Hypoglycemia Prevention During and After Moderate Exercise in Adults with Type 1 Diabetes Using an Artificial Pancreas with Exercise Behavior Recognition

Protocol Chair

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Participating Institutions

University of Virginia

Version Number: v1.4

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KEY ROLES

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Study Licensed Medical Investigator	
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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AP	Artificial Pancreas
BG	Blood Glucose
BT/BTLE	Bluetooth, Bluetooth low energy
CGM	Continuous Glucose Monitoring
CLC	Closed-Loop Control
CSII	Continuous Subcutaneous Insulin Injection
DiAs	Diabetes Assistant
DKA	Diabetic Ketoacidosis
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
IDE	Investigational Device Exemption
IOB	Insulin-on-Board
JDRF	Juvenile Diabetes Research Foundation
NIH	National Institutes of Health
POC	Point-of-Care
QC	Quality Control
UI	User Interface

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133 # *PROTOCOL VERSION HISTORY*

Version Number	Author(s)	Approver	Effective Date	Revision Description
1.0	Marc Breton	Marc Breton	15-Dec-2018	Original Protocol
1.1	Sue Brown, Mary Oliveri	Marc Breton	11-Feb-2019	▪ FDA review edits requested
1.2	Sue Brown, Mary Oliveri	Marc Breton	12-Feb-2019	▪ FDA review edits requested ▪ FDA approved 02/15/19
1.2	N/A	N/A	26-Feb-2019	▪ IRB Approved _
1.3	Sue Brown, Mary Oliveri	Sue Brown	29-Jul-2019	▪ Modified screening labs and eligibility criteria relating to those labs ▪ Added status of menses during screening ▪ Personal CGM may be inserted prior to discharge
1.4	Mary Oliveri	Mary Oliveri	04 Nov-2019	▪ Study CGM will be worn until discharge or until the current sensor expires.

SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: Hypoglycemia Prevention During and After Moderate Exercise in Adults with Type 1 Diabetes Using an Artificial Pancreas with Exercise Behavior Recognition

Protocol Version/Date: v1.4/04-Nov-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: University of Virginia

PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	Hypoglycemia Prevention During and After Moderate Exercise in Adults with Type 1 Diabetes Using an Artificial Pancreas with Exercise Behavior Recognition
Investigational Device	Tandem t:AP Insulin Pump with the EnMPC Controller
Objectives	To evaluate the safety and efficacy of the artificial pancreas system with exercise behavior recognition to prevent hypoglycemia before, during, and after exercise.
Study Design	A randomized crossover trial with 1:1 randomization to admission sequence of Control AP system (rMPC) vs. Experimental AP system (EnMPC) over approximately 4 months.
Number of Sites	1
Endpoint	The occurrence of hypoglycemia as determined by CGM <70 or administration of carbohydrate treatment without insulin from 30 minutes prior to exercise until dinner time.
Population	**Key Inclusion Criteria** • Age 18-65 • Diagnosis of Type 1 Diabetes **Key Exclusion Criteria** • Inability to be active for at least 30 minutes per day
Sample Size	15 participants to complete randomized trial
Treatment Groups	**Control Admission followed by the Experimental Admission** • Participants will undergo Data Collection then complete the exercise admissions first with the rMPC AP controller followed by the admission utilizing the EnMPC AP controller **Experimental Admission followed by the Control Admission** • Participants will undergo Data Collection then complete the exercise admissions first with the EnMPC AP controller followed by the admission utilizing the rMPC AP controller
Participant Duration	Up to 4 months
Protocol Overview/Synopsis	After consent is signed, eligibility will be assessed. Eligible participants will proceed to the Data Collection Phase for approximately 28 days. If the participant collected adequate data during the Data Collection Phase, they will be randomized 1:1 and begin the study admissions, which will be completed within 90 days of the end of data collection. The sequence of the admissions (Control-Experimental vs. Experimental-Control) will be determined by the randomization [**Figure 1**].

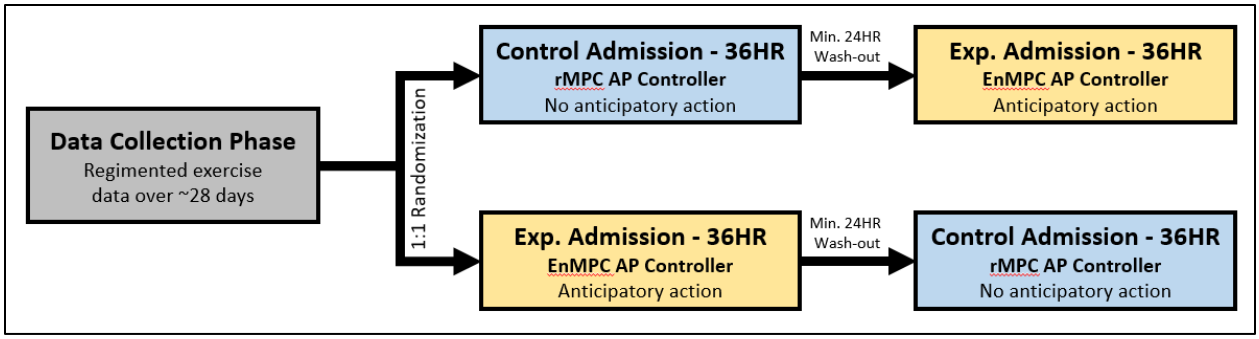

Figure 1-1: Study Design: Participants Randomized 1:1 to Control & Experimental Admission Sequence

