A Closed-Loop Study to Evaluate Safety of Zone MPC based Artificial Pancreas in Pediatric Subjects

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1. Background and Rationale

The management of type 1 diabetes (T1D) can be complex, burdensome, and frustrating, requiring multiple tests of blood glucose levels daily, multiple injections of insulin (or manual dosing of an insulin pump), and monitoring of physical activity and carbohydrate intake. Real-time adjustments must be made on a daily basis for unplanned activities or foods, illness, and emotional factors that impact blood glucose levels; and even with adherence to the most rigid food, exercise, blood glucose, and insulin administration schedules, inherent pharmacological and physiological variability results in glucose swings out of desirable, or even safe, ranges. In no group of people is this more problematic than in young children, in whom eating and physical activity levels are highly variable and unpredictable, sensitivity to insulin renders small errors in insulin dosing prone to dangerous swings in blood glucose levels, and awareness of symptoms to warn of impending hypoglycemia or ability to effectively communicate this awareness is limited. Furthermore, most, if not all, diabetes management tasks in this age group must be performed by others: for the most part, parents (typically the mother), but also babysitters, other adult caregivers, and school personnel. At the same time, the demonstrated, well-known adverse neurological effects of hypoglycemia, and the increasingly apparent adverse consequences of hyperglycemia on the developing brain, raise the stakes for good control even higher in this population, who must live the longest with the burden of diabetes.

Many parents cope with these uncertainties by being very watchful and closely monitoring their child. Research with mothers of young children describes this state as one of "constant vigilance". This sense of continuous responsibility to protect their child is especially burdensome during those early years, during which time pediatric parenting stress levels seem to be higher, particularly for mothers. Nighttime caregiving, including nocturnal blood sugar monitoring, is practiced by upwards of 40% of parents, and is associated with sleep deficit and increased anxiety and stress. Nearly a quarter of mothersof young children report clinically significant levels of anxiety and depression, the levels for which, not surprisingly, were highest for those who found it more upsetting to cope with T1D-related stress. Moreover, parents who experience more frequent and difficult T1D-related stress also tend to feel less confident in their capacity to perform these tasks, and have greater fear of hypoglycemia. There is evidence that over time, higher parental depressive symptoms, and parent stress, are associated with decreased parent involvement and greater family conflict. Taken together, these data raise many red flags about the impact the unremitting demands that T1D management can have on a parent's well-being, particularly mothers who still tend to be primary caretakers.

Modern technological improvements have had limited success in improving diabetes management in this age group. Despite the known benefits of long-term control of blood glucose, only 27% of children meet the current American Diabetes Association and International Society for Pediatric and Adolescent Diabetes A1c target of < 7.5%.

The artificial pancreas platform employed under study is centered about the following four key innovations: 1) A zone model predictive control strategy that is at the same time very safe with respect to hypoglycemia, and can simultaneously and independently be

tuned with respect to its response to hyperglycemia; 2) Zone control with diurnal blood-glucose target zones; 3) Models of insulin-glucose physiology and insulin on board; 4) A system for alarming and notification of impending hypoglycemia and technical malfunctions: the Health Monitoring System. These features have been evaluated in several clinical trials in adults with unannounced meals and exercise.

The proposed study will evaluate enhancements to our previous system tailored for the special needs of pediatric subjects: 1) A control strategy with responses to hyperglycemia and hypoglycemia spanning wide ranges, as is typical with children; 2) The use of time-dependent zones specific for pediatric subjects; 3) The development of models for young children, capturing the greater physiologic variability, and ensuring cautious insulin delivery; 4) remote alarming and notification systems that are useful to parents.

2. Objectives

The aim of this clinical study is to determine the feasibility, safety, and preliminary effectiveness of the Zone-Model Predictive Control Artificial Pancreas (ZMPC_AP) system in pediatric subjects with type 1 diabetes in an ambulatory semi-supervised environment over a short duration of 3 days and 2 nights, or up to 60 hours.

