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Study Title	Feasibility Study with Personalized Closed Loop (PCL)
NCT Number	NCT04203823
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Clinical Investigation Plan

Clinical Investigation Plan/Study Title	Feasibility Study with Personalized Closed Loop (PCL)
Clinical Investigation Plan Identifier	CIP326
Study Product Name	Various products as parts of the PCL system
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1. Glossary

Abbreviation	Definition
AE	Adverse Event
ADE	Adverse Device Effect
AHCL	Advanced Hybrid Closed Loop
AI	Artificial Intelligence
ASIC	Application Specific Integrated Circuit
BG	Blood Glucose
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CHO	Carbohydrate
CSII	Continuous Subcutaneous Insulin Infusion
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EIS	Electrochemical Impedance Spectroscopy
EOS	End of Study
ER	Emergency Room
FDA	United States Food and Drug Administration
FST	Frequent sample testing
GCP	Good Clinical Practice

Abbreviation	Definition
HCL	Hybrid Closed Loop
HCP	Health Care Provider
HIPAA	Health Insurance Portability and Accountability Act of 1996
IB	Investigator's Brochure
ICF	Informed Consent Form
IEC	Independent Ethic Committee
IFU	Instructions for Use
IRB	Institutional Review Board
IV	Intravenous
MC2	Medtronic Core Clinical Solutions
MDI	Multiple Daily Injection
NGSP	National Glycohemoglobin Standardization Program
OC-RDC	Oracle Clinical Remote Data Capture
PC	Personal Computer
PCL	Personalized Closed Loop
RF	Radio Frequency
SAE	Serious Adverse Event
SADE	Serious Adverse Device Events
SAP	Sensor Augmented Pump
SG	Sensor Glucose
SMBG	Self-Monitoring of Blood Glucose
TDD	Total Daily Dose
TLS	Transport Layer Security

Abbreviation	Definition
TS	Technical Support
TSH	Thyroid-stimulating hormone
UADE	Unanticipated Adverse Device Effect

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2. Synopsis

Title	Feasibility Study with Personalized Closed Loop (PCL)
Investigational Device Exemption (IDE) Number	**G190301**
Devices	*Feasibility 2: Investigational Devices* • Cloud-based Digital Twin Algorithm • Cloud-based Meal Prediction Algorithm • MiniMed™ 670G Insulin Pump, version 4.0 Tel-D (MMT-1740) – AHCL • PCL Mobile Application- referred to as App in the protocol (MMT-TBD) *Feasibility 2: Non-Investigational/Exempt devices* • Guardian™ Link (3) Transmitter (MMT-7811) • Guardian™ Sensor (3) Glucose Sensor (MMT-7020)- referred to as Guardian Sensor (3) throughout this protocol • One-Press Serter (MMT-7512) - referred to as the Serter throughout this protocol • Transmitter Charger (MMT-7715) • Tester (MMT-7736L) • Medtronic CareLink™ Personal Therapy Management Software for Diabetes (MMT-7333) –– referred to as CareLink™ Personal For Clinical Research software throughout this protocol; Class I exempt device • CONTOUR® NEXT LINK 2.4 Blood Glucose Meter (MMT-1352)- referred to as the CONTOUR® NEXT LINK 2.4 study meter throughout this protocol • Subject-owned Smartphone to accommodate Medtronic PCL Mobile App
Purpose	The purpose of this study is to: • Evaluate subject safety related to automated recommendations for device setting changes that are formulated by the Cloud-based Digital Twin algorithm and impact insulin delivery.

	• Evaluate subject safety related to carbohydrate estimates for meals that are calculated by the Cloud-based Meal Prediction algorithm.
Objective(s)	The objective of the study is to collect device data to assist in the development of a Personalized Closed Loop (PCL) system.
Study Design	This is a single arm study comprised of a series of feasibility studies. Please see below: [redacted] **<u>Feasibility Study Part 2 (i.e. Feasibility 2)</u>: Feasibility 2 is the focus of the current protocol.** [redacted] This study may include up to 3 separate **Cohorts** of individuals, based on which algorithm is being studied: **Cohort A:** The main purpose of this cohort is to test the Digital Twin insulin delivery algorithm adaptation (Feasibility [redacted]) [redacted] **Cohort C:** The main purpose of this cohort is to test a meal prediction algorithm (Feasibility 2[redacted]) **Study Phases** This study consists of one or more phases. See Table 1 for a Summary of phases for Feasibility 2. • Phases may be repeated per sponsor direction • Phases in different cohorts may proceed simultaneously • Same subjects may participate in multiple phases • Subjects who have participated in a phase will not be required to repeat the run-in period if they have already participated in prior phase as per Sponsor discretion. • When subjects are using Auto Mode with the AHCL system, the automatic basal insulin delivery target should be set to 100 mg/dL.

Table 1. Summary of Phases for Feasibility 2

Cohort	Phase	Age	Algorithm	Challenge
A	1	14+	Digital Twin	Manual Mode/ Auto Mode Transition – at home
A	2	2-13	Digital Twin	Manual Mode/ Auto Mode Transition – at home
A	3	14+	Digital Twin	Missed Meal Bolus – at home
A	4	2-13	Digital Twin	Missed Meal Bolus – at home
C	5	14+	Meal Prediction	In Clinic Observation
C	6	2-13	Meal Prediction	In Clinic Observation

Study Population

For Feasibility 2, the study population will include patients with type 1 diabetes. Ages 14 and up will be enrolled first, followed by the younger age groups.

Staged Enrollment in all Cohorts

- Enrollment of pediatric subjects 2-13 years of age into a specific phase may not proceed until N=10 subjects 14 years and older have completed the corresponding phase and safety data has been reviewed by the Data Monitoring Committee (DMC).
- Study subjects 2-6 years of age will be enrolled in Cohort A and Cohort C only after completing an in clinic observational study using the AHCL system. See details about the observational study procedures below.

Study Design	**Study Procedures:** **General:** All subjects will be trained on diabetes management principles, such as the treatment of hyperglycemia and hypoglycemia. In addition, there will be training regarding the need to have access to oral glucose and glucagon in case of hypoglycemia. Subjects will be asked to continue performing routine self-monitoring of blood glucose (SMBG) checks, as they were doing prior to enrolling in the study. For study purposes, subjects will be instructed to perform SMBG if they are experiencing a severe hyperglycemic event or Diabetic Ketoacidosis (DKA). Please note: If a subject has a severe hypoglycemic event, subject should attempt to retrieve SMBG result from person providing assistance. As a precaution, subjects will be told that they should keep their own insulin pump supplies in a safe place and to have back up supplies on hand (such as insulin and syringe) in the event they are asked to revert back to their own therapy during the study or experience study pump issues (i.e. infusion set occlusion with high glucose). Subjects will be instructed to insert glucose sensors only in the locations that are specified in the User Guide materials. **SMBG recommendations**: Typically, SMBG is required for calibration. Occasionally, subjects may receive a notification if the pump needs a BG to enter or stay in Auto Mode. For study purposes, subjects will be instructed to perform SMBG if they are feeling low (but sensor glucose [SG] is not low) and treat as needed. They should also perform SMBG if they are experiencing a severe hyperglycemic event or DKA. Please note: If a subject has a severe hypoglycemic event, subject should attempt to retrieve a SMBG result from the person providing assistance. If SMBG is required for monitoring, it will be detailed in the visit study procedures. **FEASIBILITY 2** Subjects who participated in [redacted] will complete Visit 10, where they will choose to either participate in Feasibility 2 or exit the study. **Cohort A: Insulin Delivery Recommendations Derived from the Digital Twin Algorithm** The Digital Twin algorithm resides in the Medtronic Data Cloud. By wearing the system during the run-in period, the patient starts to accumulate device data that will be uploaded to CareLink™ after 3 full weeks (22 midnights). The algorithm will then calculate individualized insulin delivery recommendations that will be made available to the investigator. **Digital Twin Challenge #1: Alternating Between Auto Mode & Manual Mode**

	Purpose: The purpose of this challenge is to observe subject safety when subjects frequently exit Auto Mode and transition back and forth between Auto Mode and Manual Mode. The purpose of this data collection is also to assist in the development of the Digital twin algorithm. **Rationale:** Patients sometimes intentionally switch from Auto Mode to Manual Mode for brief periods of time depending on their circumstances. **Run-in Period for Digital Twin Challenge #1** At the conclusion of the run-in period, insulin delivery recommendations (i.e., insulin carbohydrate ratio, basal rate changes, insulin sensitivity and active insulin time) will be calculated by the cloud-based Digital Twin algorithm based on uploaded CareLink™ data. **Run-in Period Study Procedures Based on Therapy at Screening** • Patients who come in using pump with CGM at Screening will spend a minimum of 30 days using the AHCL system during the run-in period. Device settings may be adjusted as needed • Patients who are using MDI therapy or a pump without CGM (CSII) at Screening will spend at least 2 additional weeks using the AHCL system during the run-in period. Part of the extra time will be used to collect blinded CGM data as a baseline. The rest of the time will be used to allow subjects get used to pump and CGM. Device settings may be adjusted as needed. • With the AHCL system, the auto basal rate target should be set to 100mg/dL for the duration of the study, unless the investigator considers this setting to be a safety issue for a subject. At the investigator's discretion, the setpoint may be set to 120mg/dL. • All subjects will be asked to upload the pump and meter weekly during the run-in period. **Study Period Procedures for Digital Twin Challenge #1** Following the run-in period, subjects will participate in a study period lasting approximately 5-6 weeks. For the duration of the study period, subjects will be asked to switch back and forth between Auto Mode and Manual Mode, according to a schedule that will be provided to each site by the Sponsor. Subjects will be instructed to upload the pump and meter at specific time points during the study period. Device settings recommendations will be provided during this study period. Investigators should make every attempt to follow these recommendations, except if they do not agree with the device settings recommendations, based on safety concerns. Investigators may adjust device settings based on safety. **Device Setting changes** • At the start of the study period, insulin delivery settings based on data collected during the run-in period will be made available to the investigator.