SCHEMATIC OF STUDY DESIGN

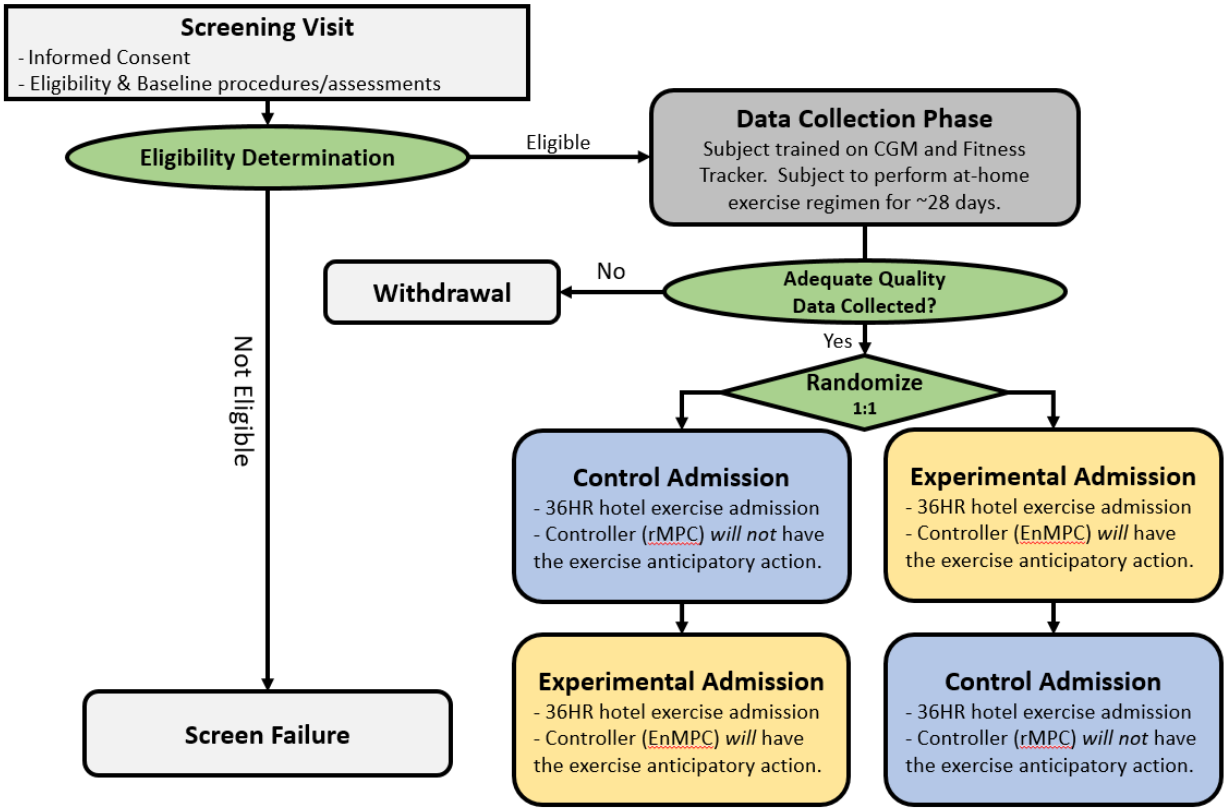

Figure 1-2: Schematic of Study Design

166 **Table 1.** Schedule of Study Visits and Procedures

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	Pre	Pre	Randomization	Pre-Admission	First Admission	Follow-Up	Second Admission	Follow-Up
Location	**Clinic**	**Home**	**Remote**	**Home**	**Hotel / Gym**	**Home**	**Hotel / Gym**	**Home**
Comment	**Screen / Enroll**	**Exercise & Data Collection**	**Randomization**	**Phone, Email, Text**	**Exercise Admission**	**Phone, Email, Text**	**Exercise Admission**	**Phone, Email, Text**
Informed Consent	**X**							
Eligibility Assessment	**X**							
Medical History	**X**							
HbA1c	**X**							
Blood Testing: TSH, CMP (as necessary)	**Optional**							
Randomization			**X**					
Pregnancy test (if applicable)	**X**				**X**		**X**	
Electrocardiogram (ECG)	**X**							
Physical Exam	**X**							
Vital Signs (including height/weight)	**X**							
Device Data download(s)	**X**	**X**		**X**	**X**		**X**	
Exercise Regimen **- Min. 4 times/week, 30 minutes**		**X**						
Wear Study CGM and Fitness Tracker		**X**			**X**		**X**	
Group 1: - Control Admission then Experimental Admission					**X** rMPC Controller		**X** EnMPC Controller	
Group 2: - Experimental Admission then Control Admission					**X** EnMPC Controller		**X** rMPC Controller	
Review diabetes management and AEs	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

Chapter 1: Background Information

1.1 Introduction

A Century of Diabetes Technology: Since the discovery of insulin in 1921, the treatment of T1D has become interdisciplinary with a significant bioengineering component. In 1964, an insulin pump delivering intravenous (i.v.) insulin and glucagon was reported by Kadish[1]. In 1969, the first portable blood glucose (BG) meter, –the Ames Reflectance meter, –was manufactured. The first subcutaneous insulin pump, –the Auto Syringe, –was introduced in the 1970s, and by the end of the decade the first trials of continuous subcutaneous insulin infusion (CSII) were reported by Pickup et al. in the U.K.[2] and Tamborlane *et al*. in the US[3], showing the feasibility of this minimally-invasive mode of insulin replacement. The next step was automated insulin delivery (AID) controlled by an algorithm, known as closed-loop control of T1D, or "artificial pancreas (AP)." The progress of AID technologies suitable for outpatient use began with the introduction of continuous glucose monitoring (CGM)[4,5] and numerous studies have documented its benefits[6,7,8,9] and charted guidelines for its use for closed-loop control[10,11,12,13]. Attempts to fully automate glucose control in T1D using CGM and CSII linked via closed-loop algorithm began with the early work of Hovorka[14] and Steil[15], and the launch of the JDRF Artificial Pancreas Consortium which in 2006 sponsored research on closed loop control in several centers in the US and Europe. In 2008, NIH/NIDDK launched its AP initiative, in 2009 JAMA stated that "*Artificial pancreas may soon be a reality*"[16]. and in 2010 the European AP@Home Consortium was established. A roadmap towards a viable AP was proposed[17] and by 2010 the AP became a global multidisciplinary research topic.

The Last Decade, Thus Far: In May 2012, a Diabetes Outlook was published in *Nature*[18] which highlighted the AP, and shortly thereafter, *Science* featured the same topic[19]. In July 2016, *Diabetes Care* published a symposium exclusively dedicated to outpatient AP studies with portable systems[20-24], including trials at patient's homes lasting a month or more[20-23] and studies in children[24]. Some of the major AP related activities over the past two years are: (i) completion of a pivotal trial of the first commercial hybrid AID system – the Medtronic 670G which automatically modulates basal rate but not the insulin boluses[25]; (ii) a six-month feasibility study reported improvement in glycemic control and reduction of hypoglycemia with long-term AP use[26]; (iii) NIH/NIDDK invested in four pivotal trials intended to bring AP to market, and (iv) multiple camp setting validation of AP in children and adolescents, culminating with the first use of AP during conditions as challenging as a 1 week ski camp (5 hours of skiing per day for 5 days)[27]. These AP related progresses are summarized in the following reviews[20,28-30], including an overview the transition of AP to clinical practice in 2017[31].

