Signature Page

Control-IQ Technology in Individuals with Type 2 Diabetes (2IQ)

Protocol Identifying Number: TP-0009569

IND/IDE Sponsor: Tandem Diabetes Care, Inc.

Version Number: v. 3.0

19 Oct 2021

JCHR Protocol Director	
Name, degree	John Lum, MS / Jaeb Center for Health Research
Signature/Date	John Lum I am electronically signing this document 2021-11-09 09:01-05:00
Sponsor	Tandem Diabetes Care, Inc.
Name, degree	Jordan Pinsker, M.D.
Signature/Date	Jordan Pinsker Digitally signed by Jordan Pinsker Date: 2021.11.10 08:31:57 -08'00'
Clinical Lead Investigator	
Name, degree	Carol Levy, M.D. / Icahn School of Medicine at Mount Sinai
Signature/Date	carol levy Digitally signed by carol levy Date: 2021.11.10 14:13:13 -05'00'
Medical Monitor	
Name, degree	Roy Beck, MD, Ph.D. / Jaeb Center for Health Research
Signature/Date	Roy Beck I am digitally signing this document 2021-11-09 14:18-05:00

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KEY ROLES

Protocol Chair/Director	
Name, degree	Carol Levy, M.D.
Institution Name	Icahn School of Medicine at Mount Sinai
JCHR Coordinating Center Director	
Name, degree	John Lum, MS
Institution Name	Jaeb Center for Health Research
Medical Monitor	
Name, degree	Roy Beck, M.D., Ph.D.
Institution Name	Jaeb Center for Health Research
Sponsor	
Name, degree	Jordan Pinsker, M.D.
Institution Name	Tandem Diabetes Care, Inc. 11075 Roselle Street San Diego, CA 92121

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse Event
AID	Automated Insulin Dosing
AUC	(Glucose) Area under the curve
CGM	Continuous Glucose Monitoring
CRF	Case Report Form
Control-IQ System	t:slim X2 insulin pump with Control-IQ technology
CSII	Continuous Subcutaneous Insulin Infusion
DCA2000	Siemens/Bayer DCA 2000+ Hematology Analyzer
DKA	Diabetic Ketoacidosis
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ECG	Electrocardiogram
FDA	United States Food and Drug Administration
HbA1c	Hemoglobin A1c
HCL	Hybrid Closed-loop
HHS	Hyperosmolar Hyperglycemic Syndrome
ICF	Informed Consent Form
IDE	Investigational Device Exemption
MDI	Multiple Daily Injections of insulin
POC	Point-Of-Care
QC	Quality Control
QoL	Quality of Life
SD	Standard Deviation
T2D	Type 2 diabetes
TDD	Total Daily Dose of insulin
TIR	Time in range

SITE PRINCIPAL INVESTIGATOR STATEMENT OF COMPLIANCE

Protocol Title: Control-IQ Technology in Individuals with Type 2 Diabetes (2IQ)

Protocol Version/Date: 3.0 / 19 Oct 2021

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 and providing the Jaeb Center for Health Research, which serves as the Coordinating Center for the protocol, with complete and timely information, as outlined in the protocol. 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 the principles of Good Clinical Practice (GCP) and as required by the following (use applicable regulations depending on study location and sponsor requirements; examples follow): 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: _____

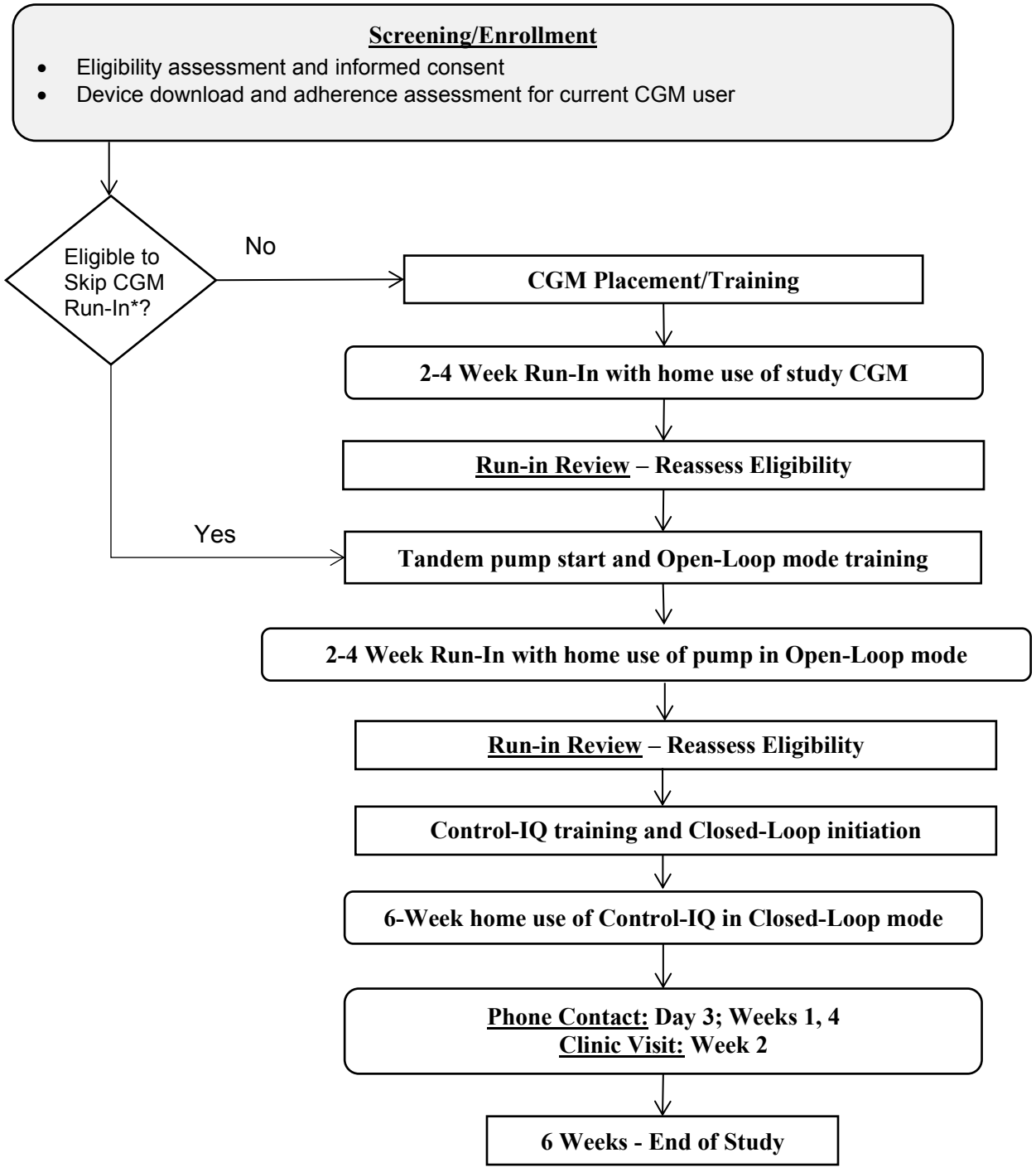
Site Name/Number: _____

PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	Control-IQ Technology in Individuals with Type 2 Diabetes (2IQ)
Précis	A prospective, single-arm study of 6 weeks of home use of the Control-IQ automated insulin delivery system in individuals with type 2 diabetes age 18 and older.
Investigational Device	t:slim X2 insulin pump with Control-IQ technology v1.5 (Control-IQ System)
Objectives	The objectives of the study are to assess safety and explore glycemic outcomes with use of a closed loop control (CLC) system (t:slim X2 with Control-IQ Technology) in adults with type 2 diabetes to provide data to design a subsequent larger study.
Study Design	After an initial run-in period to ensure that participants can successfully use the study CGM and study pump in open-loop mode, all participants will use the study system (pump and CGM) in closed-loop mode for 6 weeks.
Number of Sites	~3 US clinical centers
Key Safety Endpoints	Key Safety Endpoints: • Severe Hypoglycemia • Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic Syndrome • Other reportable adverse events (see section 7.2.2) • Unanticipated adverse device effects
Other Endpoints	Other Endpoints: • CGM-measured % below 54 mg/dl • CGM-measured % above 180 mg/dL • CGM-measured post-prandial glycemic peak • Various other CGM-measured glycemic outcomes over 24 hours, daytime, and nighttime, as well as CGM outcomes with respect to announced meals • Total daily insulin use, daily basal and bolus insulin, and Weight *Primary and secondary endpoints will be analyzed in total together, as well as separately for Group A (prior users of basal insulin only) and Group B (prior users of multiple daily injections) participants.*
Population	**Inclusion Criteria** 1. Age ≥18 years old and residing in the US 2. Clinical diagnosis, based on investigator assessment, of type 2 diabetes for at least one year 3. Using a stable insulin dose for at least 3 months, to include A) basal insulin only, or B) MDI, to include CSII (including use of AID systems other than Tandem Control-IQ) 4. Total daily insulin dose ≤200 units/day 5. Willing to use only aspart (novolog) or lispro (humalog) insulin with the study pump, with no use of concentrated insulin above U-100, long-acting basal insulin injections, or inhaled insulin 6. For females, not currently known to be pregnant *If female of child-bearing potential, must agree to use a form of contraception to prevent pregnancy while a participant in the study as documented in the study records. A negative serum or urine*

PARTICIPANT AREA	DESCRIPTION
	pregnancy test will be required for all females of child-bearing potential. Participants who become pregnant will be discontinued from the study. Also, participants who during the study develop and express the intention to become pregnant within the timespan of the study will be discontinued. 7. HbA1c ≥ 7.5% and ≤ 12% at screening 8. Has current glucagon product to treat severe hypoglycemia (injectable or nasal) at home (*will provide prescription if they do not have one*) 9. Be willing to exercise for 30 minutes or more at least once per week during the main phase of the study 10. Has the ability to read and understand written English. 11. Investigator believes that the participant has the capacity such that they can provide informed consent and successfully and safely operate all study devices and is capable of adhering to the protocol and completing the study **Exclusion Criteria** 1. Prior use of Tandem t:slim X2 insulin pump with Control-IQ technology 2. Two or more episodes of severe hypoglycemia (needing assistance) in the past 6 months 3. History of inpatient psychiatric treatment in the past 6 months 4. History of drug abuse (defined as any illicit drug use) or history of alcohol abuse prior to screening or unwillingness to agree to abstain from illicit drugs throughout the study. 5. History of significant heart disease, lung disease, liver disease, chronic kidney disease, or other systemic disease determined by investigator to interfere with the study, or make required exercise unsafe 6. History of significant vision, hearing, or dexterity problems that will impair use of the closed loop system 7. Use of glucocorticoids, beta blockers, sulfonylureas, meglitinides or other medications specifically listed in section 8.3 of the protocol or determined by investigator to interfere with the study 8. Unstable dose of SGLT-2 inhibitor, GLP-1 receptor agonist, or other adjuvant medication specifically listed in section 8.3 of the protocol, or starting a new glucose lowering agent during the trial. 9. Unstable dose of any medication used for weight loss, as listed in section 8.3 of the protocol, or starting a new medication for weight loss during the trial. 10. Abnormal screening electrocardiogram consistent with increased risk during exercise, such as arrhythmia, ischemia, or prolonged QTc interval (>450 ms) 11. History of hemodialysis 12. History of adrenal insufficiency 13. Uncontrolled hypo- or hyperthyroidism 14. Significant diabetes related complications, based on investigator assessment 15. Immediate family member (spouse, biological or legal guardian, child, sibling, parent) who is an investigative site personnel directly affiliated with this study or who is an employee of Tandem Diabetes Care, Inc.