- If the investigator agrees with the new settings, they will be programmed into a subject's study pump.
- If the investigator does not agree with the recommendations, they may be implemented gradually over a period of time, e.g. 1-2 weeks.
- If the investigator does not agree with the recommendations and does not wish to implement them gradually, details about the disagreement will be noted on the applicable CRF.

- After approximately 2 weeks of the study period, following a pump upload by subjects at home, new device settings will be made available.
  - If the investigator agrees with the new settings, they will be programmed into a subject's study pump.
  - If the investigator does not agree with the recommendations, the investigator will enter details about the disagreement on the applicable CRF.
- After approximately 3 weeks of the study period, following a pump upload by subjects at home, new device settings will be made available.
  - If the investigator agrees with the new settings, they will be programmed into a subject's study pump.
  - If the investigator does not agree with the recommendations, the investigator will enter details about the disagreement on the applicable CRF.
- After approximately 4 weeks of the study period, following a pump upload by subjects at home, new device settings will be made available.
  - If the investigator agrees with the new settings, they will be programmed into a subject's study pump.
  - If the investigator does not agree with the recommendations, the investigator will enter details about the disagreement on the applicable CRF.

The table below shows an example of a transition schedule between Auto Mode and Manual Mode; different variations will be provided by the Sponsor to the investigational center. The transitions between Auto Mode and Manual Mode should occur between 7am and 12 Noon.

Table 2. Example of Manual mode Transitions during the study period - Digital Twin Challenge #1

Week	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1	**Manual Mode**	Auto Mode	Auto Mode	Auto Mode	Auto Mode	Auto Mode	Auto Mode

2	Auto Mode	Auto Mode	**Manual Mode**	Auto Mode	Auto Mode	Auto Mode	Auto Mode
3	Auto Mode	Auto Mode	Auto Mode	Auto Mode	**Manual Mode**	Auto Mode	Auto Mode
4	Auto Mode	**Manual Mode**	Auto Mode	Auto Mode	Auto Mode	Auto Mode	Auto Mode
5	Auto Mode	Auto Mode	Auto Mode	**Manual Mode**	Auto Mode	Auto Mode	Auto Mode

Digital Twin Challenge #2: Eating a Meal without Giving an Insulin Bolus

Purpose: The challenge is designed to test the post prandial effect of a subject eating a meal without giving an insulin meal bolus. The purpose of this data collection is also to assist in the development of the Digital twin algorithm.

Rationale: During routine diabetes management, patients with diabetes may forget to give insulin for their meal. This challenge helps to collect data on how the Digital Twin algorithm will make insulin delivery recommendations in patients who forget to take insulin with their meal.

Run-in Period for Digital Twin Challenge #2

At the conclusion of the run-in period, insulin delivery recommendations (i.e. insulin carbohydrate ratio, basal rate changes, insulin sensitivity and active insulin time) will be calculated by the cloud-based Digital Twin algorithm based on uploaded CareLink™ data.

Run-in Period Study Procedures Based on Therapy at Screening

- Patients who come in using pump with CGM at Screening will spend a minimum of 30 days using the AHCL system during the run-in period. Device settings may be adjusted as needed
- Patients who are using MDI therapy or pump without CGM (CSII) at Screening will spend at least 2 additional weeks using the AHCL system during the run-in period. Part of the extra time will be used to collect blinded CGM data as a baseline. The rest of the time will be used to allow subjects get used to pump and CGM. Device settings may be adjusted as needed.
- With the AHCL system, the auto basal rate target should be set to 100mg/dL for the duration of the study, unless the investigator considers this setting to be a safety issue for a subject. At the investigator's discretion, the setpoint may be set to 120mg/dL.
- All subjects will purposely withhold insulin at either breakfast or lunch on each day of the run-in period (approximately 23 days)
- Subjects will check their blood glucose at the start of the missed bolus meal as well as 2 hours after the start of the meal; they will give correction insulin as needed. Confirmation of BG is entered on an electronic log

- Subjects will record the calculated CHO on an electronic log, because it is not entered into the Bolus Wizard
- Subjects will be asked to upload their pumps and meters weekly

Study Period for Digital Twin Challenge #2 (at study site selected by Sponsor)

Following the run-in period, subjects will participate in a study period lasting approximately 5-6 weeks. Subjects will be divided into separate groups:

Group 1: Approximately 50% of subjects will purposely withhold insulin for either Breakfast or lunch on each day during weeks 1 through 3. The amount of CHO will be collected on a log, because it is not entered into the Bolus Wizard. Subjects will also check their glucose at the start of the meal as well as 2 hours after the start of the meal and give correction insulin as needed. For the remainder of the study, i.e. weeks 4 and 5, subjects in this group will give standard insulin at all meals.

Group 2: Approximately 50% of subjects will give standard insulin at all meals for the duration of the study period. CHO data will be collected directly from subject's data entry into the pump through CareLink™.

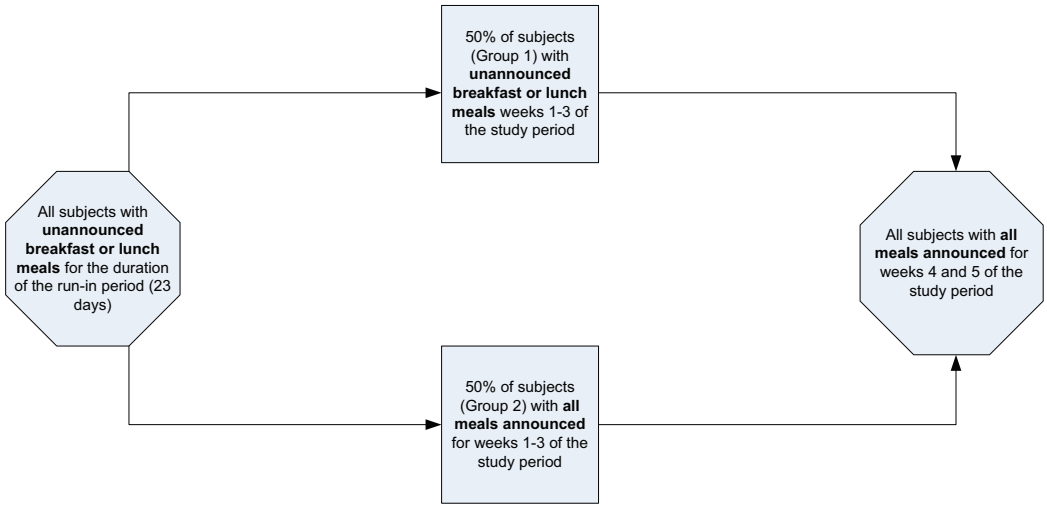
Subjects will be instructed to upload the pump and meter at specific time points during the study period. Device settings recommendations will be provided during this study period. Investigators should make every attempt to follow these recommendations, except if they do not agree with the device settings recommendations, based on safety concerns. Investigators may adjust device settings based on safety.

Device Setting

- At the start of the study period, insulin delivery settings based on data collected during the run-in period will be made available to the investigator.
  - If the investigator agrees with the new settings, they will be programmed into a subject's study pump.
  - If the investigator does not agree with the recommendations, they may be implemented gradually over a period of time, e.g. 1-2 weeks.
  - If the investigator does not agree with the recommendations and does not wish to implement them gradually, details about the disagreement will be noted on the applicable CRF
- After approximately 2 weeks of the study period, following a pump upload by subjects at home, new device settings will be made available.
  - If the investigator agrees with the new settings, they will be programmed into a subject's study pump.
  - If the investigator does not agree with the recommendations, the investigator will enter details about the disagreement on the applicable CRF.
- After approximately 3 weeks of the study period, following a pump upload by subjects at home, new device settings will be made available.
  - If the investigator agrees with the new settings, they will be programmed into a subject's study pump.

- If the investigator does not agree with the recommendations, the investigator will enter details about the disagreement on the applicable CRF

- After approximately 4 weeks of the study period, following a pump upload by subjects at home, new device settings will be made available.
  - If the investigator agrees with the new settings, they will be programmed into a subject's study pump.
  - If the investigator does not agree with the recommendations, the investigator will enter details about the disagreement on the applicable CRF.



Cohort C: Meal Time Prediction Algorithm

The meal prediction algorithm will look at pump data collected during the run-in period and uploaded to the Medtronic Data Cloud, in order to determine the timing of meal-time predictions. Subjects will not use the App during the run-in period.

Due to a limitation with regard to the availability of the Medtronic PCL App to subjects under 13 years of age, who rely exclusively on the use of Apple products, i.e., iPhones, an Android phone may be provided for use during the study.

While there are ***no specific challenges*** for this cohort the following study procedures will be implemented:

Run-in Period Study Procedures Based on Therapy at Screening

- Patients who come in using pump with CGM at Screening will spend a minimum of 30 days using the AHCL system during the run-in period. Device settings may be adjusted as needed
- Patients who are using MDI therapy or pump without CGM (CSII) at Screening will spend at least 2 additional weeks using the AHCL system during the run-in period. Part of the extra time will be used to collect blinded CGM data as a

baseline. The rest of the time will be used to allow subjects get used to pump and CGM. Device settings may be adjusted as needed.