Our track record at UVA CDT over the last 12 years includes: (i) comprehensive *in silico* modeling the human metabolic system that culminated in the only model accepted by the FDA to date as a substitute for animal trials in the testing of diabetes treatments[32]; (ii) a number of U.S. and international studies using our AID system[30-34]; (iii) a trial of a multi-signal CLC system using heart rate to inform the control algorithm and enhance glycemic control during exercise in adolescents with T1D;[33] (iv) 6-month pilot study of AP home use[26], the longest such study to date; (v) a trial in young children with T1D[34], and (vi) the first use of AP during prolonged extensive winter-sport physical activity – the AP Ski Trial.[27] As such, we have an extensive track record

with AP systems. At present, our group leads the International Diabetes Closed Loop Trial – a $12.7M NIH-funded project (grant UC4 DK 108483) aiming to establish CLC as a clinically accepted treatment for type 1 diabetes. The study design and results of its first protocol were presented recently .[35,36]

Diabetes Assistant (DiAs): The Diabetes Assistant (DiAs) [37] platform is a smartphone-based, modular, portable AP device developed at the University of Virginia (UVa), in collaboration with the University of Montpellier (Figure 3). DiAs operates on a commercially available Android-based phone, using **a specifically modified version of Android** (Medical Android) and enabling wireless communication with satellite devices including insulin pumps, CGMs and any medical device using a standard wireless protocol including BT, BTLE, ANT+ and 802.11. Its modular architecture allows for different control modules to be swapped in real time. The DiAs platform also integrates automated data transfer to a secured server, enabling cloud functionalities, e.g. remote monitoring [40]. DiAs is filed with the FDA under master file MAF 2109 and has been approved for home clinical trials by adults and adolescents with T1DM. *DiAs is a powerful computation platform that enables both automated control of insulin and remote data collection for cloud application; it is the most advanced Glucose control platform to date and is currently being deployed for weeks in home AP trials.* ***DiAs will enable seamless integration of the exercise-informed glucose control functionalities in a form factor assessed by focus groups to be acceptable by people with T1DM.***

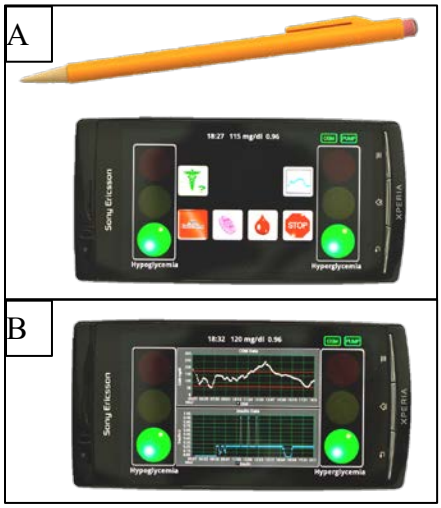

Figure 1-1: The DiAs system, the first truly mobile Glucose control platform

Unified Safety System (USS Virginia): A key control module presented by our group in 2008 and the first to have been deployed outpatient [37] is the Safety Supervision Module (SSM). Following the modular architecture, the SSM is solely responsible for hypoglycemia avoidance, and will limit both basal and correction insulin based on the perceived risk for hypoglycemia. Since 2008 the SSM has been extensively updated, using (i) model-based real-time estimation of the patient's metabolic state [41], (ii) predicted risk for hypoglycemia [41], (iii) and accounting for meals and meal associated insulin [42]. The USS is based on the SSM and adds a new module controlling basal rate to mitigate the risk for hyperglycemia as well. The USS has been tested in more than 250 adolescent and adults in inpatient and outpatient trials and has demonstrated significant improvement in both hypo- and hyperglycemia protection [39]. The USS is now deployed in the home setting. A prototype of an exercise-informed USS module assuming a fixed 30mg/dl drop due to exercise was implemented and tested

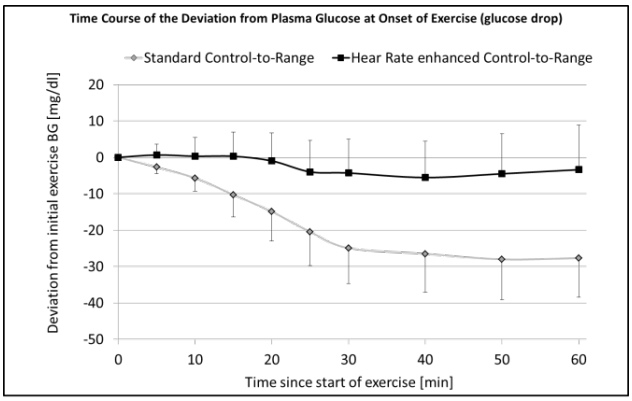

Figure 1-2: Reduction of the exercise induced drop in glycaemia using an exercise informed vs. naïve AP system

in DiAs showing significant effect on the risk of hypoglycemia during a feasibility study with 10 T1D adults.[38] Early detection of exercise using heart rate monitors allowed a significantly reduced glycemic drop during moderate exercise when compared to standard closed loop from -30 mg/dl to -5 mg/dl (Figure 4, and [38]).

This technology will **modulate insulin safely to improve glucose control** within the exercise-informed CLC.

Informing a glucose control system of current and past physical exercise will naturally derive from the explosion of commercially available exercise tracker devices (e.g. Fitbits, Jawbone, Nike Fuel, Apple Watch, Garmin Vivofit, Zephyr bioharness, to name but a very few) and from their expanding connectivity via standard communication protocols (e.g. Bluetooth). It is important to note that most of these devices rely on complex algorithms to extract key features of physical exercise from available sensors (such as heart rate monitors and accelerometers); the goal of this proposal is not to develop one more of these algorithms, as this field is mature and there is no reason to believe these algorithms would fail in diabetes. Instead, this proposal is designed to harvest existing exercise detection technologies and integrate them in our existing CLC platform.

1.2 Rationale

As described above, exercise remains a challenge to AP systems; more specifically, by the time exercise is detected it is often too late to avoid hypoglycemia without the ingestion of rapid carbohydrates or the use of rescue injections, such as glucagon. To this avail, we propose to add a novel Model Predictive Control module to our proven USS system. This module is designed to compute insulin doses every 5 minutes that are designed to "optimally" maintain glycaemia around a target of 120mg/dL. The optimality is defined mathematically as minimizing deviations from basal rate injections and the distance between current and future (up to 2h) glycaemia from a physiologically feasible trajectory back down (or up) to 120mg/dL (i.e. if current CGM is 160mg/dL the controller will not attempt to immediately reach 120mg/dL, rather it will assume a decay in time from 160 to 120). Furthermore, our novel control system, labelled Multi Stage MPC or Ensemble MPC, accounts for a preset number (currently 5) of exercise scenarios during the prediction horizon, these scenarios being derived from the user historical record; this setup allows the control system to **anticipate expected exercise bouts up to 2h in advance** while maintaining the condition for optimal glycemic control.

By adding such module to our well validated system, we expect an improvement in protection against hypoglycemia during and immediately after physical activity without increase in hyperglycemia. To demonstrate the feasibility of this approach we will compare our novel anticipatory system to a naïve AP system during highly supervised hotel admissions with afternoon exercise. Participants will be asked to exercise regularly in the late afternoon during a month of data collection to generate the patterns to be anticipated.

1.3 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.

1.3.1 Known Potential Risks

1.3.1.1 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.

1.3.1.2 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.

1.3.1.3 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.

1.3.1.4 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.

1.3.1.5 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.

1.3.1.6 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 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.

1.3.1.7 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 (i.e. activity trackers, etc…) 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.

1.3.1.8 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 the home 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.