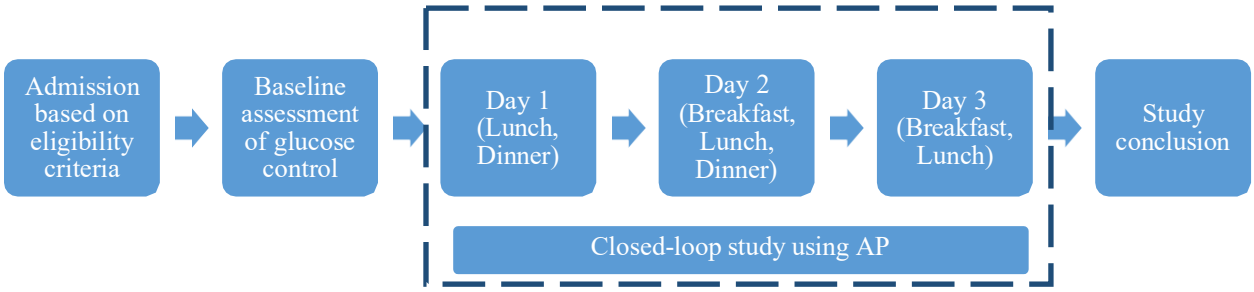

Figure 1. Outline of the proposed clinical study.

3. Study Overview

We will assess the feasibility, safety, and preliminary effectiveness of a Zone-Model Predictive Control Artificial Pancreas (ZMPC_AP) system in children and adolescents with type 1 diabetes. The study will simulate children's usual home environments, including meals of typical size and carbohydrate content, and will also include periods of afternoon exercise typical of after-school sports or other activities. This study will utilize a "hybrid" closed-loop paradigm, in which subjects (or parents) must count the carbohydrate content of the meals and announce this to the system at the time of the meal. Subjects and parents will be free to travel within a 15-minute walking distance of the study site, and they will sleep overnight in a local hotel, in which study personnel willprovide on-site supervision. The duration of closed-loop control will be up to 60 hours. The initial cohort will be comprised of adolescent subjects, age 12-17y, and if successful (i.e. no stopping criteria are met), additional cohorts will consist of progressively younger-age children (8-<12y and then <8y).

4. Study Subjects

a. Eligibility Criteria

Subjects will be eligible to participate in the study if they meet the following inclusion criteria:

1) Age <18 years; for first cohort(s), subjects will be 12-17 years; additional age brackets will be 8-11 years and then <8 years
2) Type 1 diabetes for ≥ 1 year duration – the diagnosis of type 1 diabetes will be based on the history of ketosis/ketoacidosis at diagnosis or laboratory evidence of islet-cell auto-immunity
3) A1c level ≤ 10.0%
4) Use of insulin pump and carbohydrate counting for ≥ 3 months
5) Current or past use of CGM is desirable but NOT required
6) Normal renal function as measured within 6 months of enrollment
7) Normal thyroid function within 6 months of enrollment, or if previously diagnosed with hypothyroidism, documented within 3 months of enrollment
8) Parent/guardian agrees to stay at hotel with subject for duration of hotel phase and has cell phone that can send/receive text messages
9) Subject and participating parent/guardian speak and comprehend English

b. Exclusion criteria

Subjects will be ineligible to participate in the study if they meet any of the following criteria:

1) Episode of diabetic ketoacidosis (DKA) within 6 months of enrollment
2) Episode of severe hypoglycemia (seizure, loss of consciousness) within 6 months of enrollment
3) Use of medications (other than insulin) known to affect BG levels within 4 weeks of enrollment – examples include systemic glucocorticoids, metformin, pramlintide, liraglutide, SGLT inhibitors)
4) Current use of other medications, that in opinion of investigator, would interfere with safety or effectiveness of the study including acetaminophen
5) Medical disorder, that in opinion of investigator, would be contraindication for inclusion; hypothyroidism and celiac disease are NOT exclusion if under good control
6) Female subjects of childbearing potential unwilling to have pregnancy testing
7) Female subject currently pregnant or lactating
8) History of alcohol or drug abuse, documented eating disorder, or inpatient psychiatric treatment within 6 months of enrollment
9) Subject is currently participating in another research study involving an investigational drug or device
10) Parent/guardian unable or unwilling to comply with study protocol and stay at hotel with subject for duration of study
11) Parent/guardian does not have cell phone with messaging capability

12) Parent/guardian does not comprehend written and spoken English

c. Source of Subjects

Subjects will be recruited from the clinic population at the Yale Children's Diabetes Program who meet eligibility criteria. Additional subjects may be recruited from local advertising and/or the website *clinicaltrials.gov.* Potential subjects may be emailed information regarding the study, including copies of the consent forms, and if interested will be invited to the research center for formal enrollment.