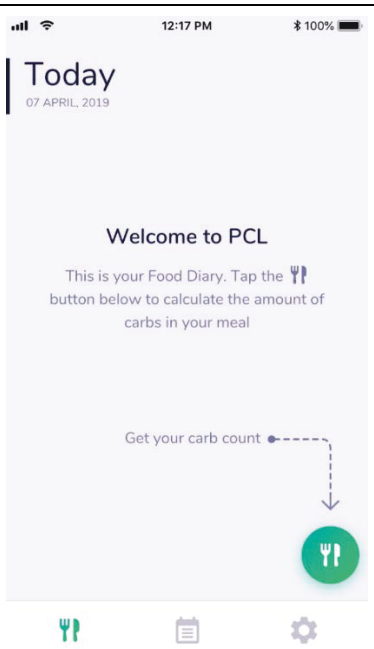
- With the AHCL system, the auto basal rate target should be set to 100mg/dL for the duration of the study, unless the investigator considers this setting to be a safety issue for a subject. At the investigator's discretion, the setpoint may be set to 120mg/dL.

At selected centers, a limited number of subjects will undergo frequent sample testing (FST). The testing is **not** done in support of study data. Rather, the FST data is being collected as a means of gaining experience with a new testing method (ABL90 by Radiometer).

Subjects who are selected to participate in the FST procedures will undergo a hematocrit blood test prior to the start of the procedures. The passing criteria for this test are that subjects should not be more than 10% below the lower limit of normal Hct for the reference range of the local lab that is testing the sample. If a subject's medical record contains evidence that the test was taken, with the result as outlined above, within 6 months prior to screening, the blood draw and test during the study will not be required.

Study Period for the Meal Prediction Cohort:

During the approximately 42-day long study period, subjects in this cohort will use the PCL Mobile App to log meals and receive CHO estimates; they will not receive insulin delivery settings recommendations. They will enter the type of meal they wish to eat along with the serving size into the App (e.g. Pasta dish, Toast and eggs, etc.). This will prompt the App to calculate a CHO estimate that is based on the search criteria the subject entered (see example of sequence below).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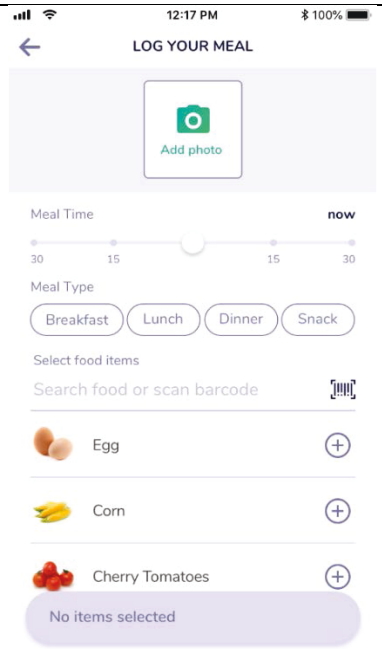
Today
07 APRIL, 2019
Welcome to PCL
This is your Food Diary. Tap the button below to calculate the amount of carbs in your meal
Get your carb count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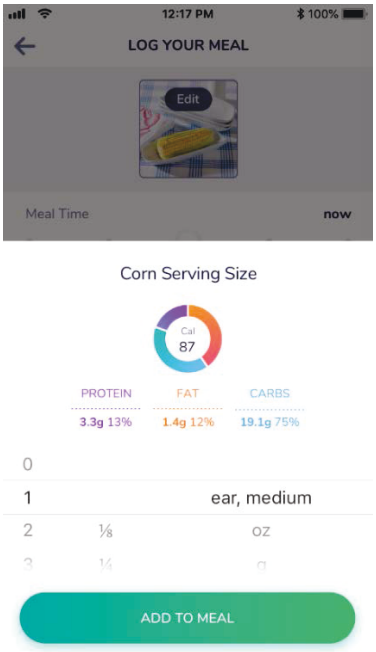
LOG YOUR MEAL
Add photo
Meal Time
now
30
15
15
30
Meal Type
Breakfast
Lunch
Dinner
Snack
Select food items
Search food or scan barcode
Egg
Corn
Cherry Tomatoes
No items selected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19.1g 75%
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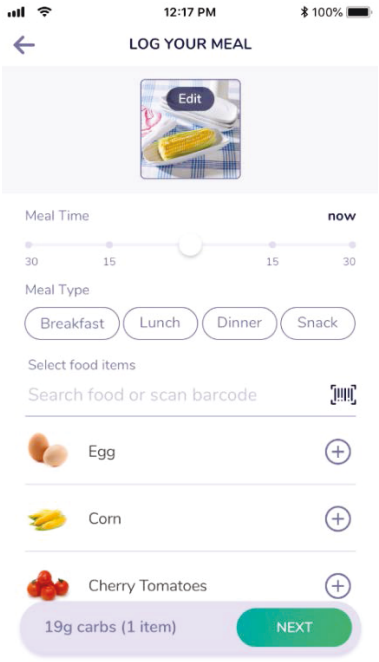
ADD TO MEAL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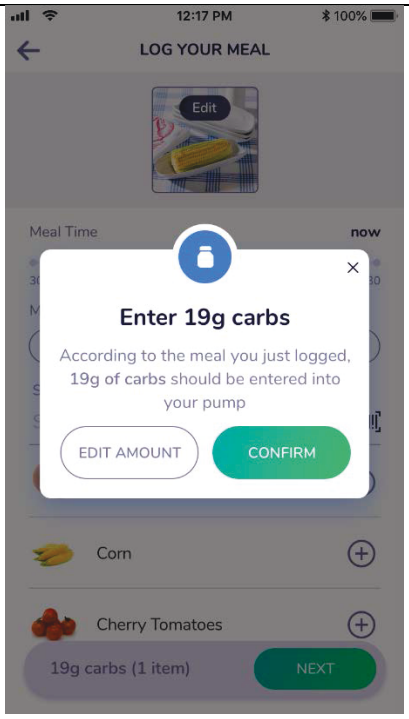
Cherry Tomatoes
19g carbs (1 item)
NEXT



Subjects will enter the CHO amount calculated and displayed on the App into the pump for bolus calculation and insulin delivery. The user may modify the amount of CHO estimated by the App prior to entering it manually into the bolus wizard.

Cohort C subjects will perform study procedures both in-clinic and at home during the Feasibility 2 study:

In-clinic:

- Diabetes Management as per investigator discretion, e.g. correction boluses
- The first two days of the study period will be spent in the clinic or in a hotel-type setting.
- If a visit to the clinic is not possible due to circumstances that would negatively impact the subjects, other subjects or Investigational center staff, e.g., COVID-19 exposure or illness, both days of Visit 11 may be conducted as Telemedicine visits.
    - Investigational center staff should be in contact with subjects via video connection to train them on the use of the App.
    - Investigational center staff should be in contact with subjects via video connection to observe use of the PCL app at appropriate times, i.e., during all meals where the App is used to collect meal information and BGs are required. BG checks are required for the 2 largest CHO content meals of the day. Subjects will be observed during meals where CHO estimates that are generated by the App's meal library are entered into the pump's bolus wizard prior to the main meals (Breakfast, Lunch, Dinner). Please note that the investigator may override CHO estimate and provide their own based on investigator's discretion.

- During clinic visits, subjects will be observed during meals where CHO estimates that are generated by the App's meal library are entered into the pump's bolus wizard prior to the main meals (Breakfast, Lunch, Dinner). Please note that investigator may override CHO estimate and provide their own based on investigator discretion.
- BG checks during the in-clinic visits will be performed at start of the 2 meals with the highest CHO content, as well as 2 hours after the start of those meals.
- FST with ABL-90 will take place at sites that are selected by the sponsor for one day of the in-clinic visit
- Testing frequency is at 30-minute intervals for approximately 8 hours.

At Home:

System will record information about meal time, CHO counting and BG checks. Subjects will follow the same process they followed during the in-clinic visit.

Study Procedures for subjects 2-6 years of age (In-Clinic Observational Study)

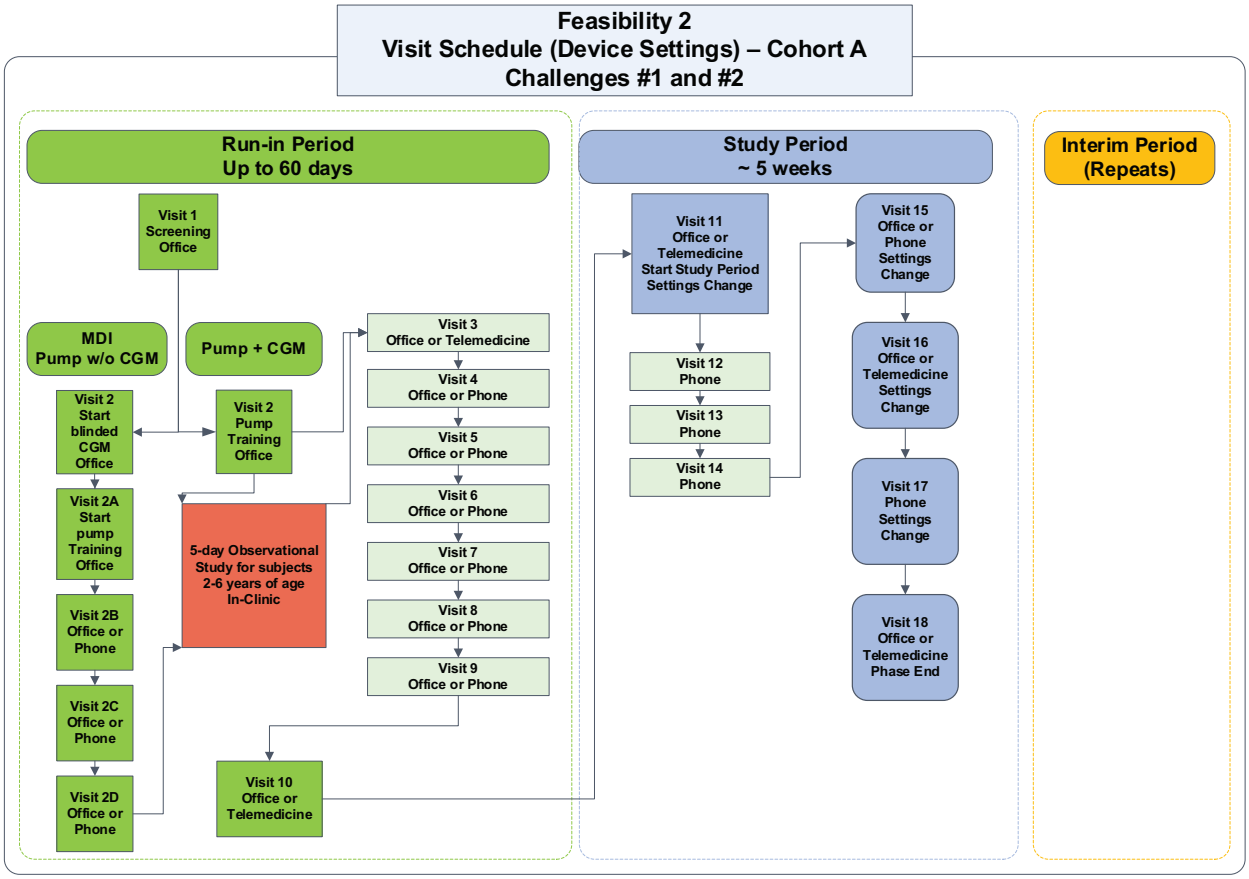
The In-Clinic observational study is intended for subjects 2-6 years of age and must be completed before they are allowed to proceed to Cohort A and Cohort C study procedures.

