Control-IQ Observational (CLIO) Post-Approval Study Protocol

t:slim X2 insulin pump with Control-IQ technology

Tandem Diabetes Care, Inc.

February 17, 2022

Protocol Identifying Number:	CLIO Study
Protocol Name:	Control-IQ Observational (CLIO) US Post-Approval Study
Phase	Post-Approval
Sponsor	Tandem Diabetes Care, Inc. 11075 Roselle St. San Diego, CA 92121 USA
Principal Investigator	Jordan Pinsker, MD
Study Device	t:slim X2 insulin pump with Control-IQ technology

STATEMENT OF CONFIDENTIALITY

Table 1: Protocol Revision History

Draft Number	Amendment Approval Date	Brief Description of Changes
01	N/A	Initial Draft Version
02	April 30, 2020	Included literature review and evaluable study endpoints; added severe hypoglycemia and DKA education to participant messaging; adjusted criteria for withdrawal from study; added options for obtaining information on inclusion/exclusion criteria and AEs; clarified CGM-autopopulated bolus analysis; and clarified definition of "CGM-naïve"
03		Changed name to Control-IQ Observational (CLIO) Post-approval Study. Amended inclusion/exclusion criteria and enrollment targets to include subjects ages 6 years and older.
04	August 19, 2020	In response to FDA request, adjusted enrollment targets for subjects ages 6-13 years old.
05	October 22, 2020	Revised wording to provide clarity to the original intention of the target enrollment sample size for the study, which was to recruit a minimum of 2063 subjects.
06.1	June 28, 2021	Changed inclusion criteria to "Agree to provide HbA1c result, obtained within the 6-month period prior to enrollment". Added to Medical History: Participants already recruited during the COVID emergency who did not have a recent HbA1c result within the past 6 months of enrollment will not be counted toward overall recruitment goals, and will be analyzed separately. Participants will be considered screen failures if Control-IQ data has not been downloaded to t:connect 120 days after the baseline survey's completion. Currently ~24% of CLIO participants that have completed their initial baseline questionnaire have not progressed to the Month 1 Survey. To avoid prolonging the overall duration of the CLIO study the individuals will be considered screen failures if they have not downloaded Control-IQ data to t:connect within

		120 days. The period of 120 days was chosen because on average 98% of CLIO's currently active participants initiated therapy with Control-IQ within that timeframe. Corrected text throughout document that mentioned that Medical Release Forms would be collected for all participants during the informed consent process. Medical Release Forms are only being collected from participants if they report adverse events that require additional information for reporting purposes. Included that participants will be contacted regarding reported adverse events to the Adverse Events section. Added that as part of the enrollment process as specific target subgroups are filled, we may elect to only enroll subjects whose subgroup recruitment goals have not been completed. Change PI to Dr. Jordan Pinsker
07	February 17, 2022	Clarified throughout document which information would be directly entered into the EDC (i.e. participant survey responses) versus verified and entered into eCRF by trained study personnel (i.e. adverse event information). Additional background material added on CGM naïve children who started Control-IQ technology, with a new reference to: (10) Renard E, Tubiana-Rufi N, Bonnemaison E, Coutant R, Della-Vale F, Bismuth E, et al. Outcomes of Hybrid Closed-Loop Insulin Delivery Activated 24/7 versus Evening and Night in Free-living Pre-pubertal Children with Type 1 Diabetes. A Multicenter Randomized Clinical Trial. Diabetes Obes Metab. epub ahead of print, November 23, 2021. Removed text, "Recruitment of CGM-naïve children in our previous clinical trial did not achieve the pre-specified target of 20%", and added per the recent data published in CGM naïve participants in (10) where 33% of

		participants were fully CGM naive, adjusted CGM naive target goals for children to represent current number enrolled in study (n=18). Changed 6-9 years old enrollment goal to 163, as recently published data of 30 children age 6-9 shows successful use of Control-IQ technology (10). Clarified that all reported Adverse Events must be verified by trained study personnel prior to entry into the eCRF and that all outreach attempts to participants follow Tandem's Customer Technical Support customer outreach procedure WIA-000005. Removed the specific section reference within QS-045. Updated Appendix C to be consistent with Tandem's Customer Technical Support customer outreach procedure WIA-000005.

PRINCIPAL INVESTIGATOR SIGNATURES

Protocol Identifying Number:	CLIO Study
Protocol Name:	Control-IQ Observational (CLIO) Post-approval Study
Protocol Version:	V07
Protocol Internal Approval Date	February 17, 2022

The Principal Investigator (undersigned) hereby declares that they have read this protocol and agree to its contents.

The undersigned confirms that the trial will be conducted and documented in accordance with the US Federal, State and Local requirements for a post-market human clinical study, the protocol, and the stipulations of the clinical trial agreement.

By written consent to this protocol, the investigators agree to the above and to fully co-operate with all monitoring and audits in relation to this trial by allowing direct access to all documentation, including source data, by authorized individuals representing Tandem Diabetes Care, Inc., IRBs and/or by the US Federal, State and local regulatory authorities.

Investigator Name: Jordan Pinsker, MD

Investigator Signature: _____

Date (DD/MMM/YYYY): _____

Terms, Acronyms, Abbreviations

ABBREVIATION	DEFINITION
AP	Artificial Pancreas
CGM	Continuous Glucose Monitoring
CRF	Case Report Form
eCRF	Electronic Case Report Form
CRM	Customer Relationship Management System
CLC	Closed-Loop Control
Control-IQ System	t:slim X2 insulin pump with Control-IQ technology
CTS	Customer Technical Support
DiAs	Diabetes Assistant
DKA	Diabetic Ketoacidosis
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
iCGM	Interoperable continuous glucose monitor
ID	Identification
iDCL	International Diabetes Closed Loop
IDE	Investigational Device Exemption
IOB	Insulin-on-Board
IQR	Interquartile Range
JDRF	Juvenile Diabetes Research Foundation
NIH	National Institutes of Health
PRO	Patient Reported Outcome
QA	Quality Assurance
QC	Quality Control
RBM	Risk-Based Monitoring
SAP	Sensor-Augmented Pump
SD	Standard Deviation
T1D	Type 1 diabetes
TDD	Total Daily Dose
UI	User Interface