d. Consent Process

The principal investigators, co-investigators, or study coordinators will introduce the studies to eligible participants and their caretakers during routine medical visits or in the form of a mailing or phone call. Prospective subjects/caretakers will have a face-to-face meeting with the investigator and/or study coordinator to address questions about the study rationale, procedures, risks and benefits. In order to identify and clarify any misconceptions, parents/caretakers will be encouraged to describe the research procedures and their associated risks in their own words, followed by correction of any errors by the investigator or study coordinator. All the subjects in the proposed studies will be minors; parent/guardian permission will be obtained for all subjects; additionally, for subjects age 7 or older, subject assent will also be obtained, as per Yale IRB guidelines. The parents/caretakers of participants will be encouraged to ask questions and will be clearly informed about the time required for these studies and their rights of non-participation and/or withdrawal. Caretakers/parents will be given copies of thesigned consents to keep. Since personal health information will be collected as part of this research protocol, parents/caretakers will also be asked for authorization to collect this information in accordance with HIPAA and Yale IRB guidelines.

e. Sample Size

We will enroll a convenience sample of 24-48 subjects (8-16 in each of the three age cohorts), the final number depending on whether additional cohorts needed to be repeated at any given age group. There is no formal sample size calculation for this study.

5. Study Procedures

The study will consist of two visits, separated by no more than two weeks: an enrollment visit and a hotel visit.

a. Enrollment Visit

Subjects and parents/caregivers invited to participate in the study will undergo the consent process as described above, and then have the following study procedures:

1) Medical History

A medical history will be elicited from subjects/parents, focusing on current diabetes management issues, prior diabetes-related history (date of diagnosis, complications and co-morbidities), history of adverse events (severe hypoglycemia, DKA), other past and

current medical problems, medications, and allergies. For subjects already attending the Yale Children's Diabetes Program, electronic medical records will be available for each subject. For subjects not attending the Yale Children's Diabetes Program, copies of medical records will be requested. Demographic data including age, sex, race/ethnicity will also be recorded. Current pump settings, glucose meter and continuous glucose monitor (CGM) logs, will be reviewed and recorded.

2) **Physical Examination**

A focused physical examination will be conducted on all subjects, including vital signs, anthropometrics, cardiac, respiratory, abdominal, and neurological systems, thyroid, skin (particularly infusion sites), and pubertal staging.

3) **Laboratory Data**

Subjects' previous laboratory records will be reviewed, and a point-of-care A1c will be obtained at the visit, to confirm eligibility. Female subjects of childbearing potential will have a urine pregnancy test; those with a negative test will be invited to participate, and those with a positive test will be offered appropriate counseling.

4) **CGM Placement**

Subjects will be fitted with a DexCom sensor for collection of baseline glycemic profile data. Subjects already using a Dexcom CGM for their routine diabetes care may continue to use their own sensors; subjects not using Dexcom CGM will be provided with one and instructed on its proper use, including insertion, calibration, interpretation of data, recharging, and troubleshooting. Subjects/parents will be reminded that ALL insulin dosing decisions should continue to be made using capillary blood glucose testing with their usual meter, NOT the sensor. Subjects will be asked to collect baseline CGM data for up to two weeks.

5) Blood Glucose Meter

Subjects will be provided with a study glucose meter, which should be used for ALL BG testing during the baseline data collection period, as well as for calibration of the CGM. Subjects and parents will be instructed to test BG at least 4 times daily, more as needed, as per their usual home routine. Calibrations of the CGM should be done at least twice daily at appropriate times.

b. Hotel Visit

Approximately 1-2 weeks after the enrollment visit, subjects and at least one parent/guardian will return for a "hotel" visit, of up to 60 hours, during which time the following will occur:

1) Initiation of Closed-Loop

Subjects will return to study site in the morning of the day of admission, for review of interim diabetes control and uploading of pump, meter and CGM data. Subjects' current

insulin pumps and sensors will be swapped for the study pump and sensor, and the system will be initialized and activated under study staff supervision. Study subjects will be trained on proper use of the system and will receive hard-copy training materials touse as reference. Before leaving the study facility, subjects will be required to demonstrate competency with basic system operations, and successful operation of the SMS alert system for subjects' and staff cell phones will be ensured. This training portion of the study may occur at the Yale Children's Diabetes Research Program facility or at a conference room at the study hotel.

2) Activities During Hotel Visit

Subjects will be encouraged to participate in usual daily activities, including exercise, eating out, shopping, etc) as long as they remain within a 15-minute walking radius of the study site, and they have a functioning cell phone with messaging capabilities. There will be age-appropriate scheduled activities with the study group as well as personal "down-time." During the entire duration of this phase, subjects will be under direct supervision of a parent or study staff member at all times. Subjects and parents will be required to return to hotel by 9 pm and have BG level checked at midnight each night they are at the hotel. A member of the study staff will be available at the hotel each night during the study to ensure subject safety and will check subjects' BG levels at midnight each night.