Study procedures for the observational study:

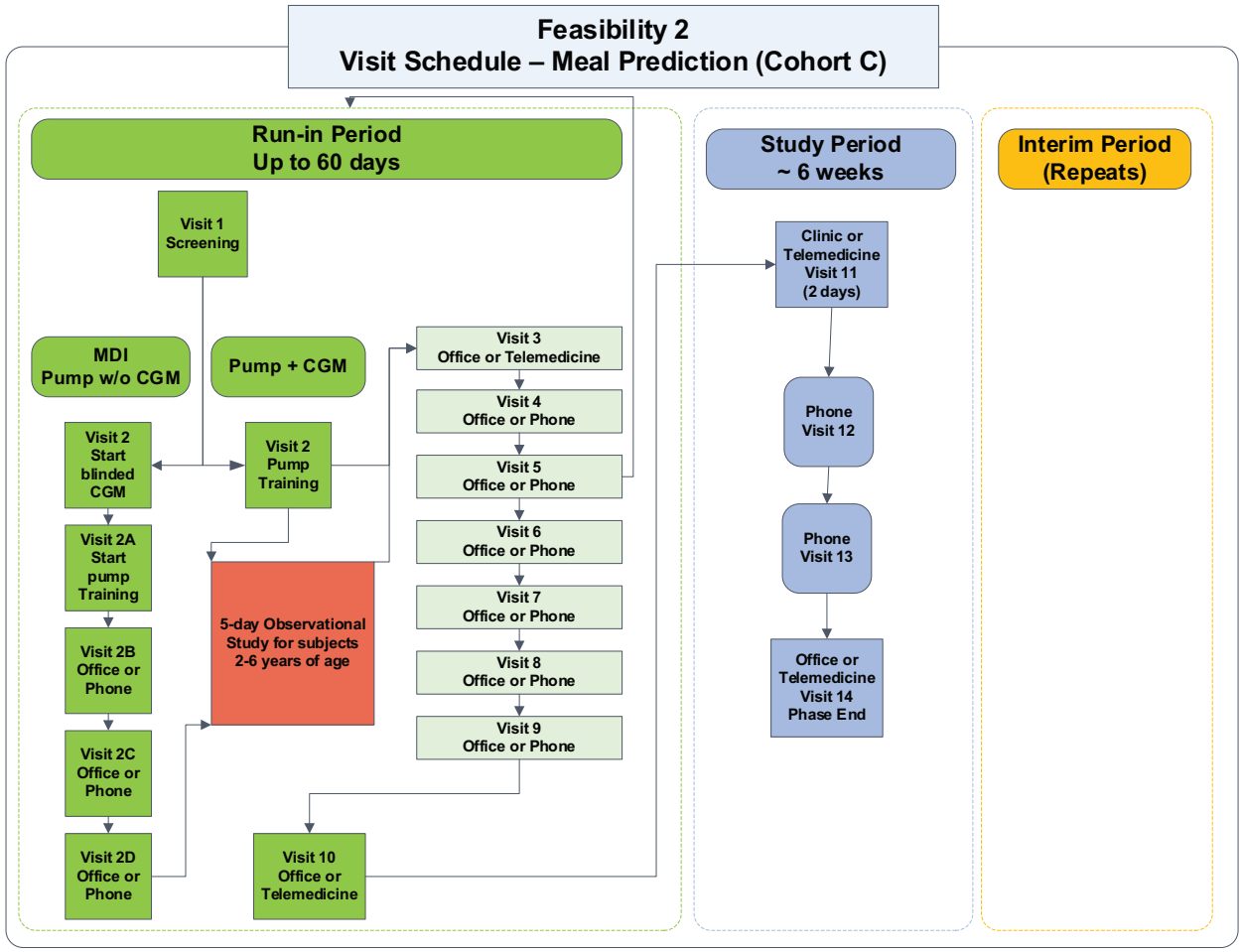
- After enrollment into the CIP326 study, subjects 2-6 years of age will initially use the AHCL system in Manual Mode. If subject was using 670G with Auto Mode at Screening, the subject may use Auto Mode with the Auto Correction feature off (i.e., not enabled).
- The in-clinic study will be conducted after completion of Visit 2 (see visit schedule).
- The in-clinic study for subjects 5-6 years of age and subjects 2-4 years of age may be conducted in parallel.
- During the 5-day in-clinic study, subjects will use the AHCL system in Auto Mode.
- After the completion of the in-clinic observation study, the Data Monitoring Committee (DMC) will convene to review the safety data.
- DMC will review in clinic data from subjects in the 5-6 year age group (N=8), in order to assess that it is safe for 5-6 year olds to perform Cohort A or Cohort C study procedures.
- DMC will review in-clinic data from both the 2-4 year age group (N=8) and the 5-6 year age group (N=8) in order to assess that it is safe for 2-4 year olds to perform Cohort A and Cohort C study procedures.
- While waiting for approval by the DMC after completing the in clinic observational study, subjects will use the AHCL system at home in Manual Mode. If subject was using 670G with Auto Mode at Screening, the subject may use Auto Mode with the Auto Correction feature off (i.e., not enabled).

	• The observational study may be divided into two different weekends based on investigator discretion to provide improved flexibility for parents and child.
	  ○ Friday to Sunday x 1
	  ○ Saturday to Sunday x 1
	• When not in clinic to perform the observational study, subjects should be in Manual Mode. If subject was using 670G with Auto Mode at Screening, the subject may use Auto Mode with the Auto Correction feature off (i.e., not enabled).
	• Upon receiving approval to proceed from the DMC, subjects may return to using Auto Mode.

Visit Schedule for Cohort A: Device Settings Adaptation (Digital Twin) – Challenges #1 and #2



Visit Schedule for Cohort C: Meal Prediction



Sample Size and Investigational Sites	A total of up to 200 subjects will be enrolled at up to 15 investigational centers across the US in order to have up to 150 subjects who complete the study. It is expected that at least N=12-18 subjects will participate in each phase during Feasibility 2.
Duration	The anticipated study duration is no longer than 18 months for all three feasibility studies. Subjects will be in the study for approximately 3.5 months.
Inclusion Criteria	*General Inclusion Criteria* 1. Subject is age 2-80 years at time of Visit 1. **Note:** See staged enrollment reference for adult and pediatric subjects in the Study Design section 2. Subject has a clinical diagnosis of type 1 diabetes. a. Subjects 7 years of age and older: Diagnosed at least 1 year prior to Visit 1 b. Subjects 2-6 years of age: Diagnosed at least 3 months prior to Visit 1 *Study-specific inclusion criteria* 3. Subject must have a minimum daily insulin requirement (Total Daily Dose) of greater than or equal to 8 units. 4. If subject has a history of hypothyroidism, must have at least 1 documented normal thyroid-stimulating hormone (TSH) on historical labs within 12 months of Visit 1. A subject without a history of hyperthyroidism is not expected to have a TSH test. 5. Subjects and their parent(s)/guardian(s) must have Internet access , a computer system that meets the requirements for uploading the study pump and Smartphone that meets study requirements. 6. Subject must have a companion or caregiver available at night for the duration of the study period who resides (or will live) in in the same building (or home). This requirement may be verified by subject report at screening visit. 7. If subject has celiac disease, it has been adequately treated as determined by the investigator. 8. Subjects and their parent(s)/guardian(s) are willing to take one of the following insulins and can financially support the use of either of the 2 insulin preparations throughout the course of the study (i.e. co-payments for insulin with insurance or able to pay full amount) a. Humalog™* (insulin lispro injection) b. NovoLog™* (insulin aspart)
Exclusion Criteria	1. Subject has a history of 1 or more episodes of severe hypoglycemia, which resulted in any the following during the last 1 year prior to Visit 1 a. Medical assistance (i.e. Paramedics, Emergency Room (ER) or Hospitalization) b. Coma c. Seizures 2. Subject is unable to tolerate tape adhesive in the area of sensor placement.