PROTOCOL SYNOPSIS

Protocol Number	V07
Protocol Title	Control-IQ Observational (CLIO) US Post-Approval Study
Device	t:slim X2 insulin pump with Control-IQ technology (Control-IQ System)
Type of Protocol	Post Approval Study
Rational	This post-approval study is primarily designed to collect safety data on this US FDA-cleared product. Several secondary endpoints assessing the effectiveness of this product in real-world use will also be collected. The t:slim X2 insulin pump with Control-IQ technology will be used as intended and in accordance with FDA-approved labeling.
Objectives	**Primary objective**: To demonstrate, in a real-world setting, the safety of the Control-IQ System for the management of type 1 diabetes by assessing the rate of severe hypoglycemia (SH) and diabetic ketoacidosis (DKA). **Secondary objective**: To demonstrate, in a real-world setting, the effectiveness of the Control-IQ System for the management of type 1 diabetes by assessing the impact on patients' glycemic outcomes and user experience in the real world, during the first 12 months of use.
Primary Endpoints	**Safety Endpoints:** 1) The incidence rates of severe hypoglycemia (SH) and diabetic ketoacidosis (DKA), and 2) The safety of the automatic population of CGM readings into the bolus calculator of the Control-IQ System **Secondary Endpoints:** 3) To determine glycemic outcomes as a measure of efficacy of the Control-IQ System, and 4) To demonstrate patient-reported satisfaction with and trust in the Control-IQ System, usability of the system, and sleep quality.
Duration of Study	All enrolled subjects will be monitored for outcome data for 12 months after starting the Control-IQ System.
Study Design	This post-approval study is a single-arm, prospective study. It is designed to assess 12-month safety in a real-world setting, and to support the continued assessment of the Control-IQ System for the treatment of type 1 diabetes in the United States. In addition, data will be collected to assess glycemic outcomes and user experience.
Study Population	Enrollment in the study will be available to all subjects who start therapy with the Control-IQ System once the Institutional Review Board (IRB) approval is received and the subject meets the indications for use and the study eligibility criteria. As specific target subgroups are filled, we may elect to only

	enroll subjects whose subgroup recruitment goals have not been completed. Electronic informed consent will be required from all subjects prior to participation in the study.
Number of Subjects	The study will recruit a minimum of 2,063 subjects. For the primary safety endpoints, the projected total recruitment sample size of at least 2,063 subjects (including 25% attrition) would provide 80% power with a 2-sided type 1 error rate of 5%. With attrition, it is expected that 1,547 subjects will complete the study. Recruitment goals for study subgroups will include: • At least 385 subjects in the 6 to 13 year-old cohort, and at least 328 subjects in the 14 to ≤18 year-old cohort. Depending on the rate of recruitment in these two age groups, the balance of the total sample will be recruited from the >18 year-old subgroup. • Details on subgroup enrollment targets can be found on page 23 “Determination of Sample Size”
Number and Location of Sites	All data for this study will be collected remotely, with no live clinical visits conducted. Data will be collected electronically, via surveys and automated uploads of pump and CGM data, as well as via in- and out-bound telephone calls and SMS messaging.
Inclusion/Exclusion Criteria	Inclusion Criteria: 1. Patients with self-reported type 1 diabetes who have been prescribed the Control-IQ system. 2. At least 6 years of age 3. Using Humalog or Novolog insulin 4. For females, not pregnant or planning pregnancy in the next 12 months. 5. Agreement to use the t:slim X2 with Control-IQ technology, and to continue use for at least 12 consecutive months after study enrollment. 6. Agree to provide HbA1c result, obtained within the 6-month period prior to enrollment. 7. Ability to respond to alerts and alarms, and to provide basic diabetes self-management. 8. Patients who reside full-time in the United States. 9. Willingness to download the t:connect Mobile application to their Smartphone and keep it active throughout the study. Patients unable to use t:connect Mobile application must be willing to manually upload their insulin pump data to t:connect every three months and at the completion of the study.

	10. Subject has read, understood and agreed to participate in the study, and has electronically signed the Informed Consent Form (ICF). Exclusion Criteria: 1. Self-reported type 2 diabetes 2. < 6 years of age 3. Use of any glucose-lowering therapy other than Humalog or Novolog insulin 4. Inability to respond to alerts and alarms, or to provide basic diabetes self-management. 5. Pregnancy 6. Subjects who have not signed the ICF.
Procedures in Screening/Baseline Period	Study subjects will be recruited via automated electronic outreach from new users of the Control-IQ System. All customers receiving new pumps and receiving Control-IQ software updates will be initially screened for inclusion/exclusion criteria electronically via filters in the CRM system. Invitations to participate will be sent to all customers who initially qualify for the study. A positive response from a customer will initiate the informed consent process and provide a second screening and baseline survey. An electronic signature of consent will be obtained from customers who qualify after the second screening. Once consent is obtained, a baseline survey will collect PROs (user experience and adverse events) related to therapy prior to starting Control-IQ.
Periodic Data Collection procedures	100% of calls to Tandem Customer Technical Support will be screened for reportable AEs based on the definitions of SH and DKA included in this protocol. Outreach surveys will be deployed to all study participants: Monthly to collect AE incidence, and at 3, 6 and 12 months to collect other PROs (See Table 1).
Management of Adverse Events	Safety information will be collected on an ongoing basis throughout the study as Tandem becomes aware of device-related AEs. These events will be recorded electronically from both inbound reports from customers and assessed through outreach to patients. The event, date of onset, severity, seriousness, duration and relationship to the device will be documented. All reported device-related AEs will be followed until they are adequately resolved or stabilized, until study completion/termination, or until number of outreach attempts made by clinical personnel corresponds with company's Customer Technical Support policy for adverse and device issue event outreach, whichever comes first. Safety events will be summarized based on FDA codes.

Statistical Analysis	Descriptive statistics will be used to evaluate outcomes vs. a comparator group. The Comparator Group will be determined using evidence from a systematic literature review examining MDI, insulin pump and sensor augmented pump (SAP) use in patients with type 1 diabetes. Primary endpoints, the risk of AE (DKA, SH), represented as risk ratio per 100 patient years, will be compared using a single sample two-tailed exact binomial test (alpha=0.05) to the expected values as extracted in the literature review. Effect size will be defined as the absolute difference in risk ratios. The safety of automatically populating CGM readings into the bolus calculator will be analyzed by correlating reported AEs, calculator usage data and CGM readings to understand if the bolus calculator may have caused the AE. This analysis will isolate AEs where three consecutive CGM readings ≤54 mg/dL, or ≥250 mg/dL existed within five hours after a correction bolus was given using an automatically populated CGM reading. Boluses using automatically populated CGM values ≥250 mg/dL will be analyzed and evaluated separately from boluses given for lower glucose values. Secondary endpoints will be calculated as means/medians as appropriate based on data extracted from the Tandem t:connect web application and patient reported outcomes. Sensor-glucose concentrations will be analyzed per recent international consensus guidelines, to include time in target range 70-180 mg/dL, time >180 mg/dL, time >250 mg/dL, time <70 mg/dL, time <54 mg/dL. Outcomes will be analyzed quarterly and tabulated using standard statistical tools such as R and Python.

The study will be conducted and documented in accordance with the US Federal and Local requirements for post-market human clinical studies, the protocol, and the stipulations of the clinical trial agreement.

Table 1: Timeline of Data Collection

Procedure/Assessment	Baseline*	Monthly	Months 3 and 6	Final
Informed Consent	X			
**Release of medical records				
Screening for eligibility	X			
Report of incoming AEs		X		X
Outreach for AEs	X	X		X
User Experience	X		X	X
Psychosocial Outcomes	X		X	X

*Includes demographics, frequency of AEs

**Only requested as needed to collect additional information on reported AEs

BACKGROUND

Disease background

Type 1 diabetes affects 1.25 million people in the United States. Approximately 70% of individuals with type 1 diabetes report poor metabolic control, and do not meet the American Diabetes Association's recommended goal of hemoglobin A_{1c} (HbA_{1c}) level of 7.5% for children (<18 years) and 7.0% for adults (≥18 years) (1). These findings indicate the need for better approaches to type 1 diabetes management.

