dose of insulin by syringe or pen
- Drink sugar-free beverages

Chapter 8: REMOTE MONITORING

8.1 Hotel Admission Monitoring

Parent/guardian(s) will remotely monitor the subjects in real-time using the DexCom G6 App capabilities provided by Dexcom® Inc. during the Hotel Admission.

Staff will remotely monitor the subjects in real-time using the DexCom G6 capabilities provided by Dexcom® Inc. . Notification will be set for CGM readings below 80mg/dl during the day and 70mg/dl at night or above 250mg/dl to alert study staff of the need treatment or SMBG confirmation. In case of remote monitoring failure, CGM alarms will be activated at low=70 mg/dL and high=250 mg/dL for the study personnel to act if alarms are set off.

8.2 Home Monitoring

Parent/guardian(s) will remotely monitor the subjects in real-time using the DexCom G6 App capabilities provided by Dexcom® Inc. Alerts will be setup for values below 70mg/dL and above 250mg/dL; families may choose to use more conservative thresholds (i.e. higher than 70 and/or lower than 250) as well as supplemental alerts.

Additionally, a smart phone with the Dexcom Share app will always be in the vicinity of the child during the home study. This app may be on a parent's phone or the study team will provide a phone that will be used with parents or caretakers.

In addition, the study staff will include the staff remote monitoring for threshold alerts but with alerts adapted to the existence of a first tier remote monitor (parent/legal guardian(s)) and the fact that they are not one site. Therefore, the study staff (Tier 2) alerts will be <70mg/dL for more than 15 minutes and >300 mg/dL for more than 60 minutes.

Chapter 9: TESTING PROCEDURES

9.1 Laboratory / Point of Care Testing

9.1.1 HbA1c

- Performed locally at the Screening visit. Blood test may be obtained within 30 days prior to enrollment.
- HbA1c level will be measured using the DCA Vantage Analyzer, a comparable point of care device or local laboratory

Chapter 10: RISKS ASSOCIATED WITH CLINICAL TRIAL

10.1 Potential Risks and Benefits of the Investigational Device

Risks and Benefits are detailed below. Loss of confidentiality is a potential risk; however, data are handled to minimize this risk. Hypoglycemia, hyperglycemia and ketone formation are always a risk in participants with type 1 diabetes and participants will be monitored for these symptoms.

10.1.1 Known Potential Risks

10.1.1.1 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.

10.1.1.2 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 finger sticks are part of the usual care for people with diabetes.

10.1.1.3 Subcutaneous Catheter Risks (CGM)

Participants 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 participant 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 participant should be further instructed to notify the study coordinator immediately if this occurs.

10.1.1.4 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 participant 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.

10.1.1.5 Risk of Hyperglycemia

Hyperglycemia and ketonemia could occur if insulin delivery is attenuated or suspended for an extended period or if the pump or infusion set is not working properly. A CGM functioning poorly and significantly under-reading glucose values could lead to inappropriate suspension of insulin delivery.

10.1.1.6 Risk of Device Reuse

The study CGM system 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 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, if used, is a hand held device. Participants 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 through the use of multiple users.

The study insulin pump is labeled for single-patient use. During the study, this device may be reused after cleaning adhering to a hospital-approved cleaning procedure. All infusion set equipment will be single patient use only (infusion set insertion kits, tubing, cartridges etc.) Participants will be informed that FDA or relevant national authorities typically approve the insulin pump device for single use and that by using them among multiple patients, bloodborne pathogens (i.e. Hepatitis B) may be spread through the use of multiple users.

The study blood glucose meter and blood ketone meter are labeled for single-patient use. During the study, these devices may be reused after cleaning adhering to a hospital-approved cleaning procedure. Participants will be informed that FDA or relevant national authorities typically approve the glucose and ketone meters 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.

10.1.1.7 Device Cleaning Instructions

CGM cleaning instructions are provided in the Dexcom G4 PLATINUM (Professional) Cleaning and Disinfection manual (current edition). The transmitter should be cleaned with Clorox Healthcare® Bleach Germicidal Cleaner or any disinfectant product in a spray bottle containing a bleach solution of 6500 parts per million with the EPA registration number 56392-7. The transmitter will be submerged in this solution and then placed on an absorbent wipe or clean surface. Two sprays will be dispensed from the Clorox cleaner onto each side of the transmitter. A nylon brush will be used to scrub the transmitter on all sides for 30 seconds. The transmitter will be placed in the Clorox Cleaner solution for one minute. Transmitter is then rinsed under flowing tap water for ten seconds. The transmitter will then be disinfected using a disinfectant product with EPA registration number 56392-7 using similar procedures as the cleaning process.