	3. Subject has any unresolved adverse skin condition in the area of sensor placement (e.g., psoriasis, dermatitis herpetiformis, rash, Staphylococcus infection). 4. Women of child-bearing potential who have a positive pregnancy test at Visit 1 or plan to become pregnant during the course of the study 5. Females who are sexually active and able to conceive will be excluded if they are not using an effective method of contraception and do not agree to continue using an effective method of contraception for the duration of the study as determined by investigator. 6. Subject has a cardiovascular condition which the Study Investigator determines should exclude the subject, e.g. ventricular rhythm disturbance, hypertrophic cardiomyopathy, recent myocardial infarction in the last year prior to Visit 1. 7. Subject is being treated for hyperthyroidism at time of Visit 1. 8. Subject has a diagnosis of adrenal insufficiency. 9. Subject has had Diabetic Ketoacidosis (DKA) within 1 year prior to Visit 1. 10. Subject has taken any oral, injectable, or intravenous (IV) glucocorticoids within 8 weeks from time of visit 1, or plans to take any oral, injectable, or IV glucocorticoids during the course of the study. 11. Subject is actively participating in an investigational study (e.g., drug or device) wherein he/she has received treatment from an investigational study (drug or device) in the last 2 weeks prior to Visit 1. Please note participation in observational study is acceptable. 12. Subject has been hospitalized or has visited the ER in the 6 months prior to Visit 1 resulting in a **primary diagnosis** of uncontrolled diabetes. 13. Subject is currently abusing illicit drugs. 14. Subject is currently abusing alcohol. 15. Subject is using pramlintide (Symlin), DPP-4 inhibitor, liraglutide (Victoza or other GLP-1 agonists), metformin, canagliflozin (Invokana or other SGLT2 inhibitors) at time of Visit 1. 16. Subject has a history of visual impairment which would not allow subject to participate in the study and perform all study procedures safely, as determined by the investigator. 17. Subject has elective surgery planned that requires general anesthesia during the course of the study. 18. Subject diagnosed with current eating disorder such as anorexia or bulimia. 19. Subject has been diagnosed with chronic kidney disease that results in chronic anemia. 20. Subject is on dialysis. 21. Subject has serum creatinine of >2 mg/dL, as confirmed through historical labs within 1 year prior to Visit 1. 22. Subject is a member the research staff involved with the study.
Study Visit Schedule	Each subject's participation will be comprised of the following scheduled visits listed below over the course of approximately 4.5 months during the run-in period and study period, and for 1 month during the interim period. With Sponsor and site approval, telemedicine (e.g., remote/virtual visit) may be performed for office visits that do not require any of the following: • Collection of blood test samples • Training • Device related procedures that require staff assistance

The schedule is planned as follows:

FEASIBILITY 2

Visit Schedule Details – Cohort A: Digital Twin Challenge #1

Run-in Period Visits: To be completed in 60 days

- Screening Visit 1 (Office): Consent and Screening
- Visit 2 (Office):
  - *Confirm Eligibility*
    Therapy at time of Screening: MDI/CSII (no CGM):
  - Study training and start of blinded CGM
  - Start run-in baseline data collection at home with own therapy (at least 7 days). Data loss may occur if a blinded CGM is worn for longer than 14 days. Sensor wear not recommended for more than 10 days.
  - **Next visit is Visit 2A**

    Therapy at time of Screening: Pump plus CGM:
  - Disburse study pump and transmitter (AHCL system)
  - Upload pump and meter
  - Verify CareLink™ credentials, complete registration
  - Provide study and device training
  - Start run-in baseline data collection at home with AHCL system (at least 7 days)
  - Auto Mode activation may occur if subjects were using Auto Mode at Screening (i.e., ok to use automated basal insulin delivery feature only)
  - **Next visit is Visit 3**

- Visit 2A (Office): Therapy at time of Screening: MDI/CSII (no CGM)
  - Return to clinic after blinded CGM data collection
  - Return blinded CGM
  - Disburse study pump and transmitter (AHCL system); use in Manual Mode
  - Upload pump and meter
  - Verify CareLink™ credentials, complete registration
  - Provide study and device training

- Visit 2B (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 1 after visit 2A
  - Review Manual Mode settings

- Visit 2C (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 2 after Visit 2A
  - Review Manual Mode settings

- Visit 2D (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 7 (+3 days) after Visit 2A

- Review Manual Mode settings

- Visit 3 (Office or Telemedicine) – Auto Mode activation, i.e. automated basal and auto correction
  - Should occur at least 7-14 days after start of wearing AHCL system; 14 days may be preferable for those who were on MDI/CSII (no CGM) at time of screening

- Visit 4 (Telephone or office) – Day 1 after Visit 3

- Visit 5 (Telephone or office) – Day 2 after Visit 3

- Visit 6 (Telephone or office) – Day 3 after Visit 3

- Visit 7 (Telephone or office) – Day 4 after Visit 3

- Visit 8 (Telephone or office) – Day 5 after Visit 3

- Visit 9 (Telephone or office) – Day 6 after Visit 3
  - Upload pump and meter

- Visit 10 (Office or Telemedicine) – Day 14 (+7 days) after Visit 3
  - Upload pump and meter during visit
  - Review CareLink™ Upload
  - Instruct subjects to Upload pump and meter at home on Day 23 or 24 after Visit 3

Study Period Visits:

- Visit 11 (Office or Telemedicine): Day 30 (+7 days) after Visit 3
  - Start Study Period
  - Retrieve insulin delivery device settings recommendations
  - Review/approve settings before programming pump (please note that investigator discretion may be used as described above)
  - Upload pump and meter during visit
  - Review CareLink™ Upload
  - Instruct subjects regarding study procedures for Challenge #1

- Visit 12 (Telephone): Day 1 after Visit 11
  - Review CareLink Upload

- Visit 13 (Telephone): Day 2 after Visit 11
  - Review CareLink™ Upload

- Visit 14 (Telephone): Day 7 (+2 days) after Visit 11
  - Review CareLink™ Upload
  - Instruct subjects to upload on Day 6 after Visit 14

- Visit 15 (Office or Telephone): Day 8 (+3 days) after Visit 14
  - Upload pump and meter during visit
  - Review CareLink™ Upload
  - Retrieve insulin delivery device settings recommendations
  - Review/approve settings before programming pump (please note that investigator discretion may be used as described above)
  - Program pump with insulin delivery settings
  - Instruct subjects to upload on Day 6 after Visit 15

- Visit 16 (Office or Telemedicine): Day 8 (+3 days) after Visit 15
  - Review CareLink™ Upload
  - Retrieve insulin delivery device settings recommendations
  - Review/approve settings before programming pump (please note that investigator discretion may be used as described above)
  - Program pump with insulin delivery settings
  - Instruct subjects to upload on Day 6 after Visit 16

- Visit 17 (Telephone): Day 8 (+3 days) after Visit 16
  - Review CareLink™ Upload
  - Retrieve insulin delivery device settings recommendations
  - Review/approve settings before programming pump (please note that investigator discretion may be used as described above)
  - Program pump with insulin delivery settings

- Visit 18 (Office or Telemedicine): Day 7 (+3 days) after Visit 17
  - Review CareLink™ Upload
  - End of Phase
  - Return AHCL system unless phase is repeated Review CareLink™ Upload

Interim Period (as applicable):

Sponsor may request subjects to repeat this phase (up to 2 times)

Wash out period for a minimum of 23 days using the AHCL system in Auto Mode should be performed before phase is repeated

Subjects will be instructed to upload weekly during the interim period

Subjects who are repeating the phase will start at Visit 11 after wash-out period

<u>Visit Schedule Details – Cohort A: Digital Twin Challenge #2</u>

Run-in Period Visits: To be completed in 60 days

- Screening Visit 1 (Office): Consent and Screening

- Visit 2 (Office):
  - *Confirm Eligibility*
    Therapy at time of screening: MDI/CSII (no CGM)
  - Study training and start of blinded CGM
  - Start run-in baseline data collection at home with own therapy (at least 7 days). Data loss may occur if a blinded CGM is worn for longer than 14 days. Sensor wear not recommended for more than 10 days.
  - **Next visit is Visit 2A**

    Therapy at time of screening: Pump plus CGM
  - Disburse study pump and transmitter (AHCL system)
  - Upload pump and meter
  - Verify CareLink™ credentials, complete registration
  - Provide study and device training
  - Start run-in baseline data collection at home with AHCL system (at least 7 days)
  - Auto Mode activation may occur if subjects were using Auto Mode at Screening (i.e., ok to use automated basal insulin delivery feature only)
  - **Next visit is Visit 3**

- Visit 2A (Office): Therapy at time of Screening: MDI/CSII (no CGM)
  - Return blinded CGM
  - Disburse study pump and transmitter (AHCL system)
  - Upload pump and meter
  - Verify CareLink™ credentials, complete registration
  - Provide study and device training

- Visit 2B (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 1 after visit 2A
  - Review Manual Mode settings

- Visit 2C (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 2 after Visit 2A
  - Review Manual Mode settings

- Visit 2D (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 7 (+3 days) after Visit 2A
  - Review Manual Mode settings

- Visit 3 (Office or Telemedicine) – Auto Mode activation, i.e. automated basal and auto correction
  - Should occur at least 7-14 days after start of wearing AHCL system; 14 days may be preferable for those who were on MDI/CSII (no CGM) at time of screening

- Visit 4 (Telephone or office) – Day 1 after Visit 3

- Visit 5 (Telephone or office) – Day 2 after Visit 3
- Visit 6 (Telephone or office) – Day 3 after Visit 3
- Visit 7 (Telephone or office) – Day 4 after Visit 3
- Visit 8 (Telephone or office) – Day 5 after Visit 3
- Visit 9 (Telephone or office) – Day 6 after Visit 3
  - Upload pump and meter
- Visit 10 (Office or Telemedicine) – Day 14 (+7 days) after Visit 3
  - Upload pump and meter during visit
  - Review CareLink™ Upload
  - Instruct subjects to Upload pump and meter at home at least 23 days after Visit 3