3) Exercise

Subjects will be encouraged to participate in exercise activities each day during the hotel visit, such as walking, jogging, exercise room, or sports. Exercise will not be announced to the controller, but subjects that usually pre-treat exercise with small amounts of carbohydrate may continue to do so after discussion with study staff. All subjects will check BG levels prior to and after the planned exercise.

4) Diabetes Management During Hotel Visit

Subjects will continue to count carbohydrates for all meals and snacks and enter this amount into the controller of the closed-loop system. For youngest age group (<8 y), manual pre-meal boluses may not necessarily be given, at discretion of the investigator,to test the robustness of the system. Subjects will not utilize "correction doses" for hyperglycemia except if instructed by study staff.

5) Hypoglycemia and Hyperglycemia Management

Subjects and parents will be instructed to test BG on the study meter for any CGM readings under 70 mg/dL or if subject develops symptoms of hypoglycemia. For any documented BG <70 mg/dL or in the setting of symptoms of hypoglycemia, study staff will be alerted, subject will be treated with 15-30 gm rapid-acting carbohydrate (such as juice or glucose tabs), and BG will be rechecked in 15 minutes. Additional treatments for hypoglycemia will be given every 15 minutes as needed until BG levels are ≥ 70 mg/dL. For CGM readings ≥ 300 mg/dL for > 1 hour, subject will test BG, and if confirmed BG ≥ 300 mg/dL, subject will test blood ketones. Subject or parent will contact investigator for any blood ketone level > 1.0 mmol/l for instructions on supplemental insulin,

changing insertion site, and continuation of closed-loop control, as per the Treatment Protocol (Table 1).

6) Remote Monitoring

Subjects' parent/guardian and study staff will receive event-based SMS (text) alerts on their cell phones for low sensor readings, or for other operational issues affecting performance of the system. For these studies, the threshold for predictive hypoglycemia alerts will be set to 65 mg/dL. If the hypo- alert is activated, subjects will be required to test BG and communicate result to study staff. If study staffs have received an SMS alert, they will call subjects on their cell phone if they have not received a call from them within 15 minutes. Subjects will be instructed to treat symptomatic hypoglycemia or confirmed BG level < 70 mg/dL with 15-30 grams of rapid-acting carbohydrate (such as juice or glucose tabs), re-check BG level in 15 minutes, and repeat as necessary until BG level is over 70 mg/dL. Study staff will advise subject/caregiver whether to continue current diabetes management or exit closed-loop control, as per the Treatment Protocol (Table 1).

7) Stopping Criteria

If an individual subject has two episodes of a confirmed BG < 50 mg/dL (separated by at least 30 minutes), blood ketones > 1.0 mmol/L for over 2 hours, or any blood ketone level > 3.0 mmol/L, then the study will be stopped for that subject. Recall that subjectwill test for ketones after a confirmed BG ≥ 300 mg/dL following CGM readings ≥ 300 mg/dL for > 1 hour. If any subject has a seizure, loss of consciousness or ketoacidosis (CO_2 < 15 mEq/L, or pH<7.3) the study will be stopped for that subject and no additionalsubjects will be enrolled until the DSMB reviews the data.

If for any subject the BG ≥ 300 mg/dL and blood ketones are > 1.0 mmol/L, the closed-loop control will be temporarily stopped, the infusion site will be changed, and supplemental insulin may be given at the discretion of the investigator. The closed-loop control will be restarted if BG <250 mg/dL and blood ketones < 0.6 mmol/L.

If for any subject the BG ≥ 400 mg/dL for any ketone levels, the closed-loop control will also be temporarily stopped, the infusion site will be changed, and supplemental insulin may be given if the investigator concludes that the issue is related to a site failure and not due to malfunction of the controller. The closed-loop control will be restarted if BG <250 mg/dL and blood ketones < 0.6 mmol/L.

Additional information is shown in the Treatment Protocol table.

8) Treatment Protocol Table

Table 1. Hypoglycemia and hyperglycemia monitoring and treatment procedures.