Per the pump manufacturer, the insulin pump will be cleaned with a damp lint-free cloth. Use of household or industrial cleaners, solvents, bleach, scouring pads, chemicals, or sharp instruments are prohibited. The pump should never be submerged in water. If needed, use only a very mild detergent, such as a bit of liquid soap with warm water. A soft towel will be used to dry the pump.

The outside of the transmitter will be wiped with a damp lint-free cloth or isopropyl alcohol wipe between uses.

The Accu-Chek Guide glucometer is cleaned and disinfected with two separate Super Sani-Cloths (EPA number 9480-4). The entire surface will be cleaned, making sure the surface stays wet for 2 minutes. This step is repeated with a clean cloth for disinfecting the device.

The Precision Xtra User's Guide suggests that healthcare professionals use 10% bleach, 70% alcohol or 10% ammonia to clean the device.

Equipment that touches intact skin will be cleaned with ethyl or isopropyl alcohol (70-90%), quaternary ammonium germicidal detergent (i.e. Cavicide, EPA number 46781) or household bleach. The contact time on the surface depends on the method used to clean the equipment. Cavicide requires three minutes on the surface of the equipment. Clorox Germicidal Bleach Wipes require two minutes on the equipment. The surface should remain wet (i.e. slightly damp) with the disinfectant to be considered effective though not wet enough to leave drops of liquid.

In the event a manufacturer updates cleaning procedures for their device, the study team will adhere to the most current recommendations.

There is the risk of blood sampling collection and 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 subject'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.

10.1.1.8 Hb1Ac Risk

An NGSP Point of Care analyzer (i.e. DCA Vantage Analyzer) will be utilized at the research site to obtain the subject's HbA1c level.

10.1.1.9 Questionnaire

As part of the study, parent/guardian(s) will complete a Technology Acceptance Questionnaire which includes questions about their private attitudes, feelings and behavior related to t:slim X2 with Control-IQ. 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.

10.1.1.10 Other Risks

Some participants may develop skin irritation or allergic reactions to the adhesives used to secure the CGM, or to secure the insulin infusion sets for the continuous subcutaneous insulin infusion. 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 and pump infusion sites 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, pump, and glucose and ketone meter 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.

The Hotel Admission will have other parents and child participants in attendance. The loss of privacy and confidentiality is a likely risk as the study team is not able to restrict other participants from sharing photographs (i.e. social media). Photographs taken by the study team may be shared at conference presentations, study brochures, or potential research donors.

10.1.2 Known Potential Benefits

It is expected that this protocol will yield increased knowledge about using an automated closed-loop system with anticipatory action to control glucose levels. The individual participant may not benefit from study participation.

10.1.3 Risk Assessment

Based on the facts that (1) adults and adolescents with diabetes experience mild hypoglycemia and hyperglycemia frequently as a consequence of the disease and its management, (2) the study intervention involves periodic automated insulin dosing that may increase the likelihood of hypoglycemia, and periodic automated attenuation of insulin delivery that may increase the likelihood of hyperglycemia, (3) mitigations are in place, and have been tested in prior studies using the investigational device system in the home setting, that limit the likelihood of excessive insulin dosing or prolonged withdrawal of insulin, and (4) rapid reversal of hypoglycemia and hyperglycemia can be achieved, it is the assessment of the investigators that this protocol falls under DHHS 46.405 which is a minor increase over minimal risk. In addition, it is the belief of the investigators that this study also presents prospect of direct benefit to the participants and general benefit to others with diabetes.

10.2 Potential Risks and Benefits of the Investigational Device

Risks and benefits are detailed below. Loss of confidentiality is a potential risk; however, data are handled to minimize this risk. Hypoglycemia, hyperglycemia and ketone formation are always a risk in participants with type 1 diabetes and participants will be monitored for these events.

10.3 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).

Whenever possible, data will be directly collected in electronic case report forms, which will be considered the source data.

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

Chapter 11: ADVERSE EVENTS, DEVICE ISSUES, AND STOPPING RULES

11.1 Adverse Events

11.1.1 Definitions

Adverse Event (AE): Any untoward medical occurrence in a study participant, irrespective of the relationship between the adverse event and the device(s) under investigation (section 11.1.2) for reportable adverse events for this protocol).