Study Period Visits:

- Visit 11 (Office or Telemedicine): Day 30 (+7 days) after Visit 3
  - Start Study Period
  - Retrieve insulin delivery device settings recommendations
  - Review/approve settings before programming pump (please note that investigator discretion may be used as described above)
  - Review CareLink™ Upload
  - Instruct subjects regarding study procedures for Challenge #2
- Visit 12 (Telephone): Day 1 after Visit 11
  - Review CareLink Upload
- Visit 13 (Telephone): Day 2 after Visit 11
  - Review CareLink™ Upload
- Visit 14 (Telephone): Day 7 (+2) after Visit 11
  - Review CareLink™ Upload
  - Instruct subjects to upload on Day 6 after Visit 14
- Visit 15 (Office or Telephone): Day 8 (+3 days) after Visit 14
  - Review CareLink™ Upload
  - Retrieve insulin delivery device settings recommendations
  - Review/approve settings before programming pump (please note that investigator discretion may be used as described above)
  - Program pump with insulin delivery settings

- Instruct subjects to upload on Day 6 after Visit 15

- Visit 16 (Office or Telemedicine): Day 8 (+3 days) after Visit 15
  - Review CareLink™ Upload
  - Retrieve insulin delivery device settings recommendations
  - Review/approve settings before programming pump (please note that investigator discretion may be used as described above)
  - Program pump with insulin delivery settings
  - Instruct subjects to upload on Day 6 after Visit 16

- Visit 17 (Telephone): Day 8 (+3 days) after Visit 16
  - Review CareLink™ Upload
  - Retrieve insulin delivery device settings recommendations
  - Review/approve settings before programming pump (please note that investigator discretion may be used as described above)
  - Program pump with insulin delivery settings

- Visit 18 (Office or Telemedicine): Day 7(+3 days) after Visit 17
  - Review CareLink™ Upload
  - End of Phase
  - Return AHCL system unless phase is repeated Review CareLink™ Upload

Interim Period (as applicable):

Sponsor may request subjects to repeat this phase (up to 2 times)

Wash out period for a minimum of 23 days using the AHCL system in Auto Mode should be performed before phase is repeated

Subjects will be instructed to upload weekly during the interim period.

Subjects who are repeating the phase will start at Visit 11 after wash-out period

<u>Visit Schedule Details – Cohort C: Meal Prediction:</u>

Run-in Period Visits:

- Screening Visit 1 (Office): Consent and Screening

- Visit 2 (Office):
  - *Confirm Eligibility*
    Therapy at time of Screening: MDI/CSII (no CGM)
  - Study training and start of blinded CGM
  - Start run-in baseline data collection at home with own therapy (at least 7 days). Data loss may occur if a blinded CGM is worn for longer than 14 days. Sensor wear not recommended for more than 10 days.
  - **Next visit is Visit 2A**

    Therapy at time of Screening: Pump plus CGM

- Disburse study pump and transmitter (AHCL system)
- Upload pump and meter
- Download App, verify CareLink™ credentials, complete registration
- Provide study and device training
- Start run-in baseline data collection at home with AHCL system (at least 7 days)
- Auto Mode activation may occur if subjects were using Auto Mode at Screening (i.e., ok to use automated basal insulin delivery feature only)
- **Next visit is Visit 3**

- Visit 2A (Office): **MDI/CSII (no CGM)**
  - Return blinded CGM
  - Disburse study pump and transmitter (AHCL system)
  - Upload pump and meter
  - Download App, verify CareLink™ credentials, complete registration
  - Provide study and device training

- Visit 2B (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 1 after visit 2A
  - Review Manual Mode settings

- Visit 2C (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 2 after Visit 2A
  - Review Manual Mode settings

- Visit 2D (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 7 (+3 days) after Visit 2A
  - Review Manual Mode settings

- Visit 3 (Office or Telemedicine) – Auto Mode activation, i.e. automated basal and auto correction
  - Should occur at least 7-14 days after start of wearing AHCL system (14 days may be preferable for those who were on MDI/CSII (no CGM) at time of screening.

- Visit 4 (Telephone or office) – Day 1 after Visit 3

- Visit 5 (Telephone or office) – Day 2 after Visit 3

- Visit 6 (Telephone or office) – Day 3 after Visit 3

- Visit 7 (Telephone or office) – Day 4 after Visit 3

- Visit 8 (Telephone or office) – Day 5 after Visit 3

- Visit 9 (Telephone or office) – Day 6 after Visit 3
  - Upload pump and meter

- Visit 10 (Office or Telemedicine) – Day 14 (+7 days) after Visit 3
  - Upload pump and meter during visit
  - Review CareLink™ Upload
  - Instruct subjects to Upload pump and meter at home at least 21 days after Visit 3

Study Period Visits:

- Visit 11 (Office or Telemedicine): Day 30 (+7 days) after Visit 3 is activated: 2-day supervised visit in clinic or remote
  - Start Study Period
  - Should occur at least 6 days after the last pump upload
  - Subject is trained and begins to use meal prediction App
  - Subject is being observed in clinic or remotely
  - Subjects may leave after day 1 and return the next day to complete the visit

  At applicable sites:
  - Eight-hour long FST will occur on one of the 2 in-clinic days at sites selected by Sponsor

- Visit 12 (Telephone): Day 14 (± 2 days) after Visit 11
  - Review CareLink™ Upload

- Visit 13 (Telephone): Day 21 (± 4 days) after Visit 11
  - Review CareLink™ Upload

- Visit 14 (Office or Telemedicine): Day 42 (+ 7 days) after Visit 11
  - Upload pump and meter during visit
  - Review CareLink™ Upload
  - End of Phase
  - Return AHCL system unless phase is repeated
  - Remove App from Smartphone

Interim Period (as applicable):

Sponsor may request subjects to repeat this phase (up to 2 times)

Wash out period for a minimum of 23 days using the AHCL system in Auto Mode should be performed before phase is repeated

Subjects will be instructed to upload weekly during the interim period.

Subjects who are repeating the phase will start at Visit 11 after wash-out period

Visit Schedule Details – Ages 2-6

Run-in Period Visits: To be completed in 90 days

- Screening Visit 1 (Office): Consent and Screening

- Visit 2 (Office):
  - *Confirm Eligibility*
    Therapy at time of Screening: MDI/CSII (no CGM):
  - Study training and start of blinded CGM
  - Start run-in baseline data collection at home with own therapy (at least 7 days). Data loss may occur if a blinded CGM is worn for longer than 14 days. Sensor wear not recommended for more than 10 days.
  - **Next visit is visit 2A**

    Therapy at time of Screening: Pump plus CGM:
  - Disburse study pump and transmitter (AHCL system)
  - Upload pump and meter
  - Verify CareLink™ credentials, complete registration
  - Provide study and device training
  - Start run-in baseline data collection at home with AHCL system (at least 7 days)
  - Auto Mode activation may occur if subjects were using Auto Mode at Screening (i.e., ok to use automated basal insulin delivery feature only)
  - **Next visit is the in-clinic Observational study**

- Visit 2A (Office): Therapy at time of Screening: MDI/CSII (no CGM)
  - Return to clinic after blinded CGM data collection
  - Return blinded CGM
  - Disburse study pump and transmitter (AHCL system); use in Manual Mode
  - Upload pump and meter
  - Verify CareLink™ credentials, complete registration
  - Provide study and device training

- Visit 2B (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 1 after visit 2A
  - Review Manual Mode settings

- Visit 2C (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 2 after Visit 2A
  - Review Manual Mode settings

- Visit 2D (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 7 (+3 days) after Visit 2A
  - Review Manual Mode settings
  - **Next visit is the in-clinic Observational Study**

	In-Clinic Study for all subjects 2-6 years of age
	• In Clinic Study Day 1 – Auto Mode activation, i.e. automated basal and auto correction, pump upload
	  ○ Should occur at least 7-14 days after start of wearing AHCL system; 14 days may be preferable for those who were on MDI/CSII (no CGM) at time of screening
	  ○ This is an in-clinic observational study to observe the safety of 2-6 year-olds using the AHCL system. No challenges will be performed.
	• In Clinic Study Day 2
	• In Clinic Study Day 3
	• In Clinic Study Day 4
	• In Clinic Study Day 5
	  ○ End of In-Clinic Study
	  ○ Instruct subjects to use the system in Manual Mode until they are notified about DMC approval to continue. If subject was using 670G with Auto Mode at Screening, the subject may use Auto Mode with the Auto Correction feature turned off (not enabled).
	  ○ Once DMC approves, Subjects will participate in their assigned cohorts
	  ▪ Cohort A: See Cohort A visit schedule. Subject will begin with **Visit 3**
	  ▪ Cohort C: See Cohort C visit schedule. Subject will begin with **Visit 3**

Safety Monitoring/ Risk Analysis	Safety monitoring/risk analysis details are outlined in Section 9.6.
Device Deficiencies	Subject and investigational center reports of device deficiencies will be collected by subjects and/or investigational centers calling the 24-Hour Technical Support (TS) for device troubleshooting and device complaints. For additional information, see Section 13.
Success Criteria for Feasibility 2 (Digital Twin and Meal Prediction)	The following criteria will be used to evaluate success of the Feasibility 2: 1. No occurrence of severe hypoglycemia or DKA due to device algorithm during the feasibility studies 2. Average time with SG below 70 mg/dL of 47 minutes or less (i.e. ≤ 3.3%) as in CER294DOC

Study Stopping Rules for Entire Study	During the study period, the following steps will be taken for: • Unanticipated Adverse Device Effects (UADE) • Algorithm-related Diabetic Ketoacidosis (DKA) • Algorithm-related Severe hypoglycemia 1. Site will notify the sponsor within approximately 24 hours of receiving knowledge of the event. 2. Sponsor will notify Food and Drug Administration (FDA) within approximately 72 hours of knowledge of the event and provide updates to those agencies as information becomes available. 3. Clinical Events Committee (CEC) is to review the event within 10 days from the time that the sponsor is notified. 4. CEC will provide recommendation to the sponsor on the following: a) If enrollment and study may continue b) If enrollment should be stopped; enrolled subjects are still allowed to continue in study c) If the entire study must be stopped, including subjects who have already received study devices 5. The study will be suspended if 2 or more algorithm-related DKA events OR 4 or more algorithm-related Severe Hypoglycemia events occur.
Subject Stopping Rules	Any episode of DKA or severe hypoglycemia will result in withdrawal of subject from study.