PARTICIPANT AREA	DESCRIPTION
Sample Size	Up to 30 individuals initiating use of the study system in closed-loop mode, with the goal of at least 24 completing the trial
Treatment Groups	All participants will use the study-assigned Control-IQ pump in closed-loop mode.
Participant Duration	~8-12 weeks, depending on duration of run-in phase
Study Duration (planned)	~5 months from first enrollment until last participant visit
Protocol Overview/Synopsis	After consent is signed, eligibility will be assessed. Eligible participants not currently using a Dexcom G6 CGM or using a Dexcom G6 CGM with <85% of possible glucose values captured during the 14 days prior to enrollment will initiate a CGM run-in phase of 2-4 weeks. Participants who skip or successfully complete the CGM run-in will be trained on use of the study pump in open-loop mode and will initiate a pump run-in phase of 2-4 weeks that will include insulin therapy adjustment to optimize open-loop glycemic control. Participants who successfully complete the open-loop pump run-in will be trained on use of the study pump in closed-loop mode and will use the study system (pump and CGM) in closed-loop mode for 6 weeks. Subjects will be asked to use programmed sleep activity each night and perform exercise challenges with exercise mode enabled at least once per week. Questionnaires will be given at the screening visit after consent; before starting closed-loop use (Control-IQ Phase); and after 6 weeks of closed-loop use. Semi-structured interviews will be performed at the end of the study to better determine the experience of using the study device <u>Study Safety Plan</u>: Participants will be given a blood glucose and ketone meter to use throughout the study, and will be trained on their use by qualified staff. BGM readings will be performed in accordance with the study safety plan and per CGM manufacturer instructions. Ketone readings will be performed per the study safety plan. Site investigators may adjust insulin delivery profile settings as needed throughout the study in accordance with their clinical practice.



* Current use of Dexcom G6 CGM with at least 85% of possible readings captured during the 14 days prior to enrollment

Figure 1: Schematic of Study Design

Table 1: Schedule of Study Visits and Procedures

	Screen-ing Visit	CGM Run-in Visit (may be repeated after 2 weeks)	Pump Training Visit and Settings Optimization (may be repeated after 2 weeks)	Control-IQ Closed-Loop Training Visit	Control-IQ Closed-Loop Use							
		2-4 weeks	2-4 weeks		3d	1w	2w	4w	6w	+3d	UV	Exercise[3]
Visit (V) or Contact (C)	**V**	**V**	**V**	**V**	**C**	**C**	**V**	**C**	**V**	**C**	**V/ C**	**C**
Informed Consent	**X**											
Eligibility Assessment	**X**											
Medical history/ physical exam	**X**											
Height, weight, blood pressure and pulse	**X**			**X[2]**					**X[2]**			
HbAlc (POC or local lab)	**X**											
Central Lab: C-peptide and Glucose; HbA1c	**X**											
ECG	**X**											
Pregnancy test (females of child-bearing potential)	**X**			**X**								
Questionnaires/Surveys	**X**		**X**	**X**					**X**			
Semi-structured interview									**X[1]**			
Assessment of CGM use	**X**	**X**										
Study system training		**X**	**X**	**X**							**X**	
AE Assessment		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Upload device data from home					**X**	**X**		**X**			**X**	
Download device data at clinic visit		**X**	**X**	**X**			**X**		**X**		**X**	

[1] Interview completed within 28 days of completion of 6-Week visit

[2] Weight only

[3] Participants will be instructed to contact study staff after each exercise challenge to review AE's and diabetes management around exercise.

Chapter 1: Background Information

1.1 Disease Background

More than 34 million people in the United States have diabetes, with type 2 diabetes accounting for approximately 90% to 95% of cases. In the last 20 years, the number of adults diagnosed with diabetes has more than doubled as the American population has aged and become more overweight or obese. Diabetes is the 7th leading cause of death in the United States (and may be underreported).

Insulin pump use in individuals with type 2 diabetes is relatively low. However, there is an increasing uptake of insulin pump use in this population. The benefits of insulin pump use with Automated Insulin Dosing (AID) technology in individuals with type 2 diabetes has not been well established in clinical trials, although long term follow-up of real-world data has shown AID use with Control-IQ technology can show significant glycemic benefits in this population, whether transitioning from multiple daily injections (MDI) or prior pump use. Retrospective analysis of 134 prior pump users with type 2 diabetes who purchased a new Tandem insulin pump with Control-IQ technology showed time in range was 76% (IQR 69-82%) and time below range was 0.5% (IQR 0.2-1.0%) at 180 days out. For 173 participants transitioning from MDI, use of Control-IQ technology resulted in time of range of 74% (IQR 63-84%) and time below range 0.3% (IQR 0.1-0.6%) at 180 days of use (1). Additionally, retrospective analysis of real-world use out to one year in 378 individuals with type 2 diabetes who software updated from Basal-IQ technology to Control-IQ technology showed significant improvements in time in range 70-180 mg/dL (69% at baseline, 78% at one year) (2).

1.2 Device Background

The t:slim X2 insulin pump with Control-IQ technology is an advanced hybrid closed-loop (HCL) system, developed and manufactured by Tandem Diabetes Care, Inc. and cleared in the U.S. by the FDA for individuals with type 1 diabetes. Control-IQ is integrated with the Dexcom G6 continuous glucose monitor (CGM) and uses CGM values to predict glucose values 30 minutes in the future. Based on the predicted glucose, Control-IQ modulates basal insulin delivery, and delivers automated correction boluses to mitigate impending hyperglycemia. The current Control-IQ system is FDA approved down to age 6 years old for individuals with type 1 diabetes, and has been found to improve time in range (70-180 mg/dL) and decrease both time <70 mg/dL and time >180 mg/dL (3,4). There are over 150,000 users of the system since it became commercially available in 2020. A recent evaluation of real-world use of the system in 9,451 users age ≥6 years with at least 12 months of system use found results comparable to those found in the randomized trials (2).

Figure 2. t:slim X2 with Control-IQ and Dexcom G6 system

Since the initial approval of the system, modifications have been made in the software, which is referred to as version 1.5. These modifications include modest usability improvements and other enhancements intended to further reduce risk. The Control-IQ 1.5 algorithm also removes the 3 units/hr basal clipping, allowing the pump to deliver programmed user profile basal rates above 3 units/hr. This has the potential to further improve outcomes in individuals with type 2 diabetes who are often using basal rates at or above this threshold.

1.3 Rationale

The objective of this single-arm, prospective study is to assess safety and explore glycemic outcomes associated with use of the Control-IQ system in adults with type 2 diabetes to provide data to design a subsequent larger study.

1.4 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 securely to minimize this risk. Hypoglycemia and hyperglycemia and ketone formation are always a risk in participants with type 2 diabetes and insulin treatment, and participants will be monitored for this.

1.4.1 Known Potential Risks

1.4.1.1 Potential Risks and Benefits of the CLC System

Even though the study system has been tested prior to this study, there is still a risk that parts of the system may not function properly. The following are possible reasons the system may deliver too much insulin or incorrectly stop insulin delivery:

- CGM sensor reads higher or lower than the actual glucose level which increases risk for hypoglycemia and hyperglycemia with automated insulin delivery system;
- Device malfunctions that could produce a suspension of insulin delivery or over delivery of insulin.

1.4.1.2 Risk of Hypoglycemia

As with any person having diabetes and using insulin, there is always a risk of 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.

1.4.1.3 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. Although less common in individuals with type 2 diabetes than in those with type 1 diabetes, DKA can still occur. Extreme levels of hyperglycemia and dehydration can lead to hyperosmolar hyperglycemic syndrome (HHS). A CGM functioning poorly and significantly under-reading glucose values could lead to inappropriate suspension of insulin delivery. All subjects will be issued a glucose meter and glucose test strips, as well as a ketone meter and ketone test strips, to use to carefully monitor for hyperglycemia and ketones and be given instructions on how to mitigate hyperglycemia and ketosis should it occur.

1.4.1.4 Fingerstick Risks

About 1 drop of blood will be removed by fingerstick for measuring blood glucose and sometimes Hemoglobin A1c (HbA1c). This is a standard method used to obtain blood for routine hospital laboratory tests. Pain is common at the time of lancing. In about 1 in 10 cases, a small amount of bleeding under the skin will produce a bruise. A small scar may persist for several weeks. The risk of local infection is less than 1 in 1000. This should not be a significant contributor to risks in this study as fingersticks are part of the usual care for people with diabetes.

1.4.1.5 Venipuncture Risks

A hollow needle/plastic tube may 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.

1.4.1.6 Subcutaneous Catheter Risks

Whenever the skin is broken there is the possibility of bleeding and bruising. The CGM sensor and pump infusion sets are inserted under the skin. It is possible that any part that is inserted under the skin may cause an infection, which could produce swelling, redness, and pain. These occur very infrequently, but if an infection were to occur, oral and/or topical antibiotics may be prescribed. The risk of skin problems could be greater if a sensor or infusion set is used for longer than it is intended to be used. Therefore, participants will be carefully instructed about proper use of these components.

On rare occasions, the CGM sensor may break and leave a small portion of the sensor probe under the skin that may cause redness, swelling or pain at the insertion site. The participant will be instructed to notify the site immediately if this occurs.

1.4.1.7 Risk of Exercise

Exercise may lead to injury, hypoglycemia or hyperglycemia, or significant events, such as myocardial infarction or other significant cardiac event. Subjects will be instructed on how to prepare for exercise by study staff, and intended use of the exercise activity feature. All subjects will undergo a screening ECG to assure exercise can be completed safely.

1.4.1.8 Risk of Device Reuse

All devices will be used by a single study participant only. There will be no device reuse.