Serious Adverse Event (SAE): Any untoward medical occurrence that:

- Results in death.
- 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 (sight threatening).
- 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 outcomes listed above).

Unanticipated Adverse Device Effect (UADE): 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 participants (21 CFR 812.3(s)).

Adverse Device Effect (ADE): Any untoward medical occurrence in a study participant which the device may have caused or to which the device may have contributed (Note that an Adverse Event Form is to be completed in addition to a Device Deficiency or Issue Form).

Device Complaints and Malfunctions: A device complication or complaint is something that happens to a device or related to device performance, whereas an adverse event happens to a participant. A device complaint may occur independently from an AE, or along with an AE. An AE may occur without a device complaint or there may be an AE related to a device complaint. A device malfunction is any failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed. (21 CFR 803.3). Note: for reporting purposes, sites will not be asked to distinguish between device complaints and malfunctions.

11.1.2 Reportable Adverse Events

For this protocol, a reportable adverse event includes any untoward medical occurrence that meets one of the following criteria:

a. A serious adverse event
b. An Adverse Device Effect as defined in section 11.1, unless excluded from reporting in section 11.2
c. An Adverse Event occurring in association with a study procedure
d. Hypoglycemia meeting the definition of severe hypoglycemia as defined below
e. Diabetic ketoacidosis (DKA) as defined below or in the absence of DKA, a hyperglycemic or ketosis event meeting the criteria defined below

Hypoglycemia and hyperglycemia not meeting the criteria below will not be recorded as adverse events unless associated with an Adverse Device Effect. Skin reactions from sensor placement are only reportable if severe and/or required treatment.

11.1.2.1 Hypoglycemic Events

Hypoglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when the following definition for severe hypoglycemia is met: 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.

11.1.2.2 Hyperglycemic Events/Diabetic Ketoacidosis

Hyperglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when one of the following 4 criteria is met:

- the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below
- evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis
- blood ketone level ≥1.5 mmol/L and communication occurred with a health care provider at the time of the event
- blood ketone level ≥3.0 mmol/L, even if there was no communication with a health care provider

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

All reportable Adverse Events—whether volunteered by the participant, 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 to verify the coding and the reporting that is required.

11.1.3 Relationship of Adverse Event to Study Device

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 device.

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 participant'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.

11.1.4 Intensity of Adverse Event

The intensity of an adverse event 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.

- MILD: Usually transient, requires no special treatment, and does not interfere with the participant's daily activities.
- MODERATE: Usually causes a low level of inconvenience or concern to the participant and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures.

- SEVERE: Interrupts a participant's usual daily activities and generally requires systemic drug therapy or other treatment.

11.1.5 Coding of Adverse Events

The Medical Monitor will review the investigator's assessment of causality and may agree or disagree. Both the investigator's and Medical Monitor's assessments will be recorded. The Medical Monitor will have the final say in determining the causality.

Adverse events that continue after the 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.

11.1.6 Outcome of Adverse Event

The outcome of each reportable adverse event will be classified by the investigator as follows:

- RECOVERED/RESOLVED – The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.
- RECOVERED/RESOLVED WITH SEQUELAE – The event persisted and had stabilized without change in the event anticipated. Record the AE/SAE stop date.
- FATAL – A fatal outcome is defined as the SAE that resulted in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the time of death; however, were not the cause of death, will be recorded as "resolved" at the time of death.
- NOT RECOVERED/NOT RESOLVED (ONGOING) – An ongoing AE/SAE is defined as the event was ongoing with an undetermined outcome.
- An ongoing outcome will require follow-up by the site in order to determine the final outcome of the AE/SAE.
- The outcome of an ongoing event at the time of death that was not the cause of death, will be updated and recorded as "resolved" with the date of death recorded as the stop date.
- UNKNOWN – An unknown outcome is defined as an inability to access the participant or the participant's records to determine the outcome (for example, a participant that was lost to follow-up).

All clinically significant abnormalities of clinical laboratory measurements or adverse events occurring during the study and continuing at study termination should be followed by the participant's physician and evaluated with additional tests (if necessary) until diagnosis of the underlying cause, or resolution. Follow-up information should be recorded on source documents.

If any reported adverse events are present when a participant completes the study, or if a participant is withdrawn from the study due to an adverse event, the participant will be contacted for re-evaluation within 2 weeks. If the adverse event has not resolved, additional follow-up will be performed as appropriate. Every effort should be made by the Investigator or delegate to contact the participant until the adverse event has resolved or stabilized.