1.3.2 Known Potential Benefits

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

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

1.4 General Considerations

The study is being conducted in compliance with the policies described in the study policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice (GCP).

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 2: Study Enrollment and Screening

2.1 Participant Recruitment and Enrollment

Up to 3 subjects will be enrolled into the Pilot study. The Pilot participants will complete all study procedures outlined for the main trial with the exception of the admission – a single admission will test both the control and experimental controller as outlined in 5.1.5. Pilot subjects will not be randomized. Pilot study participants may also participate in the main randomized trial after completion of the Pilot procedures. For Pilot participants who will also be in the main study, the data collection does not need to be repeated if the first admission for the main study is within 90 days of data collection completion. Participants who want to participate in the main study will be consented for the main study at that time, however, Pilot procedures will replace the need for performing Screening and Data Collection procedures again.

Enrollment will proceed with the goal of having 20 participants enter the main randomized trial, with the expectation that 15 participants will complete the 4 month randomized trial. A maximum of 30 individuals may be enrolled into screening for the main study in order to achieve this goal.

2.1.1 Informed Consent and Authorization Procedures

Potential eligibility may be assessed as part of a routine-care examination. Potential subjects may also be contacted by the study team in response to the subject's previous voluntary consent to be contacted for potential participation in clinical studies. Potential subjects may also contact the study team in response to advertisements, postings, etc.

The study protocol will be discussed with the potential study participant by study staff. The potential study participant will be given the Informed Consent Form to read. Potential study participants will be encouraged to discuss the study with family members and their personal physicians(s) before deciding whether to participate in the study. If the subject agrees to participate, the Informed Consent Form will be signed by the subject and the person obtaining consent. A copy of the consent form will be provided to the participant and another copy will be added to the participant's study record.

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

2.2 Participant Inclusion Criteria

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

- Age ≥18 and ≤65 years
- Clinical diagnosis of Type 1 Diabetes for at least one year
- Currently using an insulin pump for at least 6 months
- Uses insulin parameters such as carbohydrate ratio and correction factors consistently on their insulin pump in order to dose insulin for meals or corrections

- Access to internet and willingness to upload data during the study
- Willingness to be physically active for at least 30 minutes per day at least 4 times per week
- Willingness to perform the required exercise regimen during Data Collection Period
- Willingness to not perform regular exercise outside of the study-regimented exercise window
- For females, not currently pregnant or breastfeeding. If a female is of child-bearing potential and sexually active, she must agree to use a form of contraception to prevent pregnancy while participating in the study.
- An understanding and willingness to follow the protocol and sign informed consent.

2.3 Participant Exclusion Criteria

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

- History of diabetic ketoacidosis (DKA) in the 12 months prior to enrollment.
- Severe hypoglycemia resulting in seizure or loss of consciousness in the 12 months prior to enrollment.
- Pregnancy or intent to become pregnant during the trial.
- Currently being treated for a seizure disorder
- Coronary artery disease or heart failure, unless written clearance is received from a cardiologist or primary care provider and documentation of a negative stress test within the year
- History of cardiac arrhythmia (except for benign premature atrial contractions and benign premature ventricular contractions which are permitted)
- Clinically significant electrocardiogram (ECG) at time of Screening, as interpreted by the study medical physician.
- Use of non-insulin medications intended to lower glucose that are not on a stable regimen.
- A known medical condition that in the judgment of the investigator might interfere with the completion of the protocol such as the following examples:
  - Inpatient psychiatric treatment in the past 6 months
  - Presence of a known adrenal disorder
- Use of an automated insulin delivery mechanism that is not FDA approved during the data collection phase
- Use of an automated insulin delivery mechanism that is not downloadable by the subject or study team
- Inability to be physically active for at least 30 minutes per day for at least 4 times per week

- Current enrollment in another clinical trial, unless approved by the investigators of both studies or if clinical trial is a non-interventional registry trial.

2.4 Screening Procedures

After informed consent has been signed, a potential participant will be evaluated for study eligibility through the elicitation of a medical history, performance of a physical examination by licensed study personnel, an ECG, and pregnancy testing (if applicable) to screen for exclusionary medical conditions.

Individuals who do not initially meet study eligibility requirements may be rescreened at a later date per investigator discretion. The study physician will have the discretion of requesting a blood sample if concerned about eligibility. Participation is based upon physician's discretion.

2.4.1 Eligibility Screening and Testing

The following procedures and testing will be performed to ensure eligibility:

- Inclusion and exclusion criteria assessed
- Discuss the willingness of the subject to wear, and the importance of wearing, the study equipment during the study
- Discuss the importance of performing the exercise activity during the outlined time frame; and to refrain from performing regular cardiovascular exercise outside of that time
- Demographics and contact information recorded (date of birth, sex, race and ethnicity)
- Medical history including status of menses
- Concomitant medications and supplements
- Electrocardiogram (ECG)
- Pregnancy Test for women of child-bearing potential (urine or serum)
- HbA1c Level (blood)
    - Measured using the DCA2000 (or comparable point of care) or local lab
    - A historical result may be used if within 8 weeks of enrollment
    - Weight, height
    - Vital signs including measurement of blood pressure/heart rate/ temperature/respirations

Chapter 3: Data Collection Phase

3.1 Data Collection Phase Overview

This phase may begin immediately after enrollment is complete. The purpose of this data collection phase is to collect CGM, activity tracker, insulin pump, and exercise data for the participant.

During the data collection phase, participants in the Main Study will be required to exercise a minimum of 4 days per week for approximately 4 weeks during the hours of 4 p.m.– 7 p.m. for at least 30 minutes per exercise day. Pilot study participant data collection will last approximately 2 weeks. The exercise activity should be a cardiovascular exercise activity and will be the participant's choice. Participants will be asked to maintain a heart rate of approximately 110-140 beats per minute for the 30 minute period – this will be dependent on the participant. Participants will be given a study CGM and a study activity tracker to use during the data collection phase. Participants will use their personal insulin pumps during this phase. Participants will be asked to document all carbohydrates during this phase. All participants will receive training on the study CGM as detailed below. This will be an unblinded use of the study CGM. The study team will stress the importance of wearing the study devices and performing the study exercise at the appropriate time while refraining from regular cardiovascular activity outside of that time frame.

If the subject owns a personal laptop device, he/she will be asked to bring it to the visit for the study team to download specific software to be used during data collection. If the subject does not own a laptop device but owns a desktop computer, he/she will be provided with a memory drive storing the appropriate resources to be used at home.

3.1.1 Initiation and Training of Study Devices

Training will be provided to participants not experienced with CGM use as to how to use the CGM in real-time to make management decisions and how to review the data after an upload for retrospective review. The participant will be observed placing the sensor. CGM supplies and CGM user's guide will be provided to the participant.