Meter BG (mg/dL)	Ketones (mmol/L)	Clinical State	Action	Monitoring
Any		Seizure, loss of consciousness, or inability to consume oral treatment	STOP system Treat with SQ glucagon Notify MD/NP End closed-loop STOP study for this patient	Repeat BG every 15 minutes until BG≥70mg/dL
<70		Conscious, well-appearing	Treat with oral glucose Notify MD/NP Repeat MBG Continue closed-loop	Repeat BG every 15 minutes until BG≥70mg/dL
70-299		Asymptomatic and well	Continue closed-loop	Check BG (Premeal, pre and post exercise and midnight)
300-399	≤ 1.0	Asymptomatic and well	Continue with closed-loop Notify MD/NP May consider supplemental insulin	Repeat BG and ketones in 1 hour
300-399	> 1.0	Asymptomatic and well	Notify MD/NP SQ insulin correction, set change Suspend closed-loop May restart if BG 80-250 mg/dL and ketones < 0.6 mmol/L. Encourage oral fluid intake.	Repeat BG and ketones in 1 hour
≥400	Any		Notify MD/NP SQ insulin correction, set change Suspend closed-loop May restart if the investigator concludes that the issue is related to a site failure and not due to malfunction of the controller, BG 80-250mg/dL and ketones < 0.6 mmol/L. Encourage oral fluid intake.	Repeat BG and ketones in 1 hour
Any	>1.0 for >2h or >3.0 once		STOP system Notify MD/NP SQ insulin correction, set change End closed-loop STOP study for this patient	Repeat BG and ketones in 1 hour

Any	Any	Abdominal pain, vomiting, altered level of consciousness	STOP system Notify MD/NP SQ insulin correction, set change End closed-loop STOP study for this patient Transfer to ER for further Tx	Per clinical scenario

9) End of Hotel Visit

At the conclusion of the hotel visit (afternoon of 3rd day), subjects will return to their usual pre-study insulin pump and regimen. Study devices will be returned and uploaded for data analysis. Subjects and parents will participate in semi-structured interviewsand/or focus groups to give opinions about system usability, confidence in system safety, fear of hypoglycemia, and diabetes-related distress. Study staff will call subjects/parents approximately 24 hours after discharge to review BG control and assess for late adverse events.

10) Surveys and Interviews

Subjects and parents/caregivers will, at the conclusion of the hotel visit, complete several surveys/questionnaires to assess the effect of the closed-loop system on diabetes-related quality of life and distress, fear of hypoglycemia, and satisfaction with diabetes technology (see Table 2). Subjects and caregivers will also participate in focus groups or semi-structured interviews related to human factors issues, and perceived burdens and benefits, of the closed-loop system. Only the interviewer and participant(s) will be present during the interview/focus group.

Table 2. Surveys/questionnaires to assess effect of the closed-loop AP system.

CONSTRUCT:	MEASURE:
CHILD/ADOLESCENT SURVEYS	
Fear of hypoglycemia	Hypoglycemia Fear Survey
Diabetes burnout/burden	Problem Areas in Diabetes
Quality of life–diabetes specific	Pediatric QoL Inventory (PedsQL) – Diabetes Module (8-12)
Quality of life–diabetes specific	Pediatric QoL Inventory (PedsQL) – Diabetes Module (13-18)
Automated Insulin Delivery Device Acceptance	INSPIRE AID Acceptance (Draft) - Child
Automated Insulin Delivery Device Acceptance	INSPIRE AID Acceptance (Draft) – Teen
PARENT OF YOUTH W T1D SURVEYS	
Fear of hypoglycemia	Hypoglycemia Fear Survey – Parent version
Diabetes burnout/burden	Problem Areas in Diabetes – Parent version
Quality of life–diabetes specific	Pediatric QoL Inventory (PedsQL) – Diabetes Module (8-12)– Parent version
Quality of life–diabetes specific	Pediatric QoL Inventory (PedsQL) – Diabetes Module (13-18) – Parent version

CONSTRUCT:	MEASURE:
Automated Insulin Delivery Device Acceptance	INSPIRE AID Acceptance (Draft) – Parent Version
ALL AGES	
Technology Acceptance	Comfort and Use of Technology Survey
Glucose Monitoring Satisfaction	The Glucose Monitoring Satisfaction Survey (GMSS)

6. Data Analysis

a. Primary Endpoint

The primary endpoint for the short-duration hotel study is safety, as defined as: 1) no more than one confirmed BG < 50 mg/dL; 2) no more than two confirmed BG ≥ 300 mg/dL longer than 2 hours, unless determined to be from an infusion site failure; 3) no BG ≥ 400 mg/dL; 4) no blood ketone level > 1.0 mmol/l for longer than 2 hours, or any ketone level >3.0 mmol/L, unless determined to be from an infusion site failure; and 5)no significant adverse events, such as severe hypoglycemia (seizure, loss of consciousness), diabetic ketoacidosis.