1.4.1.9 Questionnaires and Semi-Structured Interviews

As part of the study, participants will complete questionnaires and participate in one-on-one semi-structured interviews which include questions about their private attitudes, feelings and behavior related to the investigational equipment as well as managing diabetes. It is possible that some people may find these questionnaires and interviews to be mildly upsetting. Similar questionnaires and interviews have been used in previous research and these types of reactions have been uncommon.

1.4.1.10 Other Risks

Some participants may develop skin irritation or allergic reactions to the adhesives used to secure the CGM, or from tape 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.

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. Downloaded data from the participant's personal CGM or pump (if any) will include data from prior to the date of the screening visit. Some people may be uncomfortable with the researchers' having such detailed information about their daily diabetes habits.

1.4.2 Known Potential Benefits

Participants may experience a significant improvement in glucose control. Hypoglycemia is the number one fear of many individuals taking insulin and this fear often prevents optimal glycemic control. Hyperglycemia will likely be reduced as well.

In addition, users of insulin pumps often take less insulin than users of basal/bolus injection therapy. This may lead to weight loss, which will be tracked over the course of the study.

It is expected that this protocol will yield increased knowledge about using an automated closed-loop to control glucose levels in people with type 2 diabetes. The individual participant may or may not benefit from study participation.

1.4.3 Risk Assessment

It is the assessment of the investigators that this protocol is a clinical investigation involving greater than minimal risk but that it does present the prospect of direct benefit to individual subjects based on the following: (1) individuals with diabetes experience mild hypoglycemia and hyperglycemia frequently as a consequence of the disease and its management, (2) the study intervention involves periodic automated insulin dosing that may reduce the likelihood of hypoglycemia, and periodic automated attenuation of insulin delivery that may reduce the likelihood of hyperglycemia, (3) if any, hypo and/or hyperglycemia occur, mitigations are in place, and have been tested in prior studies using the investigational device system in the home setting, that limit the likelihood of excessive insulin dosing or prolonged withdrawal of insulin, and (4)

rapid reversal of hypoglycemia and hyperglycemia can be achieved, In addition, it is the belief of the investigators that this study also presents prospect of general benefit to others with diabetes.

1.5 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).

There is no restriction on the number of participants to be enrolled by each clinical center toward the overall recruitment goal.

In accordance with 21 CFR 812.66, the protocol is considered a significant risk device study, due to the fact that the closed loop system is investigational in the population under study. 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

Enrollment will proceed with the goal of at least 30 participants initiating the main closed-loop study phase and 24 participants completing the trial. A maximum of 60 individuals may be consented for screening in order to achieve this goal. Participants who have signed consent and started the screening process may be permitted to continue into the trial, if eligible, even if the completion goal has been reached.

Study participants will be recruited from ~3 clinical centers in the United States. All eligible participants will be included without regard to gender, race, or ethnicity. Each site will be asked to contribute ~10 participants (5 basal only / 5 MDI) toward the overall recruitment goal.

2.1.1 Informed Consent and Authorization Procedures

Potential eligibility may be assessed as part of a routine-care examination. Before completing any procedures or collecting any data that are not part of usual care, documented informed consent will be obtained.

Once a potential study participant has been identified, 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 potential study participant is interested in the study, the investigator will schedule a virtual or in-person visit to discuss study, and if the potential study participant agrees to participate, the Informed Consent Form will be electronically signed through the JCHR website. A copy of the electronically signed consent form can be printed by the participant and another copy will be printed by the site to add to the participant's study record. The site shall print a copy of the signed consent for the participant any time at the participant's request, at no cost, and without undue delay.

As part of the informed consent process, each participant will be asked to sign an authorization for release of personal information. This will be done electronically as part of the consent process. The investigator, or his or her designee, will review the study-specific information that will be collected and to whom that information will be disclosed. After speaking with the participant, questions will be answered about the details regarding authorization.

A participant is considered enrolled when the informed consent form has been electronically signed by both the participant and the investigator, and HIPAA authorization has been provided.

This process shall be document in the study records at each site (e.g., consent process note).

2.2 Participant Inclusion Criteria

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

1. Age ≥18 years old and residing in the US
2. Clinical diagnosis, based on investigator assessment, of type 2 diabetes for at least one year

3. Using a stable insulin dose for at least 3 months, to include A) basal insulin only, or B) MDI, to include CSII (including use of AID systems other than Tandem Control-IQ)
4. Total daily insulin dose ≤200 units/day
5. Willing to use only aspart (novolog) or lispro (humalog) insulin with the study pump, with no use of concentrated insulin above U-100, long-acting basal insulin injections, or inhaled insulin
6. For females, not currently known to be pregnant
   If female of childbearing potential, must agree to use a form of contraception to prevent pregnancy while a participant in the study as documented in the study records. A negative serum or urine pregnancy test will be required for all females of child-bearing potential. Participants who become pregnant will be discontinued from the study. Also, participants who during the study develop and express the intention to become pregnant within the timespan of the study will be discontinued.
7. HbA1c ≥ 7.5% and ≤ 12% at screening
8. Has current glucagon product to treat severe hypoglycemia (injectable or nasal) at home *(will provide prescription if they do not have one)*
9. Be willing to exercise for 30 minutes or more at least once per week during the main phase of the study
10. Has the ability to read and understand written English
11. Investigator believes that the participant has capacity such that they can provide informed consent and can successfully and safely operate all study devices and is capable of adhering to the protocol and completing the study.

2.3 Participant Exclusion Criteria

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

1. Prior use of Tandem t:slim X2 insulin pump with Control-IQ technology
2. Two or more episodes of severe hypoglycemia (needing assistance) in the past 6 months
3. History of inpatient psychiatric treatment in the past 6 months
4. History of drug abuse (defined as any illicit drug use) or history of alcohol abuse prior to screening or unwillingness to agree to abstain from illicit drugs throughout the study.
5. History of significant heart disease, lung disease, liver disease, chronic kidney disease, or other systemic disease determined by investigator to interfere with the study, or make required exercise unsafe
6. History of significant vision, hearing, or dexterity problems that will impair use of the closed loop system
7. Use of glucocorticoids, beta blockers, sulfonylureas, meglitinides or other medications specifically listed in section 8.3 of the protocol or determined by investigator to interfere with the study
8. Unstable dose of SGLT-2 inhibitor, GLP-1 receptor agonist, or other adjuvant medication specifically listed in section 8.3 of the protocol, or starting a new glucose lowering agent during the trial.
9. Unstable dose of any medication used for weight loss, as listed in section 8.3 of the protocol, or starting a new medication for weight loss during the trial.

10. Abnormal screening electrocardiogram consistent with increased risk during exercise, such as arrhythmia, ischemia, or prolonged QTc interval (>450 ms)
11. History of hemodialysis
12. History of adrenal insufficiency
13. Uncontrolled hypo- or hyperthyroidism
14. Significant diabetes related complications, based on investigator assessment
15. Immediate family member (spouse, biological or legal guardian, child, sibling, parent) who is an investigative site personnel directly affiliated with this study or who is an employee of Tandem Diabetes Care, Inc.

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 study personnel and local laboratory testing if needed to screen for exclusionary medical conditions.

The screening visit must be completed within 28 days of participant enrollment.

2.4.1 Data Collection and Testing

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

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

- Inclusion and exclusion criteria assessed
- Demographics (date of birth, sex, race and ethnicity)
- Contact information (retained at the site and not entered into study database)
- Medical history, including existing comorbidities deemed clinically relevant (e.g. retinopathy, nephropathy, neuropathy, history of cardiovascular events); in addition, details specific to type 2 diabetes, including age at diagnosis, duration of disease, previous therapy, and frequency of severe hypoglycemia will be collected
- Concomitant medications
- Physical examination to include:
  - Weight, height
  - Vital signs including measurement of blood pressure and pulse
- An electrocardiogram (ECG) will be administered and read locally by the investigator to determine if the participant meets eligibility criteria with respect to the exercise component of the study
- Fingerstick or blood draw for point-of-care or local laboratory determination of baseline HbA1c level and any local laboratory testing required for eligibility assessment

- Blood draw for Central Lab determination of HbA1c and C-peptide with concurrent glucose level
- Urine or serum pregnancy test for all women who have reached menarche and are premenopausal and are not surgically sterile
    - Barrier methods, oral contraceptives, and implantable and/or IUD-type contraceptives are examples of methods that constitute acceptable methods of contraception for females of child-bearing potential, and will be discussed with all such females who are not postmenopausal or surgically sterile.
    - Females are considered premenopausal per investigator discretion, typically with less than 1 year since last menses.
- Participants will complete a set of baseline questionnaires, described in section 6.3

Screening procedures will last approximately 1-2 hours.

2.5 Screen Failures

Individuals who do not initially meet study eligibility requirements may be rescreened once at a later date per investigator discretion.

Chapter 3: CGM and Pump Run-in Phases

3.1 CGM Run-in Phase Overview

This phase must begin within 7 days of completion of the Screening visit. The purpose of this CGM run-in phase is to 1) assess compliance with study procedures and 2) to introduce the study CGM to study participants without current use of a Dexcom CGM.

Participants who currently use a Dexcom G6 CGM with at least 85% of possible CGM readings captured during the 14 days prior to enrollment can skip the CGM Run-in phase. Participants who do not currently use a Dexcom G6 CGM, or who do use that CGM but have <85% of possible CGM readings in the 14 days prior to the time of enrollment, will be required to participate in the CGM Run-in phase.

Participants will receive training on the study CGM as detailed below. This will be an unblinded use of the study CGM.

3.2 Initiation of CGM

During an in-clinic visit that may coincide with the Screening visit, study CGM supplies will be provided and the participant will be instructed to use the study CGM on a daily basis. Participants using a personal CGM prior to the study will discontinue the personal CGM beginning in this period.

3.2.1 CGM Training

CGM training will be provided by a qualified trainer to participants not currently using a personal CGM identical to the study CGM as to how to use it in real-time to make management decisions and how to review the data after an upload for retrospective review. CGM training will include:

- Instruction on how to insert the sensor and transmitter, including observation/supervision of placement of a sensor
- Instruction on how to calibrate the CGM unit, if needed
- Guidance on accessing the CGM trace, either through a manufacturer-provided software app or via a study-provided CGM receiver unit, or via a personal insulin pump if participants use a pump that integrates with the study CGM
- Participants will be asked to perform fingerstick blood glucose measurements in accordance with the labeling of the study CGM device

A copy of the study CGM user's guide will be provided to the participant.