11.2 Reportable Device Issues

All UADEs, ADEs, device complaints, and device malfunctions will be reported irrespective of whether an adverse event occurred, except in the following circumstances.

The following device issues are anticipated and will not be reported on a Device Issue Form but will reported as an Adverse Event if the criteria for AE reporting described above are met:

- Component disconnections
- CGM sensors lasting fewer than the number of days expected per CGM labeling
- CGM tape adherence issues
- Pump infusion set occlusion not leading to ketosis
- Battery lifespan deficiency due to inadequate charging or extensive wireless communication
- Intermittent device component disconnections/communication failures not leading to system replacement
- Device issues clearly addressed in the user guide manual that do not require additional troubleshooting
- Skin reactions from CGM sensor placement or pump infusion set placement that do not meet criteria for AE reporting

11.3 Timing of Event Reporting

UADEs must be reported to the FDA by the IDE Sponsor within 10 working days of the study team being notified of the event.

Other reportable adverse events, device malfunctions (with or without an adverse event), and device complaints should be reported promptly by completion of an electronic case report form, but there is no formal required reporting period.

Clinical sites will notify the IDE Sponsor of any adverse event that is serious, related, and unexpected. Notification will be made within 10 days after becoming aware of the event in order to adhere to FDA regulations.

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 or Ethics Committee.

Upon receipt of a UADE report, the Sponsor will investigate the UADE and if indicated, report the results of the investigation to the sites' IRBs, and the FDA within 10 working days of the Sponsor becoming aware of the UADE per 21CFR 812.46(b) (2). The Medical Monitor must determine if the UADE presents an unreasonable risk to participants. If so, the Medical Monitor must ensure that all investigations, or parts of investigations presenting that risk, are terminated as soon as possible but no later than 5 working days after the Medical Monitor makes this determination and no later than 15 working days after first receipt notice of the UADE.

In the case of a device system component malfunction (e.g. pump, CGM, control algorithm), information will be forwarded to the responsible company by the site personnel, to be handled by its complaint management system.

11.4 Stopping Criteria

11.4.1 Participant Discontinuation of Study Device

Rules for discontinuing study device use are described below.

- The investigator believes it is unsafe for the participant to continue on the intervention. This could be due to the development of a new medical condition or worsening of an existing condition; or participant behavior contrary to the indications for use of the device that imposes on the participant's safety
- The participant requests that the treatment be stopped
- One distinct episode of DKA
- One distinct severe hypoglycemia event as defined in section 11.1.2.1

11.4.2 Criteria for Suspending or Stopping Overall Study

In the case of an unanticipated system malfunction resulting in a severe hypoglycemia or severe hyperglycemia event (as defined in section 11.1.2.2), use of the study device system will be suspended while the problem is diagnosed.

If more than 1 serious hypoglycemia or more than 1 DKA event occurs, the study may be paused to determine a root cause prior to continuation of the study.

In addition, study activities could be similarly suspended if the manufacturer of any constituent study device requires stoppage of device use for safety reasons (e.g. product recall). The affected study activities 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 study Medical Monitor will review all adverse events and adverse device events that are reported during the study and will review compiled safety data at periodic intervals (generally timed to the review of compiled safety data by the DSMB). The Medical Monitor may request suspension of study activities or stoppage of the study if deemed necessary based on the totality of safety data available.

11.5 Independent Safety Oversight

A Medical Monitor will review all DKA and severe hypoglycemia irrespective of relatedness to study device use, and all serious events (including UADEs) related to study device use at the time of occurrence. The Medical Monitor also will be informed of any ADEs not meeting criteria for a UADE.

Chapter 12: MISCELLANEOUS CONSIDERATIONS

12.1 Prohibited Medications, Treatments, and Procedures

Child participants using glulisine at the time of enrollment will be asked to contact their personal physician to change their prescribed personal insulin to lispro or aspart for the duration of the trial.

The study devices (study insulin pump, study CGM) must be removed before Magnetic Resonance Imaging (MRI), Computed Tomography (CT) or diathermy treatment. Participants may continue in the trial after temporarily discontinuing use if requiring one of the treatments above.

12.2 Participant Withdrawal

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

12.3 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 may be shared with the third party collaborators. De-identified subject information may also be provided to collaborators involved in the study after the appropriate research agreement has been executed.