Recent estimates suggest that approximately 400,000 U.S. patients with type 1 diabetes (T1D) use insulin pumps (2). Adoption of pump therapy varies by geography and may be related to healthcare provider preference or patient characteristics and socioeconomic status. Use of insulin pumps is more common in individuals of higher socioeconomic status as reflected by race/ethnicity, private health insurance, family income, and education (3). Additionally, referrals from healthcare providers and insurance approvals are critical determinants for who becomes a pump user in the U.S.(4).

The Tandem t:slim X2 insulin pump with Control-IQ Technology is a third-generation hybrid closed-loop system retaining the same control algorithm that was initially tested by UVA's DiAs system and then implemented in the inControl system. IDE 1-9 below are specific to the implementation proposed here. For complete algorithmic and clinical background, we refer to a number of scientific publications that describe glycemic control outcomes and clinical impressions from the use of the Control-IQ System (5-9). This extensively tested control algorithm has been embedded into the t:slim X2 insulin pump with Control-IQ technology, which is the device in the current study.

The following IDEs reflect the broad scope of development and testing of the current Control-IQ System:

1. IDE #G150240: Project Nightlight: Efficacy and system acceptance of dinner/night vs. 24 hr closed loop control; 11/12/2015.
2. IDE #G160097: Clinical Acceptance of the Artificial Pancreas: The International Diabetes Closed-Loop (iDCL) Trial/Research Site Training Protocol; 06/03/16.
3. IDE#G110095: Clinical Acceptance of the Artificial Pancreas: The International Diabetes Closed-Loop (iDCL) Trial, A Pilot Test of t:slim X2 with Control-IQ Technology. 10/16/2017.
4. IDE#G170267: Real-Time Monitoring and Glucose Control During Winter-Sport Exercise in Youth with Type 1 Diabetes: The AP Ski Camp Continued. 12/01/2017.
5. IDE#G180053: Protocol 3: Clinical Acceptance of the Artificial Pancreas (DCLP3), 6/23/2018.

6. IDE#G180174: The VRIF Trial: Hypoglycemia Reduction with Automated-Insulin Delivery System, 10/5/2018.
7. IDE#G180279: Safety and Efficacy of Initializing the Control-IQ Artificial Pancreas System Using Total Daily Insulin, 11/21/2018
8. IDE#G180053/S008: Protocol 5: Clinical Acceptance of the Artificial Pancreas in Pediatrics. A Study of t:slim X2 with Control-IQ Technology (DCLP5), 12/17/2018
9. 2018-A01152-53 (French National Study ID): Freelife-Kid-AP Study: Assessment of the Efficacy of Closed-Loop Insulin Therapy (Artificial Pancreas) on the Control of Type 1 Diabetes in Prepubertal Child in Free-Life: Comparison Between Nocturnal and 24-Hour Use, 8/7/2018.

In November 2021, Renard *et al*. published the results of the FreeLife Kid AP study (NCT03739099) in France (10). The study involved 122 children with type 1 diabetes ages 6-13 who were enrolled to begin Control-IQ technology use in outpatient, free-living conditions. Participants were randomized to 24/7 use of Control-IQ technology vs. dinner and overnight only use for the first 18 weeks, then all participants continued 24/7 use of Control-IQ technology for an additional 18 weeks. Phone follow up was performed at 48 hours, 1 week and 2 weeks after Control-IQ technology initiation, and scheduled in clinic visits were performed at 6, 12 and 18 weeks. During the 18-week extension period, clinic visits were scheduled at week 27 and at week 36 for the end of the study. Adverse events were solicited at all of these visits.

Study results indicated no ketoacidosis or severe hypoglycemia for the entire study duration (10). Forty participants (33%) in this study were CGM naïve. Thirty were age 6-9. Twenty-one of these CGM naïve participants were randomized to use the system all day for 36 weeks. The other 19 used the system with Control-IQ active at dinner and overnight only for the first 18 weeks, then activated it 24/7 for the next 18 weeks. Mean age of these CGM naive participants was 8.4 years and 50% were female. Mean time in range 70-180 mg/dL was 52.5% at baseline, with 5.6% time less than 70 mg/dL. Using Control-IQ technology 24/7, mean time in range 70-180 mg/dL increased to 67% in this participant group (vs. 67% for the entire study cohort), with mean time <70 mg/dL decreasing to 2.8% (vs 2.7% for the entire study cohort) [CGM Naïve Participant Data On File].

General Description of Investigational Device

The t:slim X2 insulin pump with Control-IQ technology, the hybrid closed-loop insulin delivery system from Tandem Diabetes Care, is intended for subcutaneous delivery of insulin for the management of type 1 diabetes mellitus. The system uses advanced closed-loop control algorithms to adjust insulin delivery to help keep blood glucose in a targeted range. The current Control-IQ System components include the t:slim X2 insulin pump with Control-IQ technology and the current generation of the Dexcom G6 CGM.

Future iterations of the Control-IQ System may incorporate FDA-cleared modifications to the algorithm and integration with any FDA-cleared continuous glucose monitors that meet the iCGM criteria. Subjects in this study will be allowed to update their therapy with future products from Tandem Diabetes Care, Inc., and future FDA-cleared CGMs that meet the iCGM criteria, during the study period.

The Control-IQ Technology uses data from the CGM and other inputs to:

- decrease and/or suspend insulin delivery when hypoglycemia is predicted (or occurs);
- increase insulin delivery when hyperglycemia is predicted (or occurs), and
- deliver automated correction boluses when necessary to mitigate hyperglycemia

The system used in this study is comprised of a CGM sensor and transmitter along with an insulin pump with user interface (IU) for display of system information, and a control algorithm. The sensor is inserted subcutaneously and transmits data every 5 minutes to the pump via the transmitter.

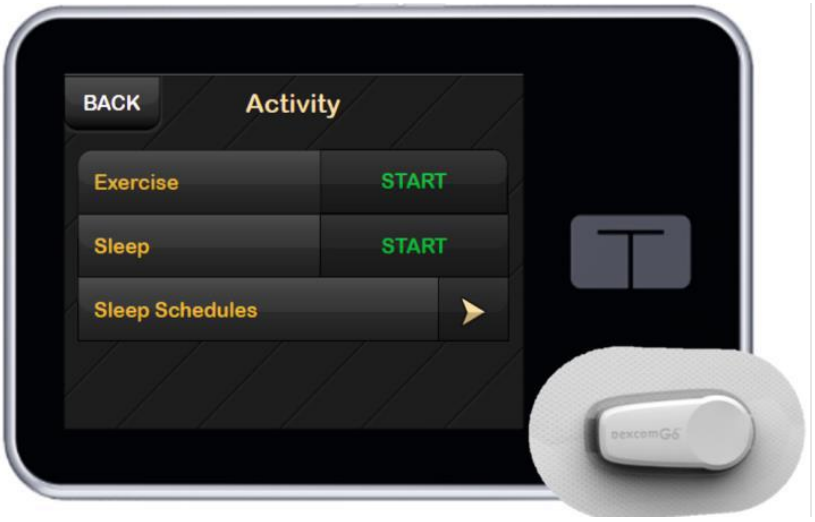

Figure 1 - Tandem Pump Control-IQ System

STUDY OBJECTIVES, DESIGN AND ENDPOINTS

Study Objectives

Primary objectives:

1) To demonstrate, in the post-approval setting, the safety of the Control-IQ System for the management of type 1 diabetes by assessing the rate of severe hypoglycemia (SH) and diabetic ketoacidosis (DKA),

2) To monitor the safety of the automatic population CGM readings into the bolus calculator of the Control-IQ System,

Secondary objectives:

3) To determine glycemic outcomes during real-world use of the Control-IQ System, and

4) To demonstrate patient-reported satisfaction with the device, trust in the Control-IQ System, usability of the system, and sleep quality.