Statistical Analysis for Endpoints and Hypothesis	**Descriptive Endpoints** There are no statistically powered endpoints or hypothesis testing but there are descriptive endpoints. **Safety Endpoints** • Severe glycemic events: (i.e., severe hypoglycemia, DKA) • Collection of ALL adverse events (i.e. Summary of device related adverse events) **Effectiveness Endpoints** • Percentage of time in target: SG <70 mg/dL, 70-180 mg/dL and > 180 mg/dL In each phase, data will be summarized and documented to evaluate the safety and effectiveness of the algorithm changes.

3. Introduction

3.1. Background

In patients with insulin-dependent diabetes mellitus, glycemic control is influenced by numerous factors, such as insulin dosage, insulin absorption, timing, physiological/ lifestyle factors such as exercise, food intake, hormones and illness. These factors may contribute to significant variability in insulin requirements, which makes self-management of type 1 diabetes challenging.

Patients who are using continuous glucose monitoring, including sensor-augmented pump therapy, may experience improvements in glycemic control. Advanced features of sensor-augmented pump therapy are now being used in clinical practice; these include automatic suspension of insulin delivery when a pre-set glucose threshold is reached (low glucose suspend) or is predicted to be reached (predictive low glucose suspend). Both approaches have shown that a significant reduction in the risk and burden of hypoglycemia can be achieved, especially in patients who are prone to experiencing hypoglycemia.

Parallel to these approaches to mitigate the risk of hypoglycemia, more progressive advancements in technology can link insulin delivery directly to glucose levels. Closed-loop insulin delivery is different from conventional pump therapy and low glucose management technology because it uses a control algorithm to automatically adjust insulin delivery based on subcutaneous sensor data to improve diabetes management. Manual meal-time announcement and prandial insulin boluses still need to be carried out by patients in order to overcome the delay in insulin action of currently available insulin analogues. The 'hybrid' closed-loop approach is in contrast to a 'fully' closed-loop approach, in which user input to the control algorithm related to meals would not be required.

The Personalized Closed Loop (PCL) system comes one step closer to the concept of a fully closed system with the introduction of a cloud-based algorithm that looks at an individual patient's recent pump data in CareLink™ and calculates optimal settings to further increase the amount of time the patient spends in euglycemic range. In its final configuration, the system will be able to transmit a variety of settings recommendations automatically to a Smartphone application, which in turn will send them to the patient's insulin pump. The early implementation of this system as part of clinical feasibility studies will ensure that all of the settings recommendations generated by the PCL algorithm are vetted and approved by a study investigator before changes are made in the pump first manually, then automatically as development of the system progresses.

The overall goal of the PCL system will be to significantly reduce the burden of self-care in managing diabetes without compromising glycemic control. The following overarching characteristics of the conceptual PCL system demonstrate its overall objective:

1. Reduced User Burden: The system will include several features aimed at improving patient quality of life by significantly decreasing the need for user input. Key features will include use of total daily dose (TDD) as a basis for bypassing the 48-hour Auto Mode warm-up period, automatic adaptation of therapy settings, and meal announcement options that will eventually remove the need for carb counting.

2. Digital Twin algorithm: The system will harness artificial intelligence (AI) technology by using historical patient data to generate a virtual model of the individual patient that mimics the patient's physiological and behavioral patterns. Virtual patient model prediction will then be used to determine optimized therapy settings including carbohydrate ratios, insulin sensitivity factor, basal rates and active insulin time. This inherently requires two-way communication between the pump and a cloud-based algorithm,

because the system will constantly be learning in order to make adjustments as the patient's behavior and physiology change over time. The learnings will modify algorithm parameters within the pump, predict behaviors, as well as occasionally notify patients/clinicians of upcoming changes, insights, or actions.

3. Meal Simplification algorithm: The Meal Simplification algorithm is intended to simplify carb counting and meal entry for closed-loop sensor-augmented pump users by providing an option to choose from a few standard, user-specific carb entry sizes instead of entering CHO estimates to the nearest gram. The algorithm is designed to identify clusters of CHO values based on the user's history of CHO entry data from the pump's Bolus Wizard and then provide the user with an individualized set of common meal sizes, such as small, medium and large, along with a corresponding range of CHO values for each meal size. A centroid carb value for the selected meal size will then be used to compute a bolus to cover the meal.

4. Meal Prediction algorithm: The Meal Prediction algorithm is intended to simplify meal-handling for closed-loop sensor-augmented pump users by predicting: (a) when the user will eat and (b) an estimate of the CHO amount the user will consume for the meal. The algorithm will comprise 2 statistical models, the meal timing model and the meal content model, generated based on the user's historical information received through the application from the pump and other sensors in the user's Smartphone or smartwatch. The meal timing model will use the user's historical information to determine the occurrence of future meals before they take place. The meal content prediction model will, based on historical patterns, estimate the most likely CHO amount that will be consumed by a user, assuming that a meal is about to occur once intent to eat is confirmed by the user.

3.2. Purpose

The purpose of this study is to:

- Evaluate subject safety related to automated recommendations for device setting changes that are formulated by the Cloud-based Digital Twin algorithm and impact insulin delivery.
- Evaluate subject safety related to carbohydrate estimates for meals that are calculated by the Cloud-based Meal Prediction algorithm.

4. Objectives and Endpoints

4.1. Objectives

4.1.1. Primary Objective(s)

The objective of the study is to collect device data to assist in the development of a Personalized Closed Loop (PCL) system.

4.2. Endpoints

4.2.1. Descriptive Endpoints

There are no statistically powered endpoints or hypothesis testing but there are descriptive endpoints.

4.2.2. Safety Endpoint

- Severe glycemic events: (i.e., severe hypoglycemia, DKA)
- Collection of ALL adverse events (i.e. Summary of device related adverse events)

4.2.3. Effectiveness Endpoints

- Percentage of time in target: SG <70 mg/dL, 70-180 mg/dL and > 180 mg/dL

In each phase, data will be summarized and documented to evaluate the safety and effectiveness of the algorithm changes.

5. Study Design

This is a single arm study comprised of a series of feasibility studies. Please see below:

[redacted]

Feasibility Study Part 2 (i.e. Feasibility 2): Feasibility 2 is the focus of the current protocol.

[redacted]

This study may include up to 3 separate **Cohorts** of individuals, based on which algorithm is being studied:

Cohort A: The main purpose of this cohort is to test the Digital Twin insulin delivery algorithm adaptation (Feasibility [redacted] 2[redacted]

[redacted]

Cohort C: The main purpose of this cohort is to test a meal prediction algorithm (Feasibility 2 [redacted])

Study Phases

This study consists of one or more phases. See Table 1 for a Summary of phases for Feasibility 2.

- Phases may be repeated per sponsor direction
- Phases in different cohorts may proceed simultaneously
- Same subjects may participate in multiple phases
- Subjects who have participated in a phase will not be required to repeat the run-in period if they have already participated in prior phase as per Sponsor discretion.
- When subjects are using Auto Mode with the AHCL system, the automatic basal insulin delivery target should be set to 100 mg/dL.

Table 1. Summary of Phases for Feasibility 2

Cohort	Phase	Age	Algorithm	Challenge
A	**1**	14+	Digital Twin	Manual Mode/ Auto Mode Transition – at home
A	**2**	2-13	Digital Twin	Manual Mode/ Auto Mode Transition – at home
A	**3**	14+	Digital Twin	Missed Meal Bolus – at home
A	**4**	2-13	Digital Twin	Missed Meal Bolus – at home
C	**5**	14+	Meal Prediction	In Clinic Observation
C	**6**	2-13	Meal Prediction	In Clinic Observation

Study Population

For Feasibility 2, the study population will include patients with type 1 diabetes. Ages 14 and up will be enrolled first, followed by the younger age groups.

Staged Enrollment in all Cohorts

- Enrollment of pediatric subjects 2-13 years of age into a specific phase may not proceed until N=10 subjects 14 years and older have completed the corresponding phase and safety data has been reviewed by the Data Monitoring Committee (DMC).
- Study subjects 2-6 years of age will be enrolled in Cohort A and Cohort C only after completing an in clinic observational study using the AHCL system. See details about the observational study procedures below.

Study Procedures:

General:

All subjects will be trained on diabetes management principles, such as the treatment of hyperglycemia and hypoglycemia. In addition, there will be training regarding the need to have access to oral glucose and glucagon in case of hypoglycemia. Subjects will be asked to continue performing routine self-monitoring of blood glucose (SMBG) checks, as they were doing prior to enrolling in the study. For study purposes, subjects will be instructed to perform SMBG if they are experiencing a severe hyperglycemic

event or Diabetic Ketoacidosis (DKA). Please note: If a subject has a severe hypoglycemic event, subject should attempt to retrieve SMBG result from person providing assistance. As a precaution, subjects will be told that they should keep their own insulin pump supplies in a safe place and to have back up supplies on hand (such as insulin and syringe) in the event they are asked to revert back to their own therapy during the study or experience study pump issues (i.e. infusion set occlusion with high glucose).