Participants may use available manufacturer-provided CGM software and features of the study CGM related to mobile data access or remote monitoring, but will be instructed not to use any third-party components for this purpose. The t:connect mobile app from Tandem Diabetes Care will not be available for use during the trial, and will not pair to the study pump.

Upon completion of the CGM training components, study staff will document, using a checklist, that the participant is familiar with the functions/features/tasks addressed during the training.

3.3 Blood Glucose and Blood Ketone Testing

Participants will receive supplies for blood glucose and blook ketone testing.

- Blood glucose testing
  - Participants will be provided with a study blood glucose meter, test strips, and any software/hardware needed to download meter data .
  - All study blood glucose meters will be QC tested with control solution if available prior to dispensation. *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.*
  - Participants will be reminded to use the study blood glucose meter for all fingerstick BGs during the study.
  - Participants will be given guidelines for treatment of low or high blood glucose.
- Blood ketone testing
  - Participants will be provided with a study blood glucose meter, test strips, and any software/hardware needed to download meter data.
  - All study blood ketone meters will be QC tested with control solution if available prior to dispensation. *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.*
  - Participants will be reminded to use the study blood ketone meters per the study hyperglycemia safety plan
  - Participants will be given guidelines for treatment of positive ketone readings.
- Participants will be required to have glucagon at home. Participants who currently do not have one will be given a prescription for glucagon as part of standard care (either emergency kit for injections or nasal glucagon per investigator discretion).

3.4 Assessment of Successful Completion of the CGM Run-in Phase

Enrolled participants will have a follow-up visit approximately 14 days after initiation of the run-in phase to assess progress or successful completion of the phase. If needed, one or more interim visits or phone contacts may occur to assist the participant with any CGM use issues. Procedures will include downloading of the study CGM data and the following:

- Assessment of compliance with the use of CGM to obtain at least 85% of possible CGM valued during the run-in period
- Assessment of skin reaction in areas where a CGM sensor was worn or other safety issues associated with CGM use
- Assessment of eligibility to continue to the pump run-in phase of the study

Participants who fail to meet the minimum CGM use requirement, or who the investigator believes may benefit from an extension of the CGM run-in period, may at the investigator's discretion be allowed to continue CGM run-in for a second ~2-week period. These participants will have another follow-up visit approximately 14 days after the prior visit for a reassessment using the same procedures as described above.

Participants who do not meet CGM use requirements after two 2-week periods of CGM run-in or otherwise fail to meet study eligibility requirements will be withdrawn from the study.

3.5 Pump Run-in Phase Overview

This phase must begin either on the same day as the final CGM run-in review visit (for participants participating in CGM run-in) or within 7 days of completion of the Screening visit (for participants skipping the CGM run-in). The purpose of the Pump Run-in phase is 1) to assess compliance with study procedures and 2) to allow the participant to transition to the study insulin pump, learn how to use it in open-loop mode, and learn infusion set care.

Participants will receive training on use of the study pump in open-loop mode as detailed below.

3.6 Initiation of the Study Pump

During an in-clinic visit, the study pump, associated supplies, and training will be provided to participants and the participant will be instructed to use the pump in open-loop mode in conjunction with the study CGM until the Pump Run-in review visit.

3.6.1 Study Pump Training

Participants will receive study pump training on use of the pump in open-loop mode by a qualified trainer:

- Participants will be fully instructed on the study insulin pump. The trainer will discuss differences from the participant's personal pump, if applicable, in important aspects such as calculation of insulin on board and correction boluses and optional additional topics such as: infusion site initiation, cartridge/priming procedures, setting up the pump, charging the pump, navigation through menus, bolus procedures including stopping a bolus, etc.
- Participants will be instructed to change the study insulin pump infusion set at least once every 3 days or per manufacturer guidelines, whichever is shorter.
- Participants using bolus insulin doses at enrollment will be trained to use the pump's bolus calculator.
    - For subjects who may only bolus one or two meals a day, or use fixed bolus amounts as part of their prior treatment plan, they may continue to do this in the study, but they will be taught to enter the same number of units in the bolus calculator (Simplified Bolus Plan).
    - Additionally, it is possible during the study some subjects in the basal only group, or using simplified boluses, may realize the need to add boluses or begin using the bolus calculator, respectively. As such, they will be advanced in their bolus strategy per investigator discretion.
- The study team will assist the participant in study pump infusion site initiation and will start the participant on the study pump. The study pump will be programmed with the participant's usual basal rates and pump parameters, if applicable. The participant's personal pump, if any, will be removed.

- The participant will be supervised with the study pump during at least one meal or snack bolus to ensure participant understanding of the pump features.
- The participant will be encouraged to review the literature provided with the pump and infusion sets after the training is completed.
- The participant will be trained on severe hypoglycemia emergency procedures including removal of the study pump and administration of glucagon.
- What to do when exercising while using the system
- The participant will be assessed for understanding of the system interface and how to react to safety/alert messages.
- To prevent insulin stacking from basal insulin that is on board, participants using basal insulin at baseline will be instructed, and supervised by study staff, to set a temp basal rate to 0% that will end 24 hours after last injection of long-acting insulin, at which time the pre-programmed basal rate will be turned on. Study investigators may adjust this procedure per their usual clinical practice, and may customize this plan based on the type of basal insulin used (for example, insulin degludec with a longer half-life may require a basal rate of 50% for a second day).

A copy of the study pump user's guide will be provided to the participant.

3.6.2 Initiation of Pump by MDI Participants

For MDI participants being started on the study pump, an initial basal insulin profile will be customized on a per-participant basis. Total daily insulin dose will be reduced by approximately 20% as a general rule, with a recommended method outlined in a separate procedures' manual. Further adjustments to total daily dose (TDD) and intraday basal rate profile may be made during the Pump run-in period.

Participants will complete training on the study pump as described above, with additional emphasis on topics relevant to new pump users, such as infusion site initiation, cartridge/priming procedures, setting up the pump, charging the pump, navigation through menus, bolus procedures including stopping a bolus, etc.

The study team will assist the participant in study pump infusion site initiation and will start the participant on the study pump. The study pump will be programmed with the participant's insulin requirements.

3.6.3 System Use Guidelines

The participant will be instructed to use the system in open-loop mode only.

Participants will be provided with sufficient supplies to last until the subsequent visit.

Participants will be provided with contact information and will be asked to call the study clinical staff for any health-related issues and for technical issues with the system.

Upon completion of the study pump training components, study staff will document, using a checklist, that the participant is familiar with the functions/features/tasks addressed during the training.

Participants will be provided Hyperglycemia and Hypoglycemia Guidelines during closed-loop use (section 5.2) for when their glucose levels are >300 mg/dL for more than 60 minutes or >400 mg/dL at any time or <70 mg/dL.

3.7 Blood Glucose Testing

Participants who skipped the CGM Run-in phase will receive supplies for blood glucose testing and blood ketone testing as described above.

3.8 Assessment of Successful Completion of the Pump Run-in Phase

Participants will have a follow-up visit approximately 14 days after initiation of the Pump Run-in phase to assess progress or successful completion of the phase. If needed, one or more interim visits or phone contacts may occur to assist the participant with any system use issues. Procedures will include downloading of the study pump and CGM data and the following:

- Assessment of compliance with use of the pump, including avoidance of closed-loop mode, timely cartridge and infusion set changes, and announcement of meal boluses throughout the run-in period
- Review of insulin therapy settings and adjustments to pump settings (basal rates, correction factor, insulin-to-carbohydrate ratio, etc.) or injection strategies in response to major trends observed in the CGM data
- Assessment of eligibility to continue to the main closed-loop phase of the study

Participants who the investigator believes may benefit from an extension of the Pump Run-in period may continue Pump Run-in for a second ~2-week period. These participants will have another follow-up visit approximately 14 days after the prior visit for a reassessment using the same procedures as described above.

Participants who do not meet system use compliance requirements after a second period of Pump Run-in or otherwise fail to meet study eligibility requirements will be withdrawn from the study.

3.9 Optimization of Insulin Therapy

Data will be obtained from CGM and/or pump downloads at the CGM and pump run-in review visit(s). Adjustments to pump settings (basal rates, correction factor, insulin-to-carbohydrate ratio, etc.) or injection strategies will be made in response to major trends observed in the CGM data, with flexibility for clinicians to adhere to guidelines and practices established at each individual practice rather than a fixed set of heuristics for all clinical centers.

Chapter 4: Control-IQ (Closed-Loop) Phase

4.1 Control-IQ Phase Overview

Initiation of the Control-IQ study phase, involving use of the study pump in closed-loop mode for 6 weeks, will coincide with the final Pump Run-in follow-up clinic visit described above.

During the Control-IQ phase, visits and contacts will be scheduled as outlined in Table 2 below:

Table 2: Control-IQ Phase Visit and Phone Contact Schedule

Target Day/Week	Contact Type[1]	Target/Allowable Window (around Target Day/Week)
3 days	P	± 2 days
1 week	P	± 2 days
2 weeks	V	± 4 days
3 weeks	P	± 4 days
6 weeks	V	± 4 days
3 days post-study	P	± 1 days
Post Exercise Challenge	C	Within 24 hours

[1] Contact Types are defined as Clinic Visit (V) or Phone call (P); Phone calls may be replaced by Videoconferences or Clinic Visits at investigator discretion

4.1.1 Study Pump Training

Participants will receive instruction from a qualified trainer on use of the study pump in closed-loop mode, to include the following:

- How to turn on and off Control-IQ technology
- How to understand when Control-IQ is increasing or decreasing basal rates
- How to administer a meal or correction boluses during closed-loop system use
- What to do when exercising while using the system in closed-loop mode
- How to enable the sleep function and set the sleep schedule
- The participant will be assessed for understanding of the system interface and how to react to safety/alert messages.

Upon completion of the study pump training components, study staff will document, using a checklist, that the participant is familiar with the functions/features/tasks addressed during the training.

4.1.2 System Use Guidelines

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

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

Participants will be provided with sufficient supplies to last until the subsequent visit.

Participants will be provided with contact information and will be asked to call the study clinical staff for any health-related issues and for technical issues with the system. Participants may use the study pump without Control-IQ activated and study CGM during periods of component disconnections or technical difficulties.

Study staff will discuss with the participant that routine contact is required and will make arrangements for the contacts. If the participant cannot be reached, the participant's other contact methods will be utilized, including an emergency contact. Participants who are not compliant with the arranged contacts on two separate occasions may be discontinued at the discretion of the investigator.

4.1.3 Home Use of the Study System

After training on closed-loop aspects of the study system has been completed, participants will proceed with home use (meaning free-living use at school, home, etc.) of the study pump. Participants will be asked to complete an exercise log, and use the exercise activity mode of the study pump at least once per week for a minimum of 30 minutes of exercise.