Subjects will be instructed on how to upload the equipment (i.e., personal insulin pump, personal glucometer, study CGM, study activity monitor). Subjects will be asked to provide uploaded data periodically during the data collection period (approximately one time per week) using a web-based diabetes management system (e.g., Diasend, CareLink Pro) and/or local diabetes device management software (e.g., Dexcom Studio).

Participants currently using a CGM may continue to wear their personal CGM along with the study CGM during the study as long as the study team is able to download their personal equipment.

Subjects will be asked to wear the study activity monitor during the data collection phase, removing prior to bathing and participating in water activities. Subjects will also wear the activity monitor to collect information on activity, exercise, heart rate, and sleep. The commercially available app associated with the activity monitor will be placed on the smartphone to facilitate weekly downloading of data.

Subjects 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.

3.1.2 Data Collection Phase Completion Assessment

Participants' CGM, insulin pump, and activity tracker data will be assessed on a weekly basis during the data collection phase to ensure data quality. The study team will notify the study subject if the data is insufficient or of poor quality and will ask the participant to extend the data collection phase. If needed, interim visits or phone contacts may occur to assist the participant with any study device issues including compliance with data collection and exercise-regimens.

Once adequate data is collected during the data collection phase, participants may continue to the Randomization Visit.

For Pilot study participants, they will continue to the Pilot exercise admission (5.1.5).

Chapter 4: Randomization Visit

4.1 Randomization Visit

Once sufficient quality data is collected during the Data Collection Phase, the participant may continue with randomization. This visit is performed remotely prior to the first exercise admission.

For Pilot participants who have completed the Pilot study and wish to participate in the Main study, the Randomization Visit may occur any time after the Pilot Admission is complete, with a minimum of 24 hours between any Admissions.

4.1.1 Randomization

Eligible participants will be randomly assigned to one of two treatment groups in a 1:1 ratio:

1. Control Admission first, followed by the Experimental Admission
2. Experimental Admission first, followed by the Control Admission

All participants will undergo the same procedures during both admissions with the exception of the type of AP system that is utilized. The Experimental Admission will use the EnMPC artificial pancreas system, while the Control Admission will use the exercise naïve artificial pancreas system (rMPC).

After randomization, participants will be notified and the admissions may begin at any time.

Chapter 5: Randomized Trial Procedures

5.1 Exercise Admission Procedures

5.1.1 General Admission Context and Setting

Pilot study participant admission procedures are outlined in 5.1.5.

Participants in Group 1 will perform the Control Admission first. Participants in Group 2 will perform the Experimental Admission first. Participants will be asked to insert a new CGM sensor approximately 48 hours prior to arrival to allow for proper warm-up of the sensor. For participants who are performing the admissions in close proximity to one another, the existing sensor used during the first admission may be used – the appropriateness of this will be determined by the study team on a case-by-case basis. The two admissions will be separated by at least 24 hours.

Every effort will be made to complete both admissions within approximately 90 days of the end of data collection for that participant. The data collection period may be completed again at the discretion of the investigator if too much time has elapsed or if there was a significant change in the participant's diabetes care that may affect the study.

All admissions will take place primarily in a hotel. The exercise sessions will be carried out at a local gymnasium. Both the Control and Experimental Admissions will consist of the same activities, as outlined in 5.1.4 below, with the exception of the type of AP system that is implemented, which is described in 5.1.2 below.

The admissions will be fully supervised by a research team located at the hotel and gym at all times. The team will consist of a minimum of one registered nurse (trained in the execution of the protocol as well as in the management of hypo- and hyperglycemia) and a technician (trained in the use and maintenance of the DiAs system). In addition, one of the study medical physicians and one senior engineer will be on call during the entire admission.

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) and will be remotely monitored in real-time during the entire admission (including exercise) by the study team via the DiAs Web Monitoring (DWM) platform. SMBG values will be collected between each exercise bout and at the end of the exercise period. The study team will respond clinically to these values. Glycemic guidelines are outlined in 5.1.6.

5.1.2 The Experimental Controller – EnMPC

We propose to add a novel Model Predictive Control module to our proven USS system. This module is designed to compute insulin doses every 5 minutes that are designed to "optimally"

maintain glycaemia around a target of 120mg/dL. The optimality is defined mathematically as minimizing deviations from basal rate injections and the distance between current and future (up to 2h) glycaemia from a physiologically feasible trajectory back down (or up) to 120mg/dL (i.e. if current CGM is 160mg/dL the controller will not attempt to immediately reach 120mg/dL, rather it will assume a decay in time from 160 to 120). Furthermore, our novel control system, labelled Multi Stage MPC (MS-MPC) or Ensemble MPC (EnMPC) [**Figure 5-1**], accounts for a preset number (currently 5) of exercise scenarios during the prediction horizon, these scenarios being derived from the user historical record; this setup allows the control system to **anticipate expected exercise bouts up to 2h in advance** while maintaining the condition for optimal glycemic control.

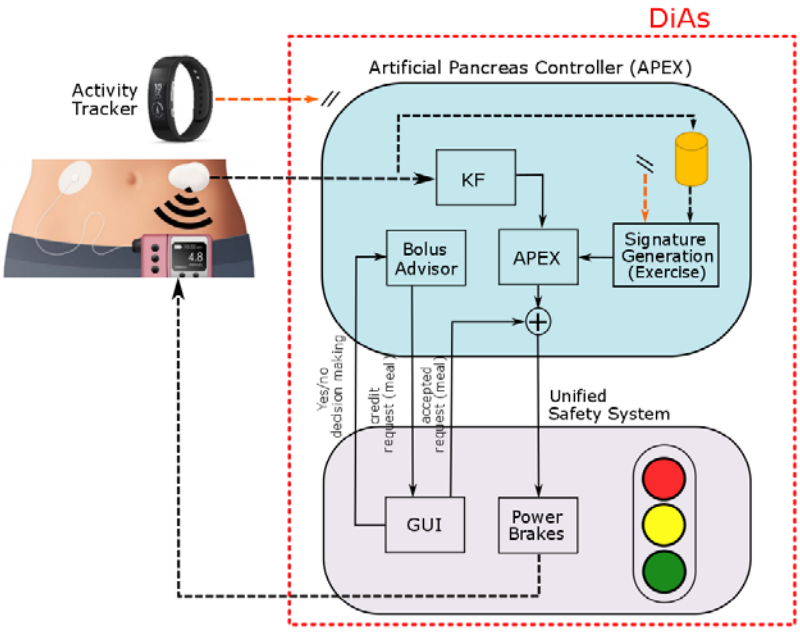

Figure 5-1: EnMPC System Architecture

All modules are implemented on the DiAs platform and together form the safety and control algorithms: (i) exercise-informed artificial pancreas controller (APEX), (ii) activity-informed pre-meal bolus; while (iii) the Power Brakes, and (iv) the IOB Supervisor form the safety system. The EnMPC Controller can be summarized as follows:

Once a new CGM value is received, the Kalman Filter (KF) estimates the current state of the system based on the individualized Subcutaneous Oral Glucose Minimal Model (SOGMM). Then, according to the exercise flag (exercise occurrence), the controller may take one of two modes of operation: (i) anticipative mode or (ii) reactive mode.