Study Design

This post-approval study is a single-arm, prospective, longitudinal study. It is designed to assess the 12-month safety and effectiveness of this FDA approved product in a post-approval setting, and to support the continued assessment of the t:slim X2 insulin pump with Control-IQ technology for the treatment of type 1 diabetes in the US. In addition, data will be collected to assess the experience of patients using the Control-IQ system.

This study will enroll a minimum of 1698 subjects over a two-year period. All enrolled subjects will be monitored from baseline through 12 months following the initiation of therapy with the Control-IQ System.

The data collected in this study will be entered into either Qualtrics, a HIPAA compliant software database, or an electronic data capture system (EDC) using electronic case report forms (eCRFs). Subject data will include participant reported demographics, medical history, and baseline therapy information along with therapy data, and follow-up measures.

Study Endpoints

- Primary Safety Endpoints: Composite rate of severe hypoglycemia and diabetic ketoacidosis through 12 months following initiation of therapy with the Control-IQ System.
- Secondary Effectiveness Endpoints
    - Glycemic outcomes (based on data from CGM sensor values):
        - % time in range (70-180 mg/dL)
        - % time <54 mg dL
        - % time <70 mg/dL
        - % time >180 mg/dL

        - %time >250 mg/dL
    - Patient-reported outcomes:
        - Satisfaction with device
        - Trust in the system
        - Usability of the system
        - Sleep quality

SUBJECT SELECTION

Subject Population

Inclusion Criteria: Patients must consent to meet the following criteria in order to be enrolled in the study:

1) Patients with self-reported type 1 diabetes who have been prescribed the Control-IQ system.
2) At least 6 years of age
3) Using Humalog or Novolog insulin
4) For females, not pregnant or planning pregnancy in the next 12 months.
5) Agreement to use the t:slim X2 with Control-IQ technology, and to continue use for at least 12 consecutive months after study enrollment.
6) Agree to provide HbA1c result, obtained within the 6-month period prior to enrollment.
7) Ability to respond to alerts and alarms, and to provide basic diabetes self-management.
8) Patients who reside full-time in the United States.
9) Willingness to download the t:connect Mobile application to their Smartphone and keep it active throughout the study. Patients unable to use t:connect mobile application must be willing to manually upload their insulin pump data to t:connect every three months and at the completion of the study.
10) Subject has read, understood and agreed to participate in the study, and has electronically signed the Informed Consent Form (ICF).

Exclusion Criteria: Patients with the following characteristics will not be considered candidates for the study:

1) Self-reported type 2 diabetes
2) < 6 years of age
3) Use of any glucose-lowering therapy other than Humalog or Novolog insulin
4) Inability to respond to alerts and alarms, or to provide basic diabetes self-management.
5) Pregnancy
6) Subjects who have not signed the ICF.

Any discrepancy in the above criteria between data in CRM and subject's self-reported criteria will be electronically alerted to study staff. Study staff will then clarify inclusion/exclusion criteria prior to enrolling the subject.

Over the course of the study as specific participant recruitment subgroups are filled, we may enroll subjects whose subgroup goals have not been completed and elect to exclude otherwise applicable participants.

Subject Withdrawal or Termination

Subjects are free to withdraw from the study at any time and will be withdrawn if they inform Tandem that they no longer wish to participate. Data collected prior to the subject's withdrawal will remain part of the study record and will be included in the analyses. All participants that have been successfully enrolled in the study will receive regular invitations to provide data. A Retention Management protocol will be initiated to attempt to re-engage participants that do not respond after three separate outreach attempts.

TREATMENT OF SUBJECTS

The t:slim X2 insulin pump with Control-IQ technology

The Control-IQ System is a US FDA-approved device indicated for the treatment of type 1 diabetes in people age 6 years and older. The Control-IQ System is integrated with the Dexcom G6 CGM and uses CGM values to adjust insulin delivery with the goal of improving glucose control (time in range of 70-180 mg/dL).

Initiation of therapy with the Control-IQ System:

- Subjects will be recruited from the population of patients initiating therapy with Control-IQ after it has been prescribed by a licensed healthcare professional.
- Subjects new to the Tandem X2 insulin pump will receive a new pump with Control-IQ technology
    - These subjects might be new to insulin pump therapy or might be switching from a different brand or type of insulin pump.
- Subjects who own a t:slim X2 insulin pump will receive a remote software update and download the Control-IQ technology onto their existing t:slim X2 insulin pump.

Enrollment procedure:

The enrollment process has been detailed in the flowchart in **APPENDIX A**. Study subjects will be enrolled using customer recruitment filters and triggers from two data sources housed within Tandem – (a) the CRM (or the Custom Relationship Management Technology) and (b) the t:connect® customer portal (web secure application designed for Tandem users to request prescriptions for any pump-related updates and complete necessary trainings). Daily automatic recruitment invite contact lists, defined by study inclusion and exclusion criteria, will be generated for eligible Tandem users and using a

secure file transfer protocol, and Qualtrics (a HIPPA compliant survey and report generating software) will deploy automated survey invites daily (via email or SMS text). The first study invite will include important information about the study eligibility criteria and an invitation to start the informed consent process, including a Release of Medical Records form and the baseline questionnaires (baseline adverse events and other PRO measures). Tandem users who indicate that they are not interested in participating will be removed from the potential recruitment list and will not receive any further communication about the study. The remaining users will receive reminder emails (as needed) and those interested will complete the IRB approved electronic consent form by providing their digital signature.

Duration of therapy and follow-up: All enrolled subjects who initiate therapy with the Control-IQ System will be monitored from baseline through 12 months following the initiation of treatment. Participants will be considered screen failures if Control-IQ data has not been downloaded to t:connect 120 days after the baseline survey's completion.

MEASUREMENTS AND EVALUATIONS

Event Schedule: The eCRFs will be completed by the investigator (or an authorized member of the investigator's staff) and entered into the EDC database per the event schedule described below.

Baseline Data Collection: The potential study subjects will be evaluated (initially via CRM filters) to ensure they are appropriate candidates for this post approval study. Interested subjects will be asked to sign the ICF electronically. Eligibility to enroll in the study will be assessed based on the inclusion/exclusion criteria and the fulfillment of specific target subgroup populations. The enrollment information will be entered via participant responses into the EDC system. In addition, demographic and relevant medical history will be collected at this time (see **APPENDIX A** for detailed steps in the screening and enrollment process).

Subject Completion or Early Withdrawal: The subject completes the study one year after initiating therapy with Control-IQ, or when they choose to withdraw from the study, if earlier than 1 year.