Follow up visits will occur per the visit listing described below. If necessary, visits should be completed out-of-window rather than missed. A visit is not considered missed until the next visit/phone window opens.

The goal will be for all participants to complete all scheduled visits. However, participants who (because of unforeseen circumstances or due to changes in contact precautions that may be needed during the evolving COVID-19 pandemic) are unable or unwilling to return for all follow-up visits will be permitted to return for key visits only as an alternative to withdrawal from the study. When a participant is placed into this status, missed visits will not be recorded as protocol deviations (since they would not be recorded as protocol deviations if the participant was dropped from the study).

Additional office visits may occur as needed.

Study Specific Guidance for the Exercise Challenges

Study staff will review with participants that for each weekly exercise challenge, they will be required to:

1. Have extra carbohydrate containing snacks on hand during and after exercise.
2. Consider activation of exercise activity up to 45 minutes ahead of actual exercise, to allow for less insulin on board when starting exercise.
3. Consider reducing the last meal bolus prior to exercise as a way to reduce insulin on board and limit hypoglycemia.

4. Participants will write down the type of exercise performed, as well as the start and stop time of each exercise session on the study logbook, as this may not correlate exactly with exercise activity use on the pump.
5. Participants will be instructed that they may stop the exercise challenges at any point for injury or development of new symptoms (development of chest pain/pressure, feeling unwell, development of hypoglycemic symptoms, undue shortness of breath, signs of poor perfusion (leg pain/claudication), or for any other reason.
6. Participants will then notify the site within 24 hours after completion of each exercise challenge. The site staff will review for adverse events or new symptoms (See section 4.1.11) and review guidance on the need to stop future exercise challenges if any adverse events or new symptoms occurred per clinician judgement based on the severity of symptoms.
7. If a participant does not call within a week, study staff should perform an unscheduled contact to remind the participant of the required follow-up and encourage completion of the remaining exercise challenges. If a participant has to reschedule their exercise sessions, or postpone them for any reason (for example, the gym where they walk on a treadmill is too crowded and they did not want to enter to limit exposures due to COVID-19), they will be allowed to do so, and this will not be considered a protocol deviation. Similarly, if future exercise challenges are cancelled due to safety concerns, this will not be considered a protocol deviation.

Each clinical site can customize this guidance per their established clinical practice, to include how long to keep exercise activity active after the exercise challenge has ended.

4.1.4 Study Device Download

Participants will be instructed to download the study CGM and pump prior to each phone contact throughout the remainder of the study.

4.1.5 3-Day Phone Contact

Study staff will perform a phone call with the participant within 3 (±2) days following initiation of closed-loop system use.

The following will occur:

- Assessment of compliance with study device use by review of any available device data
- Assessment of adverse events, adverse device effects, and device issues
- Study staff will answer any questions related to device use and follow the procedure for insulin pump optimization described above if necessary.

4.1.6 1-Week Phone Contact

Study staff will perform a phone call with the participant within 7 (±2) days following Initiation of the Control-IQ study phase.

The following will occur:

- Assessment of compliance with study device use by review of any available device data
- Assessment of adverse events, adverse device effects, and device issues

- Study staff will answer any questions related to device use and follow the procedure for insulin pump optimization described above if necessary.

4.1.7 2-Week Visit

Participants will have a follow-up visit 14 (±4) days from the date of initiation of closed-loop system use.

The participant will be offered review training to address any questions on the use of the study device including meal bolus strategies and strategies related to pump use and exercise.

The following will occur:

- Assessment of compliance with study device use by review of any available device data
- Assessment of adverse events, adverse device effects, and device issues
- Study staff will answer any questions related to device use and follow the procedure for insulin pump optimization described above if necessary.
- Download of device data (study pump, study CGM, study BG meter) as available

4.1.8 4-Week Phone Contact

Study staff will perform a phone call with the participant within 28 (±4) days from the date of initiation of closed-loop system use.

The following will occur:

- Assessment of compliance with study device use by review of any available device data
- Assessment of adverse events, adverse device effects, and device issues
- Study staff will answer any questions related to device use and follow the procedure for insulin pump optimization described above if necessary.

4.1.9 6-Week Visit

All participants will have a final visit within 42 (±4) days from the date of initiation of closed-loop system use, during which the following will occur:

- Completion of questionnaires
- Collection of exercise logbook
- Weight and height measurements will be repeated
- Assessment of adverse events, adverse device effects, and device issues
- Download of device data (study pump, study CGM, study BG meter) as available
- Study staff will supervise the participant's transition back to their prior therapy
    - Study staff will re-evaluate the subject's baseline therapy doses, noting changes in basal rates, carbohydrate ratios, and correction factors in use at the end of the trial.
    - For those subjects using basal insulin, doses will be adjusted to best match the

current daily insulin requirements from CSII use, typically = (total daily dose + 20%)/2, with further modification as per clinical site usual practice.

- Study staff will confirm subjects have carbohydrates on hand for their drive back home, and instruct subjects to check their glucose levels when they arrive at home, prior to bedtime, and at least one time overnight on the first night to monitor for hypoglycemia, reminding subjects that insulin on board can be active for the next few hours even after stopping their pump.

4.1.10 3-Day Post-Study Call

All participants will have a post-study phone call 3 (±1) days after the date of their 6-Week visit and transition back to their prior insulin therapy, during which the following will occur:

- Check on transition back to usual home diabetes care
- Assessment of adverse events

4.1.11 Exercise Challenge Follow-Up

Participants will be instructed to contact study staff within 24 hours of completing each exercise challenge, per guidance in section 4.1.3. The follow up call will review:

- The start and stop time, as well as the type of exercise performed.
- Assessment of adverse events
- Documentation of any safety concerns if future exercise challenges are cancelled.

4.2 Early Termination Visit (If Applicable)

Participants will be asked to come for an end of study visit in the event of withdrawal or early termination.

4.3 Unscheduled Visits

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

Chapter 5: Study Devices

5.1 Description of the Investigational Device

5.1.1 Insulin Pump

The study system will include the Tandem t:slim X2 insulin pump (K201214, Tandem Diabetes Care, San Diego, CA) using firmware version 1.5.

5.1.2 Continuous Glucose Monitoring

The study CGM will include Dexcom G6 transmitter and sensors. The CGM sensor will be replaced at least once every 10 days or as per manufacturer instructions.

5.1.3 Blood Glucose Meter and Strips

Blood glucose levels will be measured using the study-assigned blood glucose meter (glucometer) and the CGM device will be calibrated if needed using the study glucometer and strips in accordance with the manufacturer's labeling. (Contour NEXT or Contour NEXT ONE, Ascensia Diabetes Care US, Inc., 5 Wood Hollow Rd, Parsippany, NJ 07054 USA.

5.1.4 Ketone Meter

The study blood ketone meter is the Precision Xtra Blood Glucose and Ketone Monitoring System (Abbott Diabetes Care).

Blood ketone levels will be measured when needed to evaluate prolonged hyperglycemia. The blood glucose meter component of the Precision Xtra device will not be used.

5.1.5 Study Device Accountability Procedures

Device accountability procedures will be detailed in the site procedures manual.

5.2 Safety Measures

5.2.1 CGM Calibration

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

5.2.2 Pump Failure

The study insulin pump is designed to revert to open-loop delivery of preprogrammed basal insulin levels in the event that CGM data are not available. The pump also includes various alarms and alerts to notify the user when there is a problem with insulin delivery.

5.2.3 Hypoglycemia Threshold Alarm and Safety Protocol

When using the study device, hypoglycemia low threshold alerts will be set to no lower than 70 mg/dL, and if a participant's CGM reading is <70 mg/dL, subjects will be instructed to treat with ~15 grams of carbohydrate and perform fingerstick testing as necessary per CGM manufacturer instructions.

5.2.4 Hyperglycemia Threshold Alarm and Safety Protocol

During the course of the study, participants will be permitted to change this setting, but will be instructed to choose a value no greater than 300 mg/dL.

During the CGM run-in and open-loop pump wear period, if a participant's CGM reading is >300 mg/dL for over 2 hours:

- Perform a blood glucose meter check.
- For bolus insulin users, if the blood glucose is >300 mg/dL, give a correction dose of insulin if no bolus has been given within the last hour. If blood glucose does not decrease by 50 mg/dL within 90 minutes of the correction dose, contact study staff for further instructions.
- For basal insulin users, contact study staff for further instructions.

During the time period when the closed-loop system is operational and active, if a participant's CGM reading is >300 mg/dL for over 1 hour or ≥400 mg/dL at any point, or the participant experiences severe symptoms of hyperglycemia (nausea, vomiting, abdominal pain), the participant will be instructed to take the following steps:

- Perform a blood glucose meter check.
- If the blood glucose is >300 mg/dL, check for blood ketones with the study ketone meter.
- If the ketone level is ≥ 0.6 mmol/L (or ≥ 2.5 mmol\L at any time), take correction insulin, change insulin (pump) infusion site and contact study staff. Continue to monitor their glucose and blood ketone levels until they return to normoglycemia and ketones are < 0.6 mmol/l.
    - If ketones are <0.6 mmol/l, they will be advised to continue to monitor their glucose until it returns to normoglycemia and to repeat the ketone measurement in 90 minutes if necessary.
    - If glucose fails to correct, or symptoms persist, contact study staff immediately for further instructions, to include giving a correction dose by injection.
- If correction insulin is administered via insulin syringe, turn Control-IQ off for approximately four hours and until glucose level has returned to <180 mg/dL.
- If unable to contacts study staff and the participant is vomiting, go to the Emergency Room.

5.3 Participant Access to Study Device at Study Closure

Participants will be returned to their pre-study insulin therapy at the conclusion of the study and must return all study-assigned materials to the clinical site. Return of these materials must occur within 7 weeks (49 days) of initiation of closed-loop system use.

Chapter 6: Testing Procedures and Questionnaires

6.1 Laboratory Testing

1. HbA1c:
   - HbA1c level measured using the DCA2000 or comparable point of care device or local lab at the Screening visit, if no comparable measurement is available from the 2 weeks prior to enrollment
   - HbA1c level measured at a Central Lab from blood draw performed at Screening visit
2. C-peptide/Glucose:
   - C-peptide with concurrent glucose level measured at a Central Lab from blood draw performed at Screening visit
3. Urine Pregnancy:
   - Performed locally for females of child-bearing potential at Screening and at the Control-IQ phase initiation visit. This will also be done anytime pregnancy is suspected.

Local laboratory testing will be performed if needed to screen for exclusionary medical conditions.