In anticipative mode, the controller is fed with 5-6 behavioral signatures (signatures extracted from participant-specific CGM, pump records, and activity tracker data from data collection period) which will help to anticipate the appearance of exercise according to the participant behavior.

In reactive mode, i.e., when exercise mode is detected, the controller is fed with a single 5-min exercise signal every sampling time.

5.1.3 Pre-Admission Check-in Visit

All participants will be contacted by the study team approximately 1 week prior to each of the scheduled admission dates to verify the following information:

- Inquire about any changes to the participant's medical history
- Verify that the subject has downloaded their insulin pump, CGM, and activity tracker; and verify that that data is of sufficient quality
- Determine what pump profile(s) the subject uses on certain days
- Verify that a new CGM sensor will be placed approximately 2 days prior to the admission
- 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 rescheduled at the discretion of the investigator.

5.1.4 Admission Procedures – Control and Experimental Admissions (Main Study)

Participants will arrive to the hotel at approximately 10 a.m. on the first day of the admission. The study team will perform vital signs and inquire about any changes to the participant's medical history. Any changes to medical history will be communicated to the medical physician to ensure continued eligibility and participation. If the participant's CGM is greater than 300 mg/dL despite corrective action, they may be asked to reschedule the admission. The participant's personal insulin pump will be discontinued and the study insulin pump will be placed. The study team will ensure the proper function of the CGM, insulin pump, and activity tracker.

By approximately 11 a.m. on the first day, the participant's devices will be placed into closed-loop. The closed-loop controller used during this admission will be determined based on whether it is the Control (rMPC) or Experimental (EnMPC) Admission.

The participants will be given lunch at approximately 1 p.m. The lunch will consist of the same, or similar if needed, meal on both days of the admission and for both admissions. The meal will be limited to a maximum of 60 grams of carbohydrates.

In the afternoon, participants will be transported (e.g. hotel shuttle) to a gymnasium for the exercise session, which will begin at approximately 5:30 p.m. The exercise session will consist of three 15 minute intervals of moderate cardiovascular exercise, separated by 5 minutes of rest. The exercise will be targeted to maintain a heart rate of approximately 110-140 beats per minute.

After the exercise session is complete, participants will be transported back to the hotel. Participants will be provided with dinner at approximately 7 p.m. which may occur at the hotel or CRU. This dinner will be the same, or similar if needed, for both admissions. Participants will continue with quiet activities for the rest of the evening.

On day 2 of the admission, participants will be given breakfast at approximately 7 a.m. This breakfast will be the same, or similar if needed, for both admissions. Participants will be free to engage in low-intensity activity (walking, shopping) during the morning hours.

Participants will be given lunch on day 2 at approximately 1 p.m. After lunch, participants will engage in quiet activities until approximately 7 p.m. Personal CGM equipment may be initiated during the afternoon to allow for proper warmup of equipment. At the completion of first hotel admission, the study CGM will be worn until discharge or until the current sensor expires. A study

CGM receiver/study phone may be provided if they are unable to access CGM values on their personal smart phone. Participants completing the second hotel admission will return all study equipment. Participants will be discharged at approximately 7 p.m. when the glycemic guidelines are within parameters as outlined in 5.1.6. Dinner or a snack will be offered to the subject at the conclusion of the trial on day 2 and is not required to be identical/similar to the day 1 dinner.

5.1.5 Admission Procedures – Pilot Admission (Pilot Study)

Participants in the Pilot study will complete the Day 1 activities of both the control and experimental exercise admissions in a single two-day admission as outlined here.

Participants will arrive to the hotel at approximately 10 a.m. on the first day of the admission. The study team will perform vital signs and inquire about any changes to the participant's medical history. Any changes to medical history will be communicated to the medical physician to ensure continued eligibility and participation. If the participant's CGM is greater than 300 mg/dL despite corrective action, they may be asked to reschedule the admission. The participant's personal insulin pump will be discontinued and the study insulin pump will be placed and initiated. The study team will ensure the proper function of the CGM, insulin pump, and activity tracker.

By approximately 11 a.m. on the first day, the participant's devices will be placed into closed-loop. The closed-loop controller used on the first day of the admission will be the experimental (EnMPC) controller.

The participants will be given lunch at approximately 1 p.m. The lunch will consist of the same, or similar if needed, meal on both days of the admission. The meal will be limited to a maximum of 60 grams of carbohydrates.

In the afternoon, participants will be transported (i.e. hotel shuttle) to a gymnasium for the exercise session, which will begin at approximately 5:30 p.m. The exercise session will consist of three 15 minute intervals of moderate cardiovascular exercise, separated by 5 minutes of rest. The exercise will be targeted to maintain a heart rate of approximately 110-140 beats per minute.

After the exercise session is complete, participants will be transported back to the hotel. Participants will be provided with dinner at approximately 7 p.m. Participants will continue with quiet activities for the rest of the evening.

On day 2 of the admission, participants will be given breakfast at approximately 7 a.m. The closed-loop controller used on the second day of the admission will be the Control (rMPC) controller. Participants will be free to engage in low-intensity activity (walking, shopping) during the morning hours.

Participants will be given lunch on day 2 at approximately 1 p.m. In the afternoon, participants will be transported to a gymnasium for a similar exercise session as the previous day, which will begin at approximately 5:30 p.m. The exercise session will consist of three 15 minute intervals of moderate cardiovascular exercise, separated by 5 minutes of rest. The exercise will be targeted to maintain a heart rate of approximately 110-140 beats per minute. Participants will be transported back to the hotel after the exercise session.

Participants will be provided with dinner at approximately 7 p.m. Participants will continue with quiet activities for the rest of the evening.

On day 3 of the admission, participants will be given breakfast at approximately 7 a.m. Discharge will be at approximately 7-10 a.m. if the glycemic guidelines are within parameters outlined in 5.1.6. A snack will be offered to the participant at the time of discharge.

5.1.6 Post-Admission Check-in Visit

Study staff will contact the participant within 24-48 hours after discharge to discuss any medical events that may have occurred since the hotel admission. If the second hotel admission (or first Main study admission for Pilot subjects) is 2 days after the first admission, this information will be obtained in-person at the hotel.

5.1.7 Glycemic Guidelines during Admissions

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 is >300 mg/dL for more than 1 hour or >400 mg/dL at any time, study physician will be notified to suggest appropriate treatment and ketones will be checked. If ketone concentration is >0.6 mmol/L, the study team will check the insulin pump infusion site and correction insulin will be administered per study physician judgement via the subject's insulin pump or study-supplied insulin pens. The study team will monitor CGM changes and ketones will be checked every 60 minutes until ketone concentration is ≤0.6 mmol/L.