Chapter 13: STATISTICAL CONSIDERATION

13.1 Statistical and Analytical Plans

This trial is single-armed and not powered to detect differences between groups. The study is designed to obtain a primary safety profile on patients in this age-group.

This study is an early feasibility study that will test the safety of t:slim X2 with Control-IQ Technology in an outpatient setting. These studies would generate up to 75 days of closed-loop data. This sample size allows for subject withdrawal.

13.2 Statistical Hypotheses

13.2.1 Primary Outcome

Number of subject with less than 6% time below 70mg/dL and less than 40% time above 180mg/dL.

13.2.2 Secondary Outcome

1. % time spent <70 mg/dl, <60mg/dl, <54mg/dL, and <50mg/dL
2. % time spent >180mg/dl, and >250mg/dl, >300 mg/dl
3. % time spent between 70-180mg/dl
4. % time spent between 70-150mg/dl
5. Number of hypoglycemia below 70 mg/dL
6. Number of carbohydrate treatments, as well as total amount of carbohydrates used for treatments.
7. Time spent in closed loop
8. Time with available CGM
9. Number of subject with more than 70% time in 70-180mg/dL range with less than 4% time below 70mg/dL

13.2.3 Success Criteria / Goal

As a general rule, a session will be considered useful for data analysis if the subject completes close to 80% of the active study protocol. Sessions are considered separate: (i) Supervised Phase=complete at least 38 hours of AP; (ii) at home use=complete at least 56 hours of AP.

The primary goal will be considered met is the primary outcome is achieved for 65% or more of the subjects.

13.2.4 Statistical Analysis Plan

Proportions of subject matching primary criteria will be computed and directly compared to 65% (considered baseline). Further analysis will be performed using a chi2 test of goodness of fit. Based on prior data in 6-12 year olds we anticipate an possible effect size of 0.64, which would allow to detect a difference with 70% power considering our sample size.

Overall outcomes will be compared to the normative data below (values derived from the analysis of 30 6-12 year old T1D subjects using pumps and CGM and rounded for ease of use):

	Baseline	
	mean	std
% time below 50mg/dL	0.5%	0.5%
% time below 54mg/dL	1%	0.8%
% time below 60mg/dL	2%	1%
% time below 70 mg/dL	4%	2.5%
% time between 70-140mg/dL	40%	9%
% time between 70-180mg/dL	60%	9%
% time above 180mg/dL	35%	9%
% time above 250mg/dL	11%	5%
% time above 300mg/dL	4%	3%
Average CGM [mg/dL]	162.0	15.0

This analysis will be performed using a single group one sided t-test for mean comparison for outcomes that can be assumed normally distributed and One-Sample Wilcoxon Signed Rank test for median comparison for the others, this analysis is not powered.

Secondary outcomes will be reported for the entire period and for the supervised and home phases separately. Outcomes by phase will be compared to each other to assess possible loss of performances during the transition at home. For this purpose, McNemar's tests will be used to compare the supervised phase to the home phase for the primary outcome and secondary outcome # 6, 7, and 8. All other outcomes will be analyzed using repeated measure ANOVA. Significance of 0.05 will be used.

This analysis is not powered.

Chapter 14: DATA COLLECTION AND MONITORING

14.1 Case Report Forms and Device Data

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

When data are directly collected in electronic case report forms, this will be considered the source data. Records will be maintained in accordance with ICH E6 and institutional regulatory requirements for the protection of confidentiality of participants.

14.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practices (GCP), or procedure requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions may be developed by the site and implemented as appropriate. Major deviations will be reported to the IRB-HSR within 7 calendar days of when the study team becomes aware of the event.

Chapter 15: ETHICS/PROTECTION OF HUMAN PARTICIPANTS

15.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

15.2 Institutional Review Boards

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

15.3 Informed Consent Process

15.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to an individual's agreement to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided. Consent forms will be IRB approved and the participant will be asked to read and review the document. The investigator or their delegate will explain the research study to the parent/guardian(s) and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Parent/guardian(s) will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The parent/guardian(s) will sign the informed consent document prior to any procedures being done specifically for the study. The parent/guardian(s) may withdraw their child's consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the parent/guardian(s) for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A child participant is considered enrolled when the informed consent form has been signed.

15.3.2 Participant and Data Confidentiality

The study monitor, representatives of the IRB or device company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Virginia Center for Diabetes Technology. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by research staff will be secured and password protected. At the end of the study, all study databases may be de-identified and archived at the University of Virginia Center for Diabetes Technology.