6.2 Electrocardiogram (ECG)

An ECG will be administered using the clinic's ECG machine and read locally by the investigator at the Screening visit to determine if the participant meets eligibility criteria with respect to the exercise component of the study. The printed ECG with the investigator's evaluation, signature and date must be saved in the study records (note – making a copy of the ECG once signed preserves the integrity of the read due to the fragility of the printer paper).

6.3 Questionnaires

Questionnaires are completed by all participants at the study visits indicated in the table below.

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

Table 3. Study Questionnaire Summary

MEASURE	CONSTRUCT MEASURED/RELEVANT POINTS	ADMINISTRATION POINTS
Tandem Study-Specific Baseline Survey	A Tandem-specific 4-item questionnaire that captures information about Healthcare Provider relationships, comfort with new technologies for diabetes management, and comfort understanding written information. (3 mins)	• Screening Visit
Altarum Consumer Engagement (ACE) Measure – Commitment Subscale	A 6-item questionnaire measuring commitment to everyday health behaviors. Predicts overall health, adherence to medical guidance, and success at chronic disease management. (2 mins)	• Screening Visit

MEASURE	CONSTRUCT MEASURED/RELEVANT POINTS	ADMINISTRATION POINTS
Tandem Pump Training Survey	A Tandem-specific 4-item questionnaire that captures patient-reported experience with Tandem pump training, including overall satisfaction and time investment. (3 mins)	• Pump Run-In Initiation Visit • Control-IQ Initiation Visit
DAWN Impact of Diabetes Profile (DIDP)	A 7-item questionnaire providing a valid and reliable measure of the perceived impact of diabetes on quality of life, suitable for adults with Type 1 or Type 2 diabetes mellitus. (2 mins)	• Screening Visit • Control-IQ Initiation Visit • 6-Week Visit
Diabetes Impact and Device Satisfaction (DIDS) Scale	A 12-item questionnaire focused on satisfaction related to insulin delivery devices (e.g., trust and ease of use) and diabetes-related impact on daily life, such as worry around hypoglycemia and sleep interruptions. (3 mins)	• Screening Visit • Control-IQ Initiation Visit • 6-Week Visit
PROMIS Sleep-Related Impairment Questionnaire	An 8-item questionnaire that measures sleep disturbance and sleep-related impairment. (2 mins)	• Screening Visit • Control-IQ Initiation Visit • 6-Week Visit
System Usability Scale (SUS)	A 10-item questionnaire that measures the overall usability of a system. It is a valid and reliable measure of the perceived usability of a system and is technology-agnostic. (2 mins)	• Control-IQ Initiation Visit • 6-Week Visit

6.4 Semi-Structured Interviews

A semi-structured one-on-one interview may be completed concurrent with the 6-Week Visit or within a 28-day period following that visit. The interview will last approximately 30 minutes and will be conducted by Tandem staff using a script of open-ended questions to gather feedback and reactions to the closed loop system, the clinical trial, and QoL changes.

Interview sessions may be audio- or video-taped and transcribed by a professional transcription service. Otherwise, these recordings will not be shared for any non-study purposes. Transcriptions will use a code for participants, such as “Participant 1”, and will not contain names or other identifiers of participants.

Chapter 7: Unanticipated Problem, Adverse Event, and Device Issue Reporting

7.1 Unanticipated Problems

Site investigators will promptly report all unanticipated problems meeting the criteria below on an eCRF. Sites overseen by the JCHR IRB must report Unanticipated Problems to the IRB within seven (7) calendar days of recognition. For this protocol, an unanticipated problem is an incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places participants or others at a greater risk of harm than was previously known or recognized **(**including physical, psychological, economic, or social harm)

An example of an unanticipated problem in this study would be incidence rates of hypo- or hyperglycemia in the study (T2D) population, related to closed-loop insulin delivery, that are significantly higher than previously encountered when using the study system in the T1D population.

The Coordinating Center also will report to the IRB all unanticipated problems not directly involving a specific site such as unanticipated problems that occur study-wide or at another participating entity such as a pharmacy or laboratory. These instances must be reported to the JCHR IRB within seven (7) calendar days of recognition. The Director of the Human Research Protection Program (HRPP) will report to the appropriate regulatory authorities if the IRB determines that the event indeed meets the criteria of an Unanticipated Problem requiring additional reporting to fulfill the reporting obligations of the HRPP.

7.2 Adverse Events

7.2.1 Definitions

Adverse Event (AE): Any untoward medical occurrence (including laboratory findings) associated with study procedures, the use of a device, biologic, or drug in humans, including any comparator used, whether or not the event is considered related (i.e., irrespective of the relationship between the adverse event and the device(s) under investigation).

Serious Adverse Event (SAE): Any untoward medical occurrence that results in any of the following outcomes:

- Death.

- A life-threatening adverse event; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions (sight threatening).
- A congenital anomaly or birth defect.

An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical and surgical intervention to prevent one of the outcomes listed in this definition. Note: If either the Sponsor or investigator believes that the event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants (21 CFR 812.3(s)).

Adverse Device Effect (ADE): An adverse event related to the use of an investigational medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. This includes comparator if the comparator is a medical device. (Note that an Adverse Event Form is to be completed in addition to a Device Deficiency or Issue Form, unless excluded from reporting as defined in section 8.2).

Comparator: Medical device, therapy (e.g. active treatment, normal clinical practice), placebo or no treatment, used in the control group in a clinical investigation. (ISO 14155:2020)

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

Use Error**:** User action or lack of user action while using the medical device (3.34) that leads to a different result than that intended by the manufacturer or expected by the user. Includes the inability of the user to complete a task. Use errors can result from a mismatch between the characteristics of the user, user interface, task or use environment. Users might be aware or unaware that a use error has occurred. An unexpected physiological response of the patient is not

by itself considered a use error. A malfunction of a medical device that causes an unexpected result is not considered a use error. (ISO 14155:2020)

7.2.2 Reportable Adverse Events

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

1. An SAE as defined in section 7.2.1
2. An ADE as defined in section 7.2.1, unless excluded from reporting in section 7.3
3. An AE as defined in 7.2.1 occurring in association with a study procedure
4. An AE as defined in 7.2.1 not related to a device issue which leads to temporary or permanent discontinuation of a study device
5. An AE as defined in 7.2.1 that affects the participant's ability to complete any study procedures
6. An AE as defined in 7.2.1 for which a visit is made to a hospital emergency department
7. Hypoglycemia meeting the definition of reportable hypoglycemia as defined below
8. Diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic syndrome (HHS) as defined below; or in the absence of DKA/HHS, hyperglycemia or ketosis event meeting the criteria defined below.

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

All reportable AEs—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 AE form online. Each AE form is reviewed by the Medical Monitor to assess safety and to verify the coding and the reporting that is required.

7.2.3 Hypoglycemic Events

Hypoglycemia not associated with an Adverse Device Effect or discontinuation of the study device is only reportable as an adverse event when one of the following criteria is met:

- a hypoglycemic event occurred meeting the following definition of severe hypoglycemia: 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 loss of consciousness. These episodes may be associated with sufficient neuroglycopenia to induce seizure or loss of consciousness. 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 glucose concentration.

- evaluation or treatment was obtained at a health care provider facility for an acute event involving hypoglycemia, or the participant contacted the site and received guidance following the occurrence of an acute event involving hypoglycemia

When a severe hypoglycemia event occurs (as defined above), a Hypoglycemia Form should be completed in addition to the Adverse Event Form. Severe hypoglycemia events should be considered to be serious adverse events with respect to reporting requirements. When a severe hypoglycemia event occurs during use of a study device, it generally will be considered to be unrelated to the device (per section 7.2.5) if the device functioned as intended and there does not appear to be a flaw in how the device is intended to function.

7.2.4 Hyperglycemic/Ketotic Events

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

- the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below
- the event involved hyperosmolar hyperglycemic syndrome (HHS), as defined by the American Diabetes Association and described below
- evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis, or the participant contacted the site and received guidance on how to manage the hyperglycemia/ketosis

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

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Serum ketones >1.5 mmol/L or large/moderate urine ketones;
- Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate (or CO_2) <15; and
- Treatment provided in a health care facility

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

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Plasma glucose levels are very elevated (typically > 600 mg/dL);
- Plasma effective osmolarity is >320 mOsm/L;
- Absence of significant ketones; and
- Treatment provided in a health care facility

When a hyperglycemia/ketotic event qualifies as an SAE as defined in section 7.2.1 , a Hyperglycemia/DKA Form should be completed in addition to the Adverse Event Form. Events meeting DKA or HHS criteria should be considered to be serious adverse events with respect to reporting requirements. Hyperglycemia events not meeting criteria for DKA or HHS generally

will not be considered as serious adverse events unless one of the SAE criteria in section 7.2.1 is met.

When a hyperglycemia/DKA event occurs during use of a study device, it generally will be considered to be unrelated to the device (per section 7.2.5) if the device functioned as intended and there does not appear to be a flaw in how the device is intended to function.

7.2.5 Relationship of Adverse Event to Study Investigational Device

The study investigator will assess the relationship of any adverse event to be related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by the study device. The Medical Monitor also will make this assessment, which may or may not agree with that of the study investigator. Reporting requirements will be based on the Medical Monitor's assessment as the Sponsor's representative.

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

- **Unrelated:** The AE is clearly not related to a study drug/device and a likely alternative etiology exists such as an underlying disease, environmental or toxic factors or other therapy.
- **Unlikely Related:** The AE does not follow a reasonable temporal sequence during or after use of study drug/device and a more likely alternative etiology exists such as an underlying disease, environmental or toxic factors, or other therapy.
- **Possibly Related:** The AE occurred in a reasonable time during or after use of study drug/device; but could be related to another factor such as an underlying disease, environmental or toxic factors, or other therapy; and there is a possible, though weak, scientific basis for establishing a causal association between the AE and the study drug/device.
- **Probably Related:** The AE occurred in a reasonable time during or after use of study drug/device; is unlikely to be related to another factor such as an underlying disease, environmental or toxic factors, or other therapy; and there is a plausible, though not strong, scientific basis for establishing a causal association between the AE and the study drug/device.
- **Definitely Related:** The AE occurred in a reasonable time during or after use of study drug/device; cannot be explained by another factor such as an underlying disease, environmental or toxic factors, or therapy; and there is a strong scientific basis for establishing a causal association between the AE and the study drug/device.
- **Not Assessable:** Causality of an adverse event cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

Where these relatedness categories are used, events determined to be Possibly Related, Probably Related, or Definitely Related will be considered to meet the reasonable possibility causality standard for relatedness and necessitate reporting as required (see 21 CFR 312.32 for more information about this standard).