Data Collection:

The data will be collected per the schedule outlined below:

Procedure/Assessment	Baseline*	Monthly	Months 3 and 6	Final
Informed Consent	X			
**Release of Medical Records				
Screening for eligibility	X			
Report of incoming AEs		X		X
Outreach for AEs	X	X		X
User Experience	X		X	X

Psychosocial Outcomes	X		X	X

*Includes demographics, frequency of AEs

**Only requested as needed to collect additional information on reported AEs

Investigators will be provided a process for assigning a de-identified number to the subject and will be required to keep any study paperwork or electronic files in a secure private area. Electronic audits will be in place to help ensure that data entered is within reasonable limits.

Informed Consent Process: All subjects must electronically sign the ICF (see **APPENDIX B**) approved by the IRB to be enrolled in the study. The subject will receive study team contact information (email and telephone) and be given ample opportunities to ask questions about the procedures, required schedule of data collection, and the benefits and risks of participating in the study before signing the ICF. All subjects will receive an electronic copy of the ICF to keep for their records. Subjects will be informed of any revisions to the ICF and any revisions must be electronically signed and kept in the subject study file. In addition, a signed Release of Medical Records form may be obtained if needed to collect additional information on reported Adverse Events to allow the investigators to obtain accurate event information when necessary. Acquisition of the informed consent, Release of Medical Records form (if applicable) and any revisions will be documented in the survey database.

Demographics: The following demographic data will be obtained: date of birth, gender, race, ethnicity, educational level, socioeconomic status, residence, employment status, weight, height, and type of health insurance.

Medical History: Medical history, including existing comorbidities deemed clinically relevant (e.g. retinopathy, nephropathy, neuropathy, history of cardiovascular events) will be collected at baseline. In addition, details specific to type 1 diabetes, including age at diagnosis, duration of disease, previous therapy, most recent HbA1c within the past 6 months, frequency of SH and DKA, and family history will be collected from the study subject in the baseline questionnaire.

Participants already recruited during the COVID emergency who did not have a recent HbA1c result within the past 6 months of enrollment will not be counted toward overall recruitment goals, and will be analyzed separately.

Observation and Recording of Adverse Events: Subjects will be required to report AEs. Open-ended questions and questions specific to SH and DKA will be included in all subject outreach contacts. In addition, the Global Post-market Surveillance data base (Tandem Diabetes Care, Inc.) will be queried monthly to determine the incidence of SH and/or DKA reported by study subjects (see **APPENDIX C** for surveillance procedures).

An AE form will be completed for every adverse event reported by a subject and verified by trained study personnel. Any medical management of an event and the resolution of the event must be recorded within the internal database utilized by Tandem's Global Post-

market Surveillance team (CRM), as the source documentation, and on the appropriate eCRF using medical terminology.

Patient-reported Outcomes: Questionnaires and surveys suitable for subjects being treated for type 1 diabetes (see **APPENDIX D**) will be electronically deployed to subjects at times specified in the Data Collection Timeline.

ADVERSE EVENTS

Adverse Event Definitions

An **adverse event** (AE) is any untoward medical occurrence in a study subject, regardless of the relationship between the adverse event and the device under investigation. All AEs experienced by all subjects will be documented throughout the entirety of the study, as outlined below.

In this study, the subjects will be instructed to report AEs spontaneously or in response to general, non-directed, or directed questions. At any time during the study, the subject may volunteer information that resembles an AE. Once it is determined by trained study personnel confirming with the subject that an AE has occurred, the investigator will obtain all the information required to complete the AE form. Any medical management of an event and the date of resolution of the event must be recorded on the appropriate eCRF using medical terminology. Any AE experienced by a subject will be followed until the AE has resolved to the clinical investigator's satisfaction or is considered stable. If information about an AE (or suspected AE) is not adequately obtained via incoming calls to Customer Technical Support or electronic means, the study team will contact the participant, request medical records and/or contact the subject's physician for more information. Trained study personnel will follow Tandem's Customer Technical Support working instructions (WIA-000005) for customer outreach policies when confirming an adverse event for the study. The adverse event form will document the following:

- AE diagnosis or definition
- Serious/non-serious
- Severity
- Action taken
- Relationship to Control-IQ System
- Anticipated/Unanticipated
- Date of onset
- Date of resolution

Additional information on specific events may be recorded in the eCRF.

Each adverse event form that has been verified will be reviewed by the clinical investigator to determine the type, intensity, severity, and causality of the event, and whether anticipated or unanticipated, in order to verify the reporting that is required. The guidelines below will be followed to characterize each event.

Reportable Adverse Events:

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

1. Hypoglycemia meeting the definition of severe hypoglycemia (SH)
2. Diabetic ketoacidosis (DKA)
3. A serious adverse event (SAE)
4. An adverse device effect (ADE)

Hypoglycemia and hyperglycemia not meeting the criteria below will not be recorded as adverse events unless associated with an adverse device effect (ADE). Skin reactions from sensor placement are only reportable if severe and/or if they required treatment.

Severe Hypoglycemia:

Hypoglycemia not associated with an ADE is only reportable as an adverse event when the assistance of another person was required in order to actively administer carbohydrate, glucagon, or other resuscitative actions due to altered consciousness. This means that the subject was impaired cognitively to the point that he/she was unable to treat him/herself, was unable to verbalize his/her needs, was incoherent, disoriented and/or combative, or experienced seizure or coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. If glucose measurements are not available during such an event, neurological recovery attributable to the restoration of glycose to normal is considered sufficient evidence that the event was induced by a low glucose concentration.

Subjects will be instructed on this specific definition of severe hypoglycemia each time information is requested related to this AE.

Diabetic ketoacidosis:

DKA is reportable as an adverse event when the subject reports the following:

- Symptoms such as polyuria, polydipsia, nausea or vomiting, and
- Treatment provided in a health care facility, and
- Diagnosis of DKA made by a health care provider and self-reported by the patient.

Subjects will be instructed on this specific definition of DKA each time information is requested related to this AE.

Serious Adverse Event (SAE):

In accordance with 21 CFR Parts 803 and 812, a SAE is defined as any untoward medical occurrence that:

- Results in death,
- Is life-threatening,
- Requires hospitalization or prolongation of existing hospitalization,

- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions,
- Is a congenital anomaly or birth defect, or
- Is considered a significant medical event by the investigator based on medical judgement (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

Medical and scientific judgement will be exercised in deciding whether medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious. A serious adverse event must be reported to the FDA as soon as possible, within a maximum of 15 calendar days.

Unanticipated Adverse Device Effect (UADE)

In accordance with 21 CFR Part 812, an UADE is 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 risk assessment, the ICF as well as the protocol, or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects. An unanticipated device effect must be reported to the IRB within 5 business days and to the FDA within 10 business days.

In contrast to a UADE, an anticipated SAE is any SAE, the nature or severity of which has been reported in clinical trials of the Control-IQ System, or reported to Tandem Diabetes Care, Inc. by users of the t:slim X2 insulin pump. AEs reported during clinical studies of the Control-IQ system and post-market vigilance of the t:slim X2 insulin pump include, but are not limited to, the events shown below. The following device issues are anticipated and will not be reported on a Device Issue Form but will be reported as an Adverse Event if the criteria for AE reporting described above are met:

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

In addition, if the device issue is listed in Tandem Procedure QS-045, FDA Medical Device Reporting will be anticipated and not reported on a Device Issue Form. Any other device-related SAE will be considered an unanticipated adverse device event (UADE).