If ketone concentration is ≥3.0 mmol/L, the study subject will be discontinued, DiAs will be changed to Stopped mode, and appropriate medical treatment will be sought. If the subject is discontinued, he/she may repeat the admission at the discretion of the PI.

If CGM <60 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.

CGM must be ≥80 mg/dL to initiate exercise. If CGM is <80 mg/dL *and* has vertical downward trending arrows at any time during an exercise session, subjects will suspend the exercise activity and take approximately 8-16 grams of fast-acting rescue carbohydrates. Study team will monitor CGM rise and will consider treating again if CGM is <80 mg/dL after approximately 20 minutes. Exercise activity will resume once CGM is ≥80 mg/dL.

Prior to the subject being discharged from the admission after either completing the study procedures or discontinuation, the CGM and ketones will be checked. The subject will be discharged once the CGM reading is between 80-250 mg/dL and ketone concentration is ≤0.6 mmol/L.

5.2 Repeating Visits & Unscheduled Visits

Participants may repeat one or both of the exercise admissions once. Reasons for repeating the admissions may include discontinuation by the subject or investigator due to safety concerns or poor data collection. Repeating an admission will be at the discretion of the investigator.

Participants may have unscheduled visits during the study period if required for additional device training or other unanticipated needs per the study investigator discretion.

5.3 Participant Access to Study Device at Study Closure

Participants will return all investigational study devices and supplies (Fitness tracker, CGM, insulin pump, and related supplies) at study closure.

Chapter 6: Study Devices

6.1 Description of the Investigational Device

6.1.1 EnMPC Artificial Pancreas Controller

The EnMPC controller is an investigational software device. This investigational controller utilizes data obtained from the insulin pump, CGM, and activity tracker to administer the desired amount of insulin [**Figure 5-1**].

6.1.2 Insulin Pump

The insulin pump utilized during the Data Collection Phase of the study will be the participant's personal insulin pump. The insulin pump must be FDA approved for the administration of subcutaneous insulin in order to participate.

The insulin pump utilized during the admissions will be the Tandem t:AP insulin pump. This pump is derived from the t:slim pump which is FDA approved for the administration of subcutaneous insulin for patients with diabetes, but not approved as such. The t:AP has been used in a dozen AP trials in conjunction with a variety of control systems including DiAs over the past 6 years.

6.1.3 Continuous Glucose Monitoring

The CGM utilized during all portions of the study is the Dexcom G6. The G6 is FDA approved for the non-adjunctive measurement of blood glucose and will be the primary source of blood glucose measurements in all phases of the study (data collection and during admissions).

6.1.4 Activity Tracker

The activity tracker used during the Data Collection Phase of the study may be the Fitbit Charge 2 or the Sony Smartband 2.

The activity tracker used during the admissions is the Sony Smartband 2 as it is compatible with the use of the investigational controller.

The activity trackers will be used for the step count and heart rate capabilities and both the Fitbit and Sony devices will be considered equivalent in this regard.

6.1.5 Blood Glucose Meter and Strips

Blood glucose levels will be measured using the study-assigned blood glucose meter (glucometer) when indicated for calibration or at the investigator's discretion.

6.1.6 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 component of the Precision Xtra device will not be used.

6.1.7 Study Device Accountability Procedures

Study staff will be responsible for the accountability and will maintain records of all study devices.

6.1.8 Blood Glucose Meter Testing

All study blood glucose meters will be QC tested 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.

6.1.9 Blood Ketone Testing

All study blood ketone meters will be QC tested 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.

6.2 Safety Measures

6.2.1 CGM Calibration

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

6.2.2 System Failure

If the CGM signal becomes unavailable for more than 20 minutes consecutively, the closed-loop will not operate to automatically adjust insulin. If the CGM is not connected, the system will revert to usual function of the pump and deliver insulin with the insulin dosing parameters programmed in the system for that individual. Resumption of close-loop control will occur automatically once CGM signal is available again.

If the study system is unable to activate closed-loop control, the pump will automatically revert to preprogrammed basal insulin delivery without the need for instruction from the user.

If the t:AP detects a system error that does not allow the pump to operate, the Malfunction Alarm will display and the study team will be instructed to contact Tandem Technical Support.

6.2.3 Hypoglycemia Threshold Alert and Safety Protocol

During the course of the study, participants will be permitted to change the CGM low glucose threshold alert setting on their device or mobile app, but will be instructed to choose a value no less than 60 mg/dL.

The DiAs will sound an alert if BG is predicted to be below 70mg/dL within the next 15 minutes.

Instances of hypoglycemia will be treated as outlined in the Glycemic Guidelines section 5.1.6

6.2.4 Hyperglycemia Threshold Alert and Safety Protocol

During the course of the study, participants will be permitted to change the CGM high glucose threshold alert setting on their device or mobile app, but will be instructed to choose a value no greater than 300 mg/dL.

If the participant receives a high alert, a message appears on the UI that is accompanied by an audible alarm. This alert remains on the screen until acknowledged by the user.

If a participant's CGM reading is >300 mg/dL for over 2 hours or ≥400 mg/dL at any point, the Glycemic Guidelines will be followed as outlined in section 5.1.6.

Chapter 7: Testing Procedures

7.1 Laboratory/POC Testing

1. Hemoglobin A1C

Performed using DCA2000 (or equivalent) point of care or may be obtained at a local laboratory. A historical value within 2 weeks of enrollment may be used at discretion of the investigator.

2. Pregnancy Test (HCG urine or blood)

Performed locally for females of child-bearing potential at the Screening Visit and at the beginning of all study admissions. This will also be done anytime pregnancy is suspected.

3. Comprehensive Metabolic Panel (CMP) (at discretion of study physician)

A panel of 14 blood tests which serves as an initial broad medical screening tool. The CMP provides a rough check of kidney function, liver function, diabetic, and electrolyte and fluid balance. A historical lab values within 52 weeks of enrollment may be used. . May be obtained at a local laboratory or at the screening appointment.

Chapter 8: Adverse Events, Device Issues, and Stopping Rules

8.1 Adverse Events

8.1.1 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 (see 8.1.2 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)).

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, site will not be asked to distinguish between device complaints and malfunctions.

8.1.2 Reportable Adverse Events

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

1. A serious adverse event

2. Hypoglycemia meeting the definition of severe hypoglycemia as defined below
3. 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. Skin reactions from sensor placement are only reportable if severe and/or required treatment.

Pregnancy occurring during the study will be recorded.

8.1.2.1 Hypoglycemic Events

Hypoglycemia 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.

8.1.2.2 Hyperglycemic Events/Diabetic Ketoacidosis

Hyperglycemia 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 ≥1.0 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.

8.1.3 Relationship of Adverse Event to Study Device

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

8.1.4 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.

8.1.5 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.