7.2.6 Severity (Intensity) of Adverse Events

The severity (intensity) of an adverse event will be rated on a three point scale: (1) mild, (2) moderate, or (3) severe. A severity assessment is a clinical determination of the intensity of an event. 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, discomfort or concern to the participant and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures and participant is able to continue in study.
- SEVERE: Interrupts a participant's usual daily activities, causes severe discomfort, may cause discontinuation of study device, and generally requires systemic drug therapy or other treatment.

7.2.7 Expectedness

For a serious adverse event that is considered possibly related to study device, the Medical Monitor will classify the event as unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in the approved labelling of the study system.

7.2.8 Coding of Adverse Events

Adverse events will be coded using the MedDRA dictionary. To facilitate coding, the site will enter a preliminary MedDRA code which the Medical Monitor may accept or change (the Medical Monitor's MedDRA coding will be used for all reporting). The Medical Monitor will review the investigator's assessment of causality and may agree or disagree. Both the investigator's and Medical Monitor's assessments will be recorded. The Medical Monitor will have the final say in determining the causality as well as whether an event is classified as a serious adverse event and/or an unanticipated adverse device effect.

7.2.9 Outcome of Adverse Events

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).

If any reported adverse events are ongoing when a participant completes the study (or withdraws), adverse events classified as UADEs or related SAEs will be followed until they are either resolved, or have no prospect of improvement or change, even after the participant has completed all applicable study visits/contacts. For all other adverse events, data collection will end at the time the participant completes the study. Note: participants should continue to receive appropriate medical care for an adverse event after their participation in the study ends.

7.3 Reportable Device Issues

All UADEs and ADEs as defined in section 7.2.1 will be reported on both a device issue form and AE form, except for skin reactions from CGM sensor placement or pump infusion set placement that do not require pharmacologic treatment.

Device complaints and device malfunctions will be reported except in the following circumstances. These occurrences are expected and will not be reported on a Device Issue Form assuming criteria for a UADE or ADE have not been met:

- CGM sensor needing replacement prior to labelled maximum use duration
- Infusion set needing replacement prior to labelled maximum use duration
- CGM tape adherence issues
- Pump infusion set insertion lasting fewer days than expected per manufacturer
- Battery lifespan deficiency due to inadequate charging or extensive wireless communication
- Intermittent device component disconnections/communication failures not requiring system replacement or workaround/resolution not specified in user guide/manual.
- Device issues clearly addressed in the user guide manual that do not require additional troubleshooting

7.4 Timing of Event Reporting

SAEs possibly related to a study device or study participation and UADEs must be reported by the investigator to the Coordinating Center within 24 hours of the site becoming aware of the event. This can occur via phone or email, or by completion of the online serious adverse event form and device issue form if applicable. If the form is not initially completed, it should be competed as soon as possible after there is sufficient information to evaluate the event. All other reportable ADEs and other reportable AEs should be submitted by completion on the online form within 7 days of the site becoming aware of the event.

The Coordinating Center will notify all participating investigators of any adverse event that is serious, related, and unexpected. Notification will be made within 10 working days after the Coordinating Center becomes aware of the event.

Each principal investigator is responsible for reporting serious study-related adverse events and abiding by any other reporting requirements specific to his/her Institutional Review Board or Ethics Committee. Where the JCHR IRB is the overseeing IRB, sites must report all serious, related adverse events within seven calendar days.

Upon receipt of a qualifying event, the Sponsor will investigate the event to determine if a UADE is confirmed, and if indicated, report the results of the investigation to all overseeing IRBs, and the FDA within 10 working days of the Sponsor becoming aware of the UADE per 21CFR 812.46(b) (2). The Sponsor in conjunction with the Medical Monitor must determine if the UADE presents an unreasonable risk to participants. If so, the Sponsor 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 Sponsor makes this determination and no later than 15 working days after first receipt notice of the UADE. The investigator(s) may then be required to provide approval or acknowledgment of receipt of that notification, and must submit to their overseeing IRB as required.

The investigators are also required to report, without unjustified delay, all device deficiencies that could have led to a UADE, including device deficiencies, irrespective of whether an adverse event occurred.

Device malfunctions will be handled by the Sponsor or designee as described below. In the case of a CGM transmitter or sensor device malfunction, information will be forwarded to Dexcom by the site personnel, to be handled by their complaint management system.

7.5 Safety Oversight

The study Medical Monitor will review all adverse events and adverse device events that are reported during the study. SAEs typically will be reviewed within 24 hours of reporting. Other AEs typically will be reviewed on a weekly basis. Additionally, the Medical Monitor will review compiled safety data at periodic intervals.

The Clinical Study Director will be informed of all cases of severe hypoglycemia and DKA and the Medical Monitor's assessment of relationship to the study device; and informed of all reported device issues.

7.6 Stopping Criteria

7.6.1 Participant Discontinuation of Study Device

In the case of an unanticipated system malfunction resulting in a severe hypoglycemia or DKA event (or a malfunction that could have led to severe hypoglycemia or DKA), use of closed-loop mode will be suspended while the problem is diagnosed. The UADE will be reported to the IRB and FDA. After assessment of the problem and any correction, use of closed-loop mode will not be restarted until approval is received from the IRB and FDA.

In the absence of a device malfunction, a participant will be discontinued from the study if any of the following occur:

- 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, HHS, or severe hypoglycemia as defined above, so only a second event of any of these types may occur prior to stopping subject participation.

Each DKA or severe hypoglycemia event will be reviewed by the Medical Monitor with respect to determination of cause and whether the occurrence of the event can be attributed to use of the study device.

An additional requirement for continued study participation following a single DKA or severe hypoglycemia event will be that (1) the site investigator believes that the event is explainable, unlikely to recur, and that it is safe for the participant to continue to use the system and (2) the Medical Monitor concurs. If the Medical Monitor determines that the occurrence of the event indicates that it is not safe for the participant to continue to use the study system, the participant will be discontinued from the study.

Even if the study device system is discontinued, the participant will be encouraged to remain in the study through the final study visit.

7.6.2 Criteria for Suspending or Stopping Overall Study

In addition to the suspension of closed-loop mode use due to a UADE as described above, closed-loop system use will be suspended if there are three or more cases of severe hypoglycemia or three or more cases of hyperglycemia/ketotic events qualifying as SAEs across the entire study in participants who have initiated Control-IQ technology use.

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.

Chapter 8: Miscellaneous Considerations

8.1 Drugs Used as Part of the Protocol

Participants will use either lispro or aspart insulin prescribed by their personal physician. Participants not using lispro or aspart insulin at the time of screening may not start use of the study device until they have one of these insulins available to them for use.

8.2 Collection of Medical Conditions and Medications

Pre-Existing Condition: Any medical condition that is either present at screening, a chronic disease, or a prior condition that could impact the participant's health during the course of the study (e.g., prior myocardial infarction or stroke).

Medical Conditions during the study: In addition to conditions meeting the reporting requirements for an adverse event or device issue as described above, the following medical conditions should also be reported: (1) new diagnosis of a chronic disease (i.e., not present at the time of enrollment), and (2) any medical condition that could affect the participant's ability to carry out any aspect of the protocol or could affect an outcome assessment.

Medications: All medication for the treatment of chronic pre-existing conditions, medical conditions (including medical conditions that do not require recording), and/or adverse events that the participant is currently taking at screening and during the course of the study should be recorded. Nutraceuticals and preventative treatment also should be recorded. Medications only taken as needed either can be recorded when prescribed or only recorded if used during the study. Glucagon for treatment of severe hypoglycemia will only be recorded if used during the study.

8.3 Prohibited Medications, Devices, Treatments, and Procedures

Participants using other insulins 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.

Afrezza (inhaled insulin) or concurrent use of basal insulins will not be permitted during device use in the trial. Additional medications to treat glycemia (such as SGL-2 inhibitors or GLP-1 receptor agonists), commonly used by individuals with type 2 diabetes concurrently with insulin use, will be allowed if the participant is on a stable dose of such medication for the last 3 months. Sulfonylurea use and meglitinide use will not be allowed during the trial.

No new additional glucose lowering medications may be added during the trial.

Medications used for weight loss will be allowed if the participant is on a stable dose of such medication for the last 3 months. No new medications for weight loss may be added during the trial.

Additional medications may be excluded per judgement of the investigator.

The investigational study devices (study insulin pump, study CGM system) 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.

8.4 Precautionary Medications, Treatments, and Procedures

Not applicable.

8.5 Prophylactic Medications, Treatments, and Procedures

Not applicable.

8.6 Rescue Medications, Treatments, and Procedures

All participants will be required to have a commercially available glucagon (or glucagon analog) preparation for treatment as needed of severe hypoglycemia.

8.7 Pregnancy Reporting

If pregnancy occurs, the participant will be discontinued from the study. The occurrence of pregnancy will be reported to the Coordinating Center within seven days and to the JCHR IRB as an Unanticipated Problem within seven calendar days.

8.8 Participant Compensation

Participant compensation will be specified in the informed consent form.

8.9 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.

8.10 Confidentiality

For security and confidentiality purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the coordinating center, the Jaeb Center for Health Research in Tampa, FL. De-identified participant information may also be provided to research sites involved in the study.

Chapter 9: Statistical Considerations

9.1 Statistical and Analytical Plans

The approach to sample size and statistical analyses are summarized below.

9.2 Statistical Hypotheses

The primary outcomes for this study are CGM-measured percentage below 54 mg/dl and CGM-measured percent above 180 mg/dl over a 6-week period. The intervention will be considered effective if the 6-week follow-up % above 180 mg/dl value is superior and % below 54 mg/dl value is non-inferior to the corresponding baseline values using a statistical significance of α=0.05 and the analysis specified below in Section 6 (i.e., $p < 0.05$).

The null/alternative hypotheses are:

<u>*Percentage below 54 mg/dl:*</u>

a. *Null Hypothesis*: The difference in mean CGM-measured % below 54 mg/dl between the 6 weeks follow-up and baseline is greater than or equal to +1% (non-inferiority).
b. *Alternative Hypothesis*: The difference in mean CGM-measured % below 54 mg/dl between the 6 weeks follow-up and baseline is less than +1%.

<u>*Percentage above 180 mg/dl:*</u>

a. *Null Hypothesis*: There is no difference in mean CGM-measured % above 180 mg/dL between the 6 weeks of follow-up and baseline (superiority).
b. *Alternative Hypothesis*: The mean CGM-measured % above 180 mg/dL is different at baseline than the mean over 6 weeks of follow-up.

9.3 Sample Size

The planned cohort of N=30 participants with the goal of at least N=24 completing the study is a convenience sample not based on statistical principles.