Relationship of Adverse Event to Study Device (causality):

The clinical investigator will assess the relationship of any adverse event to be related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by the study device. To ensure consistency of adverse event causality assessments, the investigator will apply the following guidelines when determining whether an adverse event is related:

YES: There is a plausible temporal relationship between the onset of the adverse event and the study intervention, and the adverse event cannot be readily explained by the subject's clinical state, intercurrent illness or concomitant therapies; and/or the adverse event follows a known pattern of response to the study intervention; and/or the adverse event abates or resolves upon discontinuation of the study intervention.

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

Adverse Device Effect (ADE):

Any untoward medical occurrence in a study subject which the device may have caused or to which the device may have contributed (Note that a Device Deficiency or Issue Form must be completed in addition to an Adverse Event Form, if the event is determined to be an ADE.

Intensity of Adverse Event:

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

- Mild: Usually transient, requires no special treatment, and does not interfere with the subject's daily activities.
- Moderate: Usually causes a low level of inconvenience or concern to the subject and may interfere with daily activities but is usually ameliorated by simple therapeutic measures.
- Severe: Interrupts a subject's usual daily activities and generally requires systemic drug therapy or other treatment.

Expedited Safety Reports:

As the Control-IQ System is an FDA-approved and commercially available product in the US, in addition to SH, DKA, SAEs and UADEs, medical device reporting requirements (21 CFR 803) are applicable to all AEs reported through this study.

STATISTICAL CONSIDERATIONS

Determination of Sample Size

The approach to sample size and statistical analyses are summarized below. A detailed statistical analysis plan will be written and finalized prior to the first tabulation of data. In order to determine the incidence rates on which the power analyses were based, Tandem conducted a literature review (see Attachment 1 for methodology). Ranges of event rates reported in the literature for both severe hypo and DKA in patients with T1D are very broad; 0-100 events/100PY for severe hypoglycemia, and 0.4 – 26 events/100 PY for DKA (see Table 1, Attachment 1). Therefore, for purposes of power analyses for the proposed study, we used event rates from a recently published study using a large Type 1 Diabetes Exchange cohort (Foster et al, 2019). This study used a similar design as our approved post-market study, the subjects represent our intended use population, and the event rates reported in the Foster study fall within the broader rates found in the extensive body of literature reviewed.

Sample size was determined in 3 steps:

Step 1 – Power analysis for severe hypoglycemia (SH)

An overall incidence rate of 25.35 events per 100 patient years (PY) was used in the power analysis for severe hypoglycemia. We calculated that a sample size of 1,354 individuals with T1D would provide 80% power with a type 1 error rate (two-sided) of 5% to detect a difference, if there is one, between the expected SH rate (25.35) and the proposed study sample SH event rate.

A separate power analysis for the 14-18 age group used an overall SH incidence rate of 19.5 events/100PY. Results indicated that a sample size of 231 individuals with T1D between the ages of 14-18 would provide 80% power with a type 1 error rate (two-sided) of 5% to detect a difference, if there is one, between the expected SH rate (19.5) and the proposed study sample SH event rate. Of the overall sample of 1,354 subjects, at least 231 subjects will be 14-18 years old to provide sufficient power to detect risk of SH in this younger age group.

A separate power analysis for the 6-13 year old group used a SH incidence rate of 21.9 events/100PY, which is a weighted average of both MDI and pump users (since pump users were overrepresented in this age group). Results indicated that a sample size of 288 individuals with T1D between the ages of 6 and 13 would provide 80% power with a type 1 error rate (two-sided) of 5% to detect a difference, if there is one, between the expected SH rate (21.9) and the proposed study sample SH event rate. In addition to

the overall sample, at least 288 subjects will be 6-13 years old to provide sufficient power to detect risk of SH in this younger age group. *Step 2 – Power analysis for diabetic ketoacidosis (DKA)*

An overall incidence rate of 11.03 events per 100 patient years was used in the power analysis for DKA . We calculated that a sample size of 1,282 individuals with T1D would provide 80% power with a type 1 error rate (two-sided) of 5% to detect a difference, if there is one, between the expected DKA rate (11.03/100 PY) and the proposed study sample DKA event rate.

A separate power analysis for the 14-18 age group used an overall DKA incidence rate of 14.2 events/100PY. Results indicated that a sample size of 328 individuals with T1D between the ages of 14-18 would provide 80% power with a type 1 error rate (two-sided) of 5% to detect a difference, if there is one, between the expected DKA rate (14.2) and the proposed study sample DKA event rate. Of the overall sample of 1,282 subjects, at least 328 subjects will be 14-18 years old to provide sufficient power to detect risk of DKA in this younger age group.

A separate power analysis for the 6-13 year old group used an overall DKA incidence rate of 13.2 events/100PY, which is a weighted average of both MDI and pump users (since pump users were overrepresented in this age group). Results indicated that a sample size of 77 individuals with T1D between the ages of 6-13 would provide 80% power with a type 1 error rate (two-sided) of 5% to detect a difference, if there is one, between the expected DKA rate (13.2/100PY) and the proposed study sample DKA event rate. In addition to the previously determined sample, at least 77 subjects will be 6-13 years old to provide sufficient power to detect risk of DKA in this younger age group.

Step 3 – Final sample size determination

The projected total recruitment sample size of at least 2,063 subjects (including attrition) would provide 80% power with a 2-sided type 1 error rate of 5%. Considering the 25% attrition mentioned above, it is the expectation to have 1,354 subjects complete the study. Recruitment goals for study subgroups will include:

- At least 385 subjects in the 6 to 13 year old cohort, and at least 328 subjects in the 14 to ≤ 18 year old cohort. Depending on the rate of recruitment in these two age groups, the balance of the total sample will be recruited from the >18 year old subgroup.
- Of the 6-13 year old cohort:
    - At least (n=163) will be 6-9 years old, as recently published data of 30 children age 6-9 shows successful use of Control-IQ technology (10).
    - At least 25% (n=96) will have a baseline A1c ≥ 8.5%
    - At least 25% (n=96) will be pump naïve
    - At least 5% (n=18) will be CGM naïve. This percentage is based on clinical evidence of high baseline CGM use in this age group, and recently published data of 40 CGM naïve children who successfully used Control-IQ

technology (10). With the availability of this data from these 40 participants, recruitment goals for the CGM naïve cohort of children in CLIO was reduced to 18 participants.

- Of the >14 year old cohort,
    - Approximately 677 subjects each in the pump user and pump naïve subgroups at baseline.
    - Approximately 270 subjects that are CGM naïve (defined as not using CGM in the 30 days prior to enrollment).
    - Approximately 681 subjects (33% of total sample) with HbA1c ≥8.5% and 681 subjects (33% of total sample) in the <8.5% subgroup

Statistical Analysis

Descriptive statistics will be used to describe outcomes vs. a comparator group. The Comparator Group will be determined using evidence from a systematic literature review examining MDI, insulin pump therapy (IPT) and sensor augmented pump (SAP) use in patients with type 1 diabetes. Studies published since January, 2020 will be included in the analysis. This will establish the baseline sample representation and outcome metrics. Users of automated dosing systems, including low glucose suspend, predictive low glucose suspend (such as Basal-IQ technology) will not be analyzed as part of the Comparator group.