8.2 Reportable Device Issues

All UADEs, 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

8.3 Pregnancy Reporting

If pregnancy occurs, the participant will be discontinued from the study. The occurrence of pregnancy will not be considered an adverse event.

8.4 Timing of Event Reporting

Unexpected SAEs that are related or possibly related must be reported to the UVA IRB-HSR within 24 hours of awareness by the study team via the online serious adverse event form. UADEs must be reported to the UVA IRB-HSR within 10 calendar days of awareness by the study team via completion of the online serious adverse event form. The study team will notify the Medical Monitor of these events in parallel adhering to the same timelines.

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.

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

8.5 Stopping Criteria

8.5.1 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
- Participant pregnancy
- Two distinct episodes of DKA
- Two distinct severe hypoglycemia events as defined in 8.1.2.1

If pregnancy occurs, the participant will be discontinued from the study entirely. If a participant discontinues the study device for another reason, the participant may repeat the admission at the discretion of the investigators.

8.5.2 Participant Discontinuation during Exercise

Rules for discontinuing during exercise use are described below.

- If the subject feels unwell
- If the subject develops hypoglycemic symptoms, such as excessive sweating, shaking/tremors, palpitations, feelings of dread or panic, light-headedness, nausea, difficulty concentrating, etc…
- If the subject develops chest pain/pressure
- If the subject develops undue shortness of breath (SOB)
- Signs of poor perfusion: light-headedness, confusion, ataxia, pallor, cyanosis, nausea, or cold and clammy skin
- For patient preference

Subjects may be rescheduled for future testing/admission at the discretion of the study physician.

8.5.3 Criteria for Suspending or Stopping Overall Study

In the case of a system malfunction resulting in a severe hypoglycemia or severe hyperglycemia event (defined in 8.1.2.1 and 8.1.2.2, use of the study device system will be suspended while the problem is diagnosed.

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 be informed of all serious adverse events and any unanticipated adverse device events that occur during the study and will review compiled safety data at periodic intervals. 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.

8.6 Risks

The potential risks associated with use of the study devices are described in 1.3.1.

Additional risks are minor and/or infrequent and include:

- Pain, bruising, redness, or infection from blood draws
- Loss of confidentiality

Chapter 9: Miscellaneous Considerations

9.1 Drugs Used as Part of the Protocol

Participants will use either lispro or aspart insulin prescribed by their personal physician.

9.2 Prohibited Medications, Treatments, and Procedures

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.

Treatment with any non-insulin glucose-lowering agent (including metformin, GLP-1 agonists, pramlintide, DPP-4 inhibitors, SGLT-2 inhibitors, biguanides, sulfonylureas and naturaceuticals) will only be permitted if the regimen is stable. This will be at the investigator's discretion.

The study devices (study CGM systems, insulin pump, fitness tracker) 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.

9.3 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.

9.4 Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. De-identified participant information may be provided to Tandem Diabetes, Inc. and/or Dexcom, Inc. for system evaluation purposes.

Chapter 10: Statistical Consideration

10.1 Statistical and Analytical Plans

We will conduct a paired comparison of outcomes between each admission (Control vs. Experimental), using Student paired t-test for percent in ranges and average CGM, and Wilcoxon test for overtly non normally distributed outcomes such as % time below 70mg/dL (as well as 550, or 60mg/dL) and % time above 250mg/dL (or 300). Furthermore, we will use repeated measure ANOVA 2x2 with within factors if covariates are deemed necessary in the analysis

10.2 Statistical Hypotheses

The hypotheses for the primary outcome are:

a. Null Hypothesis: There is no difference in the occurrence of hypoglycemia during and immediately after exercise (~5:30pm-7pm) between EnMPC and rMPC

b. Alternative Hypothesis: There is a difference in the occurrence of hypoglycemia during and immediately after exercise (~5:30pm-7pm) between EnMPC and rMPC

10.3 Sample Size

It is important to note that this is a safety/feasibility study of a novel system and we therefore cannot accurately estimate effect size. Nonetheless, based on recently presented data on basal reduction 90min prior to exercise as well as our previous exercise AP studies, we are basing our sample size computation on a medium to large effect size of 0.7. With 80% power at a significance of 0.05, this leads to 15 participants completing the study.

10.4 Outcome Measures

10.4.1 Primary Efficacy Endpoint

- # of hypoglycemic occurrences immediately before, during, and immediately after exercise (~5-7pm) as defined by more than one consecutive CGM values below 70mg/dL or hypoglycemic treatment per glycemic guidelines.

10.4.2 Secondary Efficacy Endpoints

Additional CGM outcomes will include:

- Percent CGM below 50mg/dL
- Percent CGM below 54mg/dL
- Percent below 60mg/dL
- Percent CGM below 70mg/dL
- Percent CGM between 70 and 180mg/dL
- Percent CGM above 180mg/dL
- Percent CGM above 250mg/dL

- Percent CGM above 300mg/dL
- Average CGM
- CGM coefficient of variation
- CGM based LBGI & HBGI

Furthermore, we will compute

- Total amount of insulin used
- Number of Hypoglycemic episodes as defined by contiguous CGM below 70mg/dL
- Number of rescue CHO
- Total amount of rescues CHO

All variables will be analysis across the whole admission and for specific time segments (e.g. exercise, overnight, meals)

10.4.2.1 Safety Analyses

All randomized participants will be included in these analyses and the circumstances of all reportable cases of the following will be summarized and tabulated by treatment group:

- Severe hypoglycemia
- Diabetic ketoacidosis
- Other serious adverse events and serious adverse device events
- Unanticipated adverse device effects

10.5 Baseline Descriptive Statistics

Baseline demographic and clinical characteristics of the cohort of all randomized participants will be summarized in a table using summary statistics appropriate to the distribution of each variable. Descriptive statistics will be displayed overall and by treatment group.

Will include:

- Age
- HbA1c
- Gender
- Race/ethnicity
- CGM use before enrollment
- Diabetes duration
- BMI

10.6 Device Issues

The following tabulations and analyses will be performed by treatment group to assess device issues:

- Device malfunctions requiring study team contact and other reported device issues
- Sensor performance metrics (difference, absolute relative difference, and International Organization for Standardization criteria) – if applicable, by sensor version.
- % time CGM data available - overall and by month

The following tabulations will be performed for the CLC arm only:

- Performance metrics, describing the CLC system and its components like:
  - % time CGM data were available to the CLC system – overall and by month
  - % time in different operational modes per week - overall and by month
  - Rate of different failure events and alarms per 48
  - hours recorded by the CLC system – overall and by month

Chapter 11: Data Collection and Monitoring

11.1 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.

11.2 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.

11.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, 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 study team awareness.

Chapter 12: Ethics/Protection of Human Participants

12.1 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.

12.2 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.

12.3 Informed Consent Process

12.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing 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 to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant 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. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants 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.

12.3.2 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.

Chapter 13: References

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