9.4 Outcome Measures

9.4.1 Primary Efficacy Endpoints

- CGM-measured percentage below 54 mg/dl
- CGM measured percentage above 180 mg/dl

9.4.2 Secondary Efficacy Endpoints

- CGM-measured metrics:
  - Percentage in range 70-180 mg/dL
  - Percentage < 70 mg/dL
  - Percentage > 250 mg/dL
  - Percentage in tight glycemic range 70-140 mg/dL
  - Mean glucose

- Up to 4hr post-prandial glycemic metrics:
  - Peak
  - Area Under the Curve (AUC)

- Insulin metrics
  - Total daily insulin use
  - Total basal insulin
  - Total bolus insulin
- Weight
- Questionnaires
  - Tandem Study-Specific Baseline Survey
  - Altarum Consumer Engagement Measure
  - Tandem Pump Training Survey
  - DAWN Impact of Diabetes Profile
  - Diabetes Impact and Device Satisfaction Scale
  - PROMIS Sleep-Related Impairment Questionnaire
  - System Usability Scale

Calculation of CGM metrics

- Baseline values will be taken from the last 7 days of the run-in, or for participants who can skip the run-in baseline values will be taken from their personal CGM during the 7 days prior to initiating CLC. At least 24hr of data during this baseline period are required for the glycemic metrics to be calculated.
- Follow-up values will be calculated using CGM data from the 6-week period of CLC use. These will be limited to participants who have at least 168 hours of CGM data available during the 6-week CLC use period.
- Exploratory analyses will include all CGM data between the initiation of Open-Loop use and the start of CLC will be used. At least 24hr of data during this period are required for the glycemic metrics to be calculated.
- Separate values for each CGM metric (except for post-prandial peak and 4-hour AUC) will be calculated for:
  - Overall: 24 hours of the day
  - Daytime: CGM readings from 6:00 am – 11:59 pm
  - Nighttime: CGM readings from midnight – 5:59 am
  - During logged exercise challenges

9.4.3 Safety Endpoints

- Severe hypoglycemia (needing assistance)
- DKA
- Hyperosmolar Hyperglycemic Syndrome
- Serious Adverse Events
- Unanticipated adverse device effects

9.5 Analysis Datasets and Sensitivity Analyses

This is not a randomized trial so intent-to-treat does not apply. The primary analysis will be limited to participants with at least 168 hours of CGM data during the 6-week CLC use period.

A per-protocol analysis will be limited to participants who used the CLC for at least 80% of the time during the 6-week period. If fewer than 10% of the study participants would be excluded based on this criterion, then the per-protocol analysis will not be performed.

Safety analyses will include all participants.

9.6 Analysis of the Primary Efficacy Endpoint(s)

Summary statistics appropriate to the distribution (e.g., mean and standard deviation, or median and quartiles) will be for each of the primary efficacy endpoints (CGM-measured percentage below 54 mg/dl and percentage above 180 mg/dl) at baseline, during CLC use, and for the change values. Scatterplots and boxplots will be constructed to show the distribution of values at baseline and during CLC use.

A pre- and post-CLC comparison will be performed using a paired t-test for each metric. If the paired differences (i.e., change values) do not follow an approximate normal distribution, then a non-parametric comparison based on ranks will be performed.

9.7 Analysis of the Secondary Endpoint

Analysis of secondary endpoints will parallel the analysis described above for the primary endpoints over 24 hours, daytime, and nighttime. For the post-prandial CGM metrics (4 hour peak and AUC) and during exercise challenges, there will be no corresponding pre-study baseline. Descriptive analyses of these metrics will be limited to values during CLC use.

9.8 Safety Analyses

All participants will be included in the safety analyses. All adverse events will be tabulated with separate lists for events that occur before, during OL, and during CLC use.

Additionally, the number of events and the event rate per 100 person-years during CLC use will be calculated for each of the safety outcomes listed above:

- Severe hypoglycemia (needing assistance)
- DKA
- Hyperosmolar Hyperglycemic Syndrome
- All Serious Adverse Events
- Unanticipated adverse device effects

9.9 Intervention Adherence

Descriptive summary statistics will be given for the percentage of time that the CLC is in active mode and the amount of CGM use over the 6-week period. A scatterplot of these two percentages will be constructed. Boxplots will be given for each of these percentages for each of the 6 weeks of follow-up. Descriptive statistics will be given for the percentage of time spent in each of the CLC operational modes.

9.10 Protocol Adherence and Retention

The following measures of adherence will be tabulated during the 6-week follow-up period:

- Number of protocol and procedural deviations
- Flow chart accounting for all enrolled participants up to the end of study
- Flow chart of all enrolled participants at all scheduled visits and phone contacts post treatment initiation
- Number of and reasons for unscheduled visits and phone calls
- Number of participants who stopped OL or CLC use and reasons

9.11 Baseline Descriptive Statistics

Baseline demographic and clinical characteristics of the cohort of all enrolled participants will be summarized in a table using summary statistics appropriate to the distribution of each variable. Descriptive statistics will be displayed for the following:

- Age
- Sex
- Race/Ethnicity
- Diabetes duration
- Insulin method before enrollment (basal only or multiple daily injections)
- CGM use before enrollment
- HbA1c
- BMI
- Participant-reported number of SH and DKA 12 months prior to the start of the study
- Baseline CGM metrics including:
  - % time < 54 mg/dl
  - % time > 180 mg/dl
  - % in range 70-180 mg/dl
  - mean glucose
  - % time < 70 mg/dl

9.12 Device Issues

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

- Device malfunctions requiring study team contact and other reported device issues

- Rate of different failure events and alarms per 24 hours recorded by the Control-IQ system – overall and by study week

9.13 Planned Interim Analyses

No formal interim efficacy analyses are planned.

9.14 Sub-Group Analyses

In exploratory analyses, the primary outcomes (percent <54 mg/dl and percent >180 mg/dl) will be compared in baseline subgroups. A least squares regression will be fit with the dependent variable being the paired difference (value during CLC use minus value at baseline) and the subgroup factor as an independent variable.

Interpretation of subgroup analyses will be viewed with caution, particularly in the absence of an overall significant difference. Subgroups will be analyzed according to the following baseline factors:

- Gender
- Race/Ethnicity (if sufficient numbers in more than one category)
- Insulin
  - Basal only (Group A)
  - Multiple daily injections (Group B)

9.15 Multiple Comparison/Multiplicity

There will be no formal correction for multiple comparisons in this pilot study.

9.16 Exploratory Analyses

The primary analysis described above in Section 9.6 will be repeated with the CGM-measured percentage below 54 mg/dl and percentage above 180 mg/dl during follow-up limited to times when the CLC was in active mode.

Weekly boxplots for selected glycemic and insulin metrics will be generated.

In addition to the baseline and 6 weeks CLC use period, the glycemic and insulin analyses will be extended to include the 2-4 weeks of OL use. Only descriptive summary statistics and plots will be generated for these new analyses.

Chapter 10: Data Collection and Monitoring

10.1 Case Report Forms and Other Data Collection

The main study data are collected on electronic case report forms (CRFs). When data are directly collected in electronic case report forms, this will be considered the source data. For any data points for which the eCRF is not considered source (e.g. lab results that are transcribed from a printed report into the eCRF), the original source documentation must be maintained in the participant's study chart or medical record. This source must be readily verifiable against the values entered into eCRF. Even where all study data are directly entered into the eCRFs at office visits, evidence of interaction with a live subject must be recorded (e.g., office note, visit record, etc.)

Electronic device data files are obtained from the study software and individual hardware components. These electronic device files are considered the primary source documentation.

10.2 Study Records Retention

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

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.

10.3 Quality Assurance and Monitoring

Designated personnel from the Coordinating Center will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the clinical portion of the trial is conducted and data are generated, documented and reported in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements, as well as to ensure that the rights and wellbeing of trial participants are protected and that the reported trial data are accurate, complete, and verifiable. Adverse events will be prioritized for monitoring.

A risk-based monitoring (RBM) plan will be developed and revised as needed during the course of the study, consistent with the FDA "Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring" (August 2013). Study conduct and monitoring will conform with 21 Code of Federal Regulations (CFR) 812. This plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

The data of most importance for monitoring at the site are participant eligibility and adverse events. Therefore, the RBM plan will focus on these areas. As much as possible, remote monitoring will be performed in real-time with on-site monitoring performed to evaluate the verity and completeness of the key site data. Elements of the RBM may include:

- Qualification assessment, training, and certification for sites and site personnel
- Oversight of Institutional Review Board (IRB) coverage and informed consent procedures
- Central (remote) data monitoring: validation of data entry, data edits/audit trail, protocol review of entered data and edits, statistical monitoring, study closeout
- On-site monitoring (site visits): source data verification, site visit report
- Agent/Device accountability
- Communications with site staff
- Patient retention and visit completion
- Quality control reports
- Management of noncompliance
- Documenting monitoring activities
- Adverse event reporting and monitoring

Coordinating Center representatives or their designees may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study. The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.4 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. A significant (or major) deviation is any deviation that departs from the established materials in such a way that it poses an increase in the risk to subjects, adversely affects the welfare, rights, or safety of the research subjects, or negatively influences the scientific study integrity. As a result of a significant deviation, a corrective and preventive action plan shall be developed by the site and implemented promptly.

The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the monitoring plan.

Chapter 11: Ethics/Protection of Human Participants

11.1 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.

11.2 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.

11.3 Informed Consent Process

11.3.1 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.

11.3.2 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB, regulatory agencies or 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) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each 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 the reviewing IRB, institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Jaeb Center for Health Research (JCHR). This will not include the participant's contact or identifying information, unless otherwise specified in the informed consent form. 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 clinical sites and by JCHR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the JCHR.

Chapter 12: References

1. Morberg JN, Singh H, McElwee-Malloy M, Habif S, Constantin A. Real-World Evaluation of Glycemic Outcomes by Prior Therapy for People with Type 1 and Type 2 Diabetes Onboarding to Control-IQ Technology. *Diabetes*. 2021; 70(Supplement 1):710-P.
2. Breton MD, Kovatchev BP. One Year Real-World Use of the Control-IQ Advanced Hybrid Closed-Loop Technology. *Diabetes Technol Ther*. 2021;
3. Brown SA, Kovatchev BP, Raghinaru D, Lum JW et al. Six-month randomized, multicenter trial of closed-loop control in type 1 diabetes. *N Engl J Med*. 2019; 381(18):1707-1717.
4. Breton MD, Kanapka LG, Beck RW, Ekhlaspour L et al. A randomized trial of closed-loop control in children with type 1 diabetes. *N Engl J Med*. 2020; 383(9):836-845.