b. Secondary Endpoints

Efficacy endpoints of interest will include:

a. Mean meter and sensor glucose
b. % Time in range (70-180 mg/dL)
c. % Time below range (<70 mg/dL)
d. % Time above range (>180 mg/dL)
e. % Time in hypoglycemia (<60 mg/dL)
f. % Time in hyperglycemia (>250 mg/dL)
g. % time AP system active

The glycemic metrics will be calculated by total 24-hour period, and also broken down into daytime (6AM-11PM) and nighttime (11PM-6AM) periods.

c. Stopping

If an individual subject has two episodes of a confirmed BG < 50 mg/dL (separated by at least 30 minutes), blood ketones > 1.0 mmol/L for over 2 hours, or any blood ketone level > 3.0 mmol/L, then the study will be stopped for that subject. If any subject has a seizure, loss of consciousness or ketoacidosis (CO_2 < 15 mEq/L, or pH<7.3) the studywill be stopped for that subject and no additional subjects will be enrolled until theDSMB reviews the data.

d. Continuation

If stopping criteria are NOT met for an age cohort, then after that cohort is completed we will proceed to next lower age cohort after DSMB review and approval. However, even if stopping criteria are not met, additional cohorts at a given age range may be enrolled at discretion of investigators if adjustments to algorithm tuning parameters are desired based on glycemic results and comparison with subjects' pre-study baseline glycemic profiles.

7. Financial Considerations

a. Subject compensation

Subjects/parents will receive $50 for the enrollment visit and $100/day for the hotel visit, for a maximum of $350 compensation for participation.

b. Meal Stipend

All subject meals during the hotel stay will be covered by the study. Parents will receive $75 per day stipend for their meals and expenses during the hotel stay. Parking at the hotel will be covered by the study.

8. Adverse Event Reporting and Safety Monitoring

a. Definition

Reportable adverse events in this study include any untoward medical occurrence that meets criteria for a serious adverse event or any medical occurrence (expected or unexpected) in a study participant that is study or device-related.

Hypoglycemic events are recorded as adverse events 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 to prevent harm. This means that the subject was impaired cognitively to the point that he/she was unable to treat his or herself, was unable to verbalize his or her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma. These episodes may be associatedwith sufficient neuroglycopenia to induce seizure or coma. If glucose measurements are not available during such an event, neurological recovery attributable to the restoration of 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 if the event involved diabetic ketoacidosis, as defined by the DCCT, and had all of the following:

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Serum ketones 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

b. 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 participant, and appropriate medical intervention will be made. The study investigator will assess the relationship of any adverse event to be related or unrelated by determining if there is reasonable possibility that the adverse event may have been caused by thestudy device or study procedures.

The intensity of adverse events will be rated on a three-point scale: mild, moderate, or 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 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.

c. Reporting serious or unexpected device-related events

A serious adverse event is any untoward 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 significant disability/incapacity
- Is a congenital anomaly/birth defect

d. Unanticipated adverse device event

An unanticipated adverse device event is defined as an adverse event caused by, or associated with, a device, if that effect or problem was not previously identified in nature, severity, or degree of incidence.

Serious or unexpected adverse events must be reported to the PI immediately. The PI will notify the Yale IRB, DMSB, FDA, and device manufacturer of any adverse device event that is both serious and unexpected. Notification will be made within 5 days after the PI becomes aware of the event, as per Yale IRB requirements.

e. Data Safety Monitoring Board (DSMB)

Drs. Dassau and Weinzimer will convene a Data Safety Monitoring Board, (DSMB), comprised of independent clinicians experienced in the management of young children with type 1 diabetes, to review study protocols and safety reports with study

investigators. The DSMB will be responsible for oversight of the proposed protocol. The DSMB will monitor the ongoing safety of the studies through periodic reports, at least twice a year, provided by the clinical center, and any adverse event reports as described above requiring notification will also include the Chair of the DSMB. The DSMB will meet with Drs. Weinzimer and Dassau every six months, either in person or by conference call, to review study progress and adverse events. In addition, the DSMB will meet with study investigators before the initiation of successively younger subject cohorts, for their input on safety, before any subjects are enrolled, in order to approve the monitoring plans for each study phase at their start.