The publications included in the literature review have been identified to represent the typical population of people with type 1 diabetes, and include sample populations that mirror those described above in the target population for this study, including:

- Children age 6 years old and older
- Adolescents age 14-18 years old
- Adults >18 years old
- Patients with pump experience
- Pump naïve patients
- Patients with CGM experience
- CGM naïve patients
- Wide range of baseline HbA1c values

Primary endpoints, the risk of AE (DKA, SH), represented as risk ratio per 100 patient years, will be compared using a single sample two-tailed exact binomial test (alpha=0.05) to the expected values as extracted in the literature review. Effect size will be defined as the absolute difference in risk ratios.

Primary Outcome

Incidence rate/100 patient years for both severe hypoglycemia (SH) and diabetic ketoacidosis (DKA).

Success Criteria/Goal: Study participants will not experience a higher incidence of SH or DKA than incidence rates reported in the literature from analyses of similar populations. Overall outcomes will be compared to data below, derived from a recently published study using a large Type 1 Diabetes Exchange cohort (Foster et al., 2019). This study used a similar design as our postmarket study proposed here, the subjects represent our intended use population, and the event rates reported in the Foster study fall within the broader rates found in the extensive body of literature reviewed.

SH Incidence Rates (all ages)		SH Incidence Rates in Children			SH Incidence Rates in Adults	
All ages (13-93)			**Ages 6-12**	**Ages 13-17**	**Ages 18-93**	
All insulin delivery	25/100 PY	**All insulin delivery**	22/100 PY	20/100 PY	**All insulin delivery**	30/100 PY
MDI	37/100 PY	**MDI**	28/100 PY	34/100 PY	**MDI**	38/100 PY
IPT	23/100 PY	**IPT**	16/100 PY	13/100 PY	**IPT**	27/100 PY
DKA Incidence Rates (all ages)		DKA Incidence Rates in Children			DKA Incidence Rates in Adults	
All ages (13-93)			**Ages 6-12**	**Ages 13-17**	**Ages 18-93**	
All insulin delivery	11/100 PY	**All insulin delivery**	13/100 PY	14/100 PY	**All insulin delivery**	9/100 PY
MDI	17/100 PY	**MDI**	22/100 PY	25/100 PY	**MDI**	13/100 PY
IPT	7/100 PY	**IPT**	5/100 PY	9/100 PY	**IPT**	7/100 PY

The full literature review can be found in Attachment 1 of this protocol.

The safety of automatically populating CGM readings into the bolus calculator will be analyzed by correlating reported AEs, calculator usage data and CGM readings to understand if the bolus calculator may have caused the AE. This analysis will isolate AEs where three consecutive CGM readings ≤54 mg/dL, or ≥250 mg/dL existed within five hours of receiving a correction bolus using an automatically populated CGM reading. All CGM readings within 5 hours after the bolus is given will be evaluated. In addition, correction boluses using automatically populated CGM values ≥250 mg/dL will be analyzed and evaluated separately from boluses given for lower glucose values.

Secondary endpoints will be calculated as means/medians as appropriate based on data extracted from the Tandem t:connect web application and patient reported outcomes. Sensor-glucose concentrations will be analyzed per recent international consensus guidelines, to include time in target range 70-180 mg/dL, time >180 mg/dL, time >250 mg/dL, time <70 mg/dL, time <54 mg/dL.

Outcomes will be analyzed quarterly and tabulated using standard statistical tools such as SPSS, R and Python.

Data Management

Data from the study will be collected via study databases. Data will be sent in a secured validated format to Tandem Diabetes Care, Inc. on an ongoing basis.

Trained study personnel will be responsible for entering data on the adverse events, as specified in the protocol, applicable device issues and any unscheduled contacts with participants into the eCRF system and according to the eCRF instructions. All other data such as eligibility, medical history and other assessments will be captured directly by participants as part of their responses to the surveys and collected directly as part of the survey database. The eCRF instructions will also provide data entry instructions. Risk-based monitoring of data will be conducted. Data entered in the eCRF will be immediately saved to a central database and changes tracked to provide an audit trail. When data have been entered, reviewed, edited and source data verification (SDV) performed as specified per the clinical monitoring plan, the investigator will be notified to sign the eCRF electronically as per the agreed upon project process, and data will be locked to prevent further editing. A copy of the eCRF will be archived at Tandem Diabetes Care, Inc.

Data verification and data validation checks will be performed by Tandem Diabetes Care, Inc., or its designee(s), using electronic checks comprised of validated computer programs and manual data review. Any data discrepancies will be referred back to the investigator for resolution. After the database has been declared clean it will be locked, and editing in the database will only be allowed with the proper documentation. After database lock, data will be extracted for analysis.

LEGAL/ETHICS AND ADMINISTRATIVE PROCEDURES

Good Clinical Practice/Regulatory Compliance

The procedures described in this study protocol pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigators abide with FDA regulations in accordance with 21 CFR, Parts 50, 56, and 812; applicable state and local regulations; and the standard operating procedures (SOPs) of Tandem Diabetes Care, Inc., and its designee(s).

Independent Institutional Review Boards (IRBs) will provide oversight per local requirements and review documents associated with the study to determine that they comply with all federal, state, and local laws and that the risks to subjects are minimized and reasonable in relation to anticipated benefits per the US Code of Federal Regulations (CFR), Title 21, Part 56, Section 56.111(a).

It is the investigators' responsibility to ensure that adequate time and appropriate resources are available in order to conduct the study. The investigators should also be

able to estimate or demonstrate the potential for recruiting the required number of suitable subjects within the agreed upon recruitment period. The investigators will maintain a list of appropriately qualified personnel to whom the investigators have delegated significant study-related tasks.

Investigator Qualification / CV

The investigators will provide the sponsor with a current curriculum vita and any revisions/updates during the study, as well as those of any staff personnel with significant study responsibilities.

Statement of Investigator

The investigators are required to sign and date a Statement of Investigator form for the original and each subsequent amendment of the protocol, prior to enrolling any subjects under that protocol version.

Financial Disclosure

Financial disclosure statements will be completed for the investigators to disclose potential conflicts of interest (per 21 CFR Part 54). Financial disclosure information will be kept updated as necessary throughout the duration of the study.

Investigator Training

Investigators and their designees will be trained in the informed consent, screening and enrollment procedures, as well as proper documentation of all procedures. Investigators must provide recent certification of GCP training.

Responsibilities

Sponsor Responsibilities

The sponsor of this study is Tandem Diabetes Care, Inc. of San Diego, CA, US. The sponsor is committed to:

- Protecting the rights, health, safety and welfare of study subjects by the review of IRB approvals and verification of the subject informed consent process.
- Verification of data in CRM, used to initially qualify customers for participation in the study.
- Periodically reviewing the data to ensure that the study is being conducted in compliance with the protocol and the investigators' agreement. Providing the investigators with access to the EDC system and study eCRFs.
- Maintaining a system of study documentation.
- Providing training on key elements of the protocol, including subject inclusion/exclusion criteria, EDC system, and all study procedures.
- Reviewing eCRFs to ensure completeness and accuracy of study data. Investigators will be required to resolve discrepancies via the EDC system.

Responsibilities of the Principal Investigators

The investigators will affirm by their signatures on the Investigator Agreement that they will fulfill their responsibilities relative to the study. The investigator responsibilities include:

- Ensuring that all subjects entering the study conform to the subject inclusion criteria and that no exclusion criteria apply.
- Obtaining IRB approval to conduct the study, prior to enrolling any subjects.
- Submitting the ICF to the IRB for approval prior to initiation of the study.
- Obtaining written informed consent from each subject prior to enrollment and verifying that the correct and approved IRB version is used. The electronically signed ICF will be maintained in the subject's record, and a copy of the signed ICF will be part of each subject's case report file retained by the investigator.
- Accurately reporting adverse events in a timely manner by obtaining information from incoming calls to Customer Technical Service, by outreach via surveys, SMS text and phone, and by review of medical records or physician contact if necessary.
- The investigator will review, correct as needed, and sign off on the accuracy and completeness of the data entered in the EDC system. Original laboratory reports, medical records, etc (if applicable). are to be retained by the investigator, and the resulting data shall be entered onto the appropriate eCRFs.

Institutional approval of the protocol

It is the responsibility of the investigator to submit this protocol, the informed consent form, relevant supporting information and all types of subject recruitment information to the IRB for review and approval prior to site initiation. A copy of the written approval of the protocol and ICF must be received by the sponsor prior to the recruitment of subjects.

Prior to implementing changes in the study, the sponsor and IRB must approve any revised informed consent documents and amendments to the protocol with documentation of the approvals submitted to the sponsor. The approval document must clearly state the study reference, date of review, and actions taken. The investigator will be responsible for keeping the IRB apprised of the progress of the study, any changes to the protocol, deviations from the protocol, and SAEs or UADEs.

IRB Membership Roster

The investigator must submit a complete and current roster of the IRB to the sponsor.

Informed Consent – Ethical Compliance

It is the responsibility of the investigator or a trained delegate to obtain electronic informed consent from subjects prior to the conduct of any study procedures. All consent documentation must be consistent with applicable regulations and Good Clinical Practice.

Each subject or the subject's legally authorized representative is required to sign the ICF after the subject has received and read the information and received an explanation of the study, including but not limited to: a description of the study, expected duration, statement of the subject's right to decline to participate or to withdraw from the study at any time and for any reason without fear of retribution, potential risks and benefits, limits of confidentiality, and contact information of the research personnel. A copy of the informed consent documentation must be provided to the subject or the subject's legally authorized representative.

Acquisition of the informed consent will be documented in the subject record, and the ICF must be electronically signed and dated by the subject. Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

Subject Privacy and Confidentiality

The sponsor and investigators affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, all data collected and analyzed by the sponsor or designee will be treated confidentially and identified by an identification number.

To verify compliance with the protocol, the sponsor will periodically audit the subject's de-identified study record (including but not limited to laboratory results and medical records, if applicable).

Data collected during this study may be used to support the development, approval or marketing of Tandem products. Collected data may be reviewed by the sponsor and/or its representatives, independent auditors who validate the data on behalf of the sponsor, third parties with whom the sponsor may collaborate, national or local regulatory authorities, and the IRB which granted approval for the study to proceed.

Study Monitoring

Monitoring of the study will be detailed in the study clinical monitoring plan and will be performed by qualified personnel from the sponsor or sponsor designee. At the monitoring visits, the progress of the study will be discussed with the investigators or designees. The ICFs will be reviewed for signatures and the eCRFs checked for completeness and accuracy. Subject source data must be available for review. The investigator and staff are expected to cooperate with the study monitor and be available during at least a portion of the monitoring visit to review the eCRFs and any queries/resolutions, answer questions, and provide any missing information.

Modification of the Protocol

All amendments to the protocol must be documented in writing, reviewed and approved by the investigators and sponsor, and submitted to the IRB for approval prior to initiation. If the protocol amendment substantially alters the study design or potential risk to the

subject, new written informed consent must be obtained from each subject for continued participation in the study.

Suspension or Termination of the Study

If conditions arise requiring further clarification before the decision can be reached to proceed with or terminate the study, the study will be suspended until the situation has been resolved.

The sponsor has the right to terminate this study at any time.

Departure from Protocol

No deviation may be made from the protocol except to protect the health and welfare of a study subject. Further, changes to the study protocol will be implemented only after an amendment has been agreed to in writing by the sponsor, and the protocol amendment is approved by the IRB.

Protocol deviations will be tracked according to the following categories:

- Major protocol deviations
- Minor protocol deviations

Major protocol deviations are defined as:

- Enrollment eligibility criteria deviations
- Informed consent process not followed

All other protocol deviations will be classified as minor protocol deviations.

Potential Risks to Subjects

There are limited risks to subjects as a result of having their data collected for this study. The study procedures and data being collected are part of routine subject follow-up or standard of care.

Potential Benefits to Subjects and Society

In the future, subjects may benefit from results that lead to a better understanding of the safety and effectiveness of the t:slim X2 insulin pump with Control-IQ technology in the broader context of other options for the treatment of type 1 diabetes. The healthcare system may benefit from a better overall understanding of effectiveness and costs of this system. The study may also help define new standards of care for the treatment of type 1 diabetes.

Financial Considerations

Subject Compensation

Each study subject will potentially receive $110 for completing the study. Participants who complete all assessments (including monthly AEs) will receive a bonus of $40 (a total of

$150 for completing the study. Compensation will be weighted toward the end of the study to incentivize completion.

Recording, Access to and Retention of Source Data

Investigators are required to prepare and maintain adequate source documentation which includes records covering subject participation in the study including basic identification information, and medical records obtained during the study. In most cases, information is documented directly per survey responses into the study database, which act as source documentation.

The monitor (auditors, IRB or regulatory inspectors) may check the eCRF entries against the source documents. The consent form will include a statement by which the subjects allow access to source data that substantiate information recorded in the eCRF. In addition, the Release of Medical Records form will allow for the review of medical records and contact with the subject's physician when necessary. Study personnel, bound by professional ethics, will not disclose any personal information or personal health information.

As described in the US FDA regulation 21 CFR 812.140, investigator records, including eCRFs, source documents, consent forms, laboratory test results (if applicable), and device records, should be retained by the investigator until at least two years after the date on which the investigation is terminated or completed, or the date that the records are no longer required.

Electronic Case Report Forms

The investigator is responsible for maintaining adequate and accurate source documents from which accurate information will be transcribed into eCRFs that have been designed to capture all observations and other data pertinent to the clinical investigation. eCRFs should be completed by the investigator or delegate as states on the Delegation of Authority Log. Overwriting of information or use of correcting fluid or tape is not allowed in source documentation.

Once the study monitor has verified the contents of the completed eCRFs against the source data, queries may be raised if the data are unclear or contradictory. The eCRFs must be reviewed and electronically signed and dated by the investigator as required by the clinical monitoring plan, once all data has been entered and all queries resolved.

Audits/Inspections

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of the FDA, the sponsor and its representatives, and the IRB.

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