Subjects will be instructed to insert glucose sensors only in the locations that are specified in the User Guide materials.

SMBG recommendations:
Typically, SMBG is required for calibration. Occasionally, subjects may receive a notification if the pump needs a BG to enter or stay in Auto Mode. For study purposes, subjects will be instructed to perform SMBG if they are feeling low (but sensor glucose [SG] is not low) and treat as needed. They should also perform SMBG if they are experiencing a severe hyperglycemic event or DKA. Please note: If a subject has a severe hypoglycemic event, subject should attempt to retrieve a SMBG result from the person providing assistance. If SMBG is required for monitoring, it will be detailed in the visit study procedures.

FEASIBILITY 2

Subjects who participated in [redacted] 1 will complete Visit 10, where they will choose to either participate in Feasibility 2 or exit the study.

Subjects who participated in [redacted] and choose to transition to Feasibility 2 will be re-consented. They will be required to undergo an inclusion/exclusion criteria evaluation.

Subjects who are transitioning from [redacted] to Feasibility 2 will be required to participate in the full the run-in period for Feasibility 2, since they will be using a new device system.

If any subject meets withdrawal criteria after participating in [redacted], he/she will not be allowed to continue in Feasibility 2.

If a subject exits from [redacted], he/she cannot be re-consented to participate in Feasibility 2.

Cohort A: Insulin Delivery Recommendations Derived from the Digital Twin Algorithm

The Digital Twin algorithm resides in the Medtronic Data Cloud. By wearing the system during the run-in period, the patient starts to accumulate device data that will be uploaded to CareLink™ after 3 full weeks (22 midnights). The algorithm will then calculate individualized insulin delivery recommendations that will be made available to the investigator.

Digital Twin Challenge #1: Alternating Between Auto Mode & Manual Mode

Purpose: The purpose of this challenge is to observe subject safety when subjects frequently exit Auto Mode and transition back and forth between Auto Mode and Manual Mode. The purpose of this data collection is also to assist in the development of the Digital twin algorithm.

Rationale: Patients sometimes intentionally switch from Auto Mode to Manual Mode for brief periods of time depending on their circumstances.

Run-in Period for Digital Twin Challenge #1

At the conclusion of the run-in period, insulin delivery recommendations (i.e., insulin carbohydrate ratio, basal rate changes, insulin sensitivity and active insulin time) will be calculated by the cloud-based Digital Twin algorithm based on uploaded CareLink™ data.

Run-in Period Study Procedures Based on Therapy at Screening

- Patients who come in using pump with CGM at Screening will spend a minimum of 30 days using the AHCL system during the run-in period. Device settings may be adjusted as needed
- Patients who are using MDI therapy or a pump without CGM (CSII) at Screening will spend at least 2 additional weeks using the AHCL system during the run-in period. Part of the extra time will be used to collect blinded CGM data as a baseline. The rest of the time will be used to allow subjects get used to pump and CGM. Device settings may be adjusted as needed.
- With the AHCL system, the auto basal rate target should be set to 100mg/dL for the duration of the study, unless the investigator considers this setting to be a safety issue for a subject. At the investigator's discretion, the setpoint may be set to 120mg/dL.
- All subjects will be asked to upload the pump and meter weekly during the run-in period.

Study Period Procedures for Digital Twin Challenge #1

Following the run-in period, subjects will participate in a study period lasting approximately 5-6 weeks. For the duration of the study period, subjects will be asked to switch back and forth between Auto Mode and Manual Mode, according to a schedule that will be provided to each site by the Sponsor. Subjects will be instructed to upload the pump and meter at specific time points during the study period. Device settings recommendations will be provided during this study period. Investigators should make every attempt to follow these recommendations, except if they do not agree with the device settings recommendations, based on safety concerns. Investigators may adjust device settings based on safety.

Device Setting changes

- At the start of the study period, insulin delivery settings based on data collected during the run-in period will be made available to the investigator.
    - If the investigator agrees with the new settings, they will be programmed into a subject's study pump.
    - If the investigator does not agree with the recommendations, they may be implemented gradually over a period of time, e.g. 1-2 weeks.
    - If the investigator does not agree with the recommendations and does not wish to implement them gradually, details about the disagreement will be noted on the applicable CRF.
- After approximately 2 weeks of the study period, following a pump upload by subjects at home, new device settings will be made available.
    - If the investigator agrees with the new settings, they will be programmed into a subject's study pump.
    - If the investigator does not agree with the recommendations, the investigator will enter details about the disagreement on the applicable CRF.
- After approximately 3 weeks of the study period, following a pump upload by subjects at home, new device settings will be made available.
    - If the investigator agrees with the new settings, they will be programmed into a subject's study pump.

  - If the investigator does not agree with the recommendations, the investigator will enter details about the disagreement on the applicable CRF.
- After approximately 4 weeks of the study period, following a pump upload by subjects at home, new device settings will be made available.
  - If the investigator agrees with the new settings, they will be programmed into a subject's study pump.
  - If the investigator does not agree with the recommendations, the investigator will enter details about the disagreement on the applicable CRF.

Note: The following list of reasons for rejecting device settings recommendations will be available to the investigator on the applicable CRF:

1. Device settings recommendations are being rejected in order to extend observation from the last device settings recommendations
2. Device settings recommendations are being rejected, because they are too aggressive, e.g. would cause low glucose
3. Device settings recommendations are being rejected, because they are too conservative, e.g. they would cause high glucose
4. Device settings recommendations are being rejected – Other: (Enter comment)

The table below shows an example of a transition schedule between Auto Mode and Manual Mode; different variations will be provided by the Sponsor to the investigational center. The transitions between Auto Mode and Manual Mode should occur between 7am and 12 Noon.

Table 2. Example of Manual mode Transitions during the study period - Digital Twin Challenge #1

Week	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
1	**Manual Mode**	Auto Mode	Auto Mode	Auto Mode	Auto Mode	Auto Mode	Auto Mode
2	Auto Mode	Auto Mode	**Manual Mode**	Auto Mode	Auto Mode	Auto Mode	Auto Mode
3	Auto Mode	Auto Mode	Auto Mode	Auto Mode	**Manual Mode**	Auto Mode	Auto Mode

Week	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
4	Auto Mode	**Manual Mode**	Auto Mode	Auto Mode	Auto Mode	Auto Mode	Auto Mode
5	Auto Mode	Auto Mode	Auto Mode	**Manual Mode**	Auto Mode	Auto Mode	Auto Mode

Digital Twin Challenge #2: Eating a Meal without Giving an Insulin Bolus

Purpose: The challenge is designed to test the post prandial effect of a subject eating a meal without giving an insulin meal bolus. The purpose of this data collection is also to assist in the development of the Digital twin algorithm.

Rationale: During routine diabetes management, patients with diabetes may forget to give insulin for their meal. This challenge helps to collect data on how the Digital Twin algorithm will make insulin delivery recommendations in patients who forget to take insulin with their meal.

Run-in Period for Digital Twin Challenge #2

At the conclusion of the run-in period, insulin delivery recommendations (i.e. insulin carbohydrate ratio, basal rate changes, insulin sensitivity and active insulin time) will be calculated by the cloud-based Digital Twin algorithm based on uploaded CareLink™ data.

Run-in Period Study Procedures Based on Therapy at Screening

- Patients who come in using pump with CGM at Screening will spend a minimum of 30 days using the AHCL system during the run-in period. Device settings may be adjusted as needed
- Patients who are using MDI therapy or pump without CGM (CSII) at Screening will spend at least 2 additional weeks using the AHCL system during the run-in period. Part of the extra time will be used to collect blinded CGM data as a baseline. The rest of the time will be used to allow subjects get used to pump and CGM. Device settings may be adjusted as needed.
- With the AHCL system, the auto basal rate target should be set to 100mg/dL for the duration of the study, unless the investigator considers this setting to be a safety issue for a subject. At the investigator's discretion, the setpoint may be set to 120mg/dL.
- All subjects will purposely withhold insulin at either breakfast or lunch on each day of the run-in period (approximately 23 days)
- Subjects will check their blood glucose at the start of the missed bolus meal as well as 2 hours after the start of the meal; they will give correction insulin as needed. Confirmation of BG is entered on an electronic log
- Subjects will record the calculated CHO on an electronic log, because it is not entered into the Bolus Wizard
- Subjects will be asked to upload their pumps and meters weekly

Study Period for Digital Twin Challenge #2 (at study site selected by Sponsor)

Following the run-in period, subjects will participate in a study period lasting approximately 5-6 weeks. Subjects will be divided into separate groups:

Group 1: Approximately 50% of subjects will purposely withhold insulin for either Breakfast or lunch on each day during weeks 1 through 3. The amount of CHO will be collected on a log, because it is not entered into the Bolus Wizard. Subjects will also check their glucose at the start of the meal as well as 2 hours after the start of the meal and give correction insulin as needed. For the remainder of the study, i.e. weeks 4 and 5, subjects in this group will give standard insulin at all meals.

Group 2: Approximately 50% of subjects will give standard insulin at all meals for the duration of the study period. CHO data will be collected directly from subject's data entry into the pump through CareLink™.

Subjects will be instructed to upload the pump and meter at specific time points during the study period. Device settings recommendations will be provided during this study period. Investigators should make every attempt to follow these recommendations, except if they do not agree with the device settings recommendations, based on safety concerns. Investigators may adjust device settings based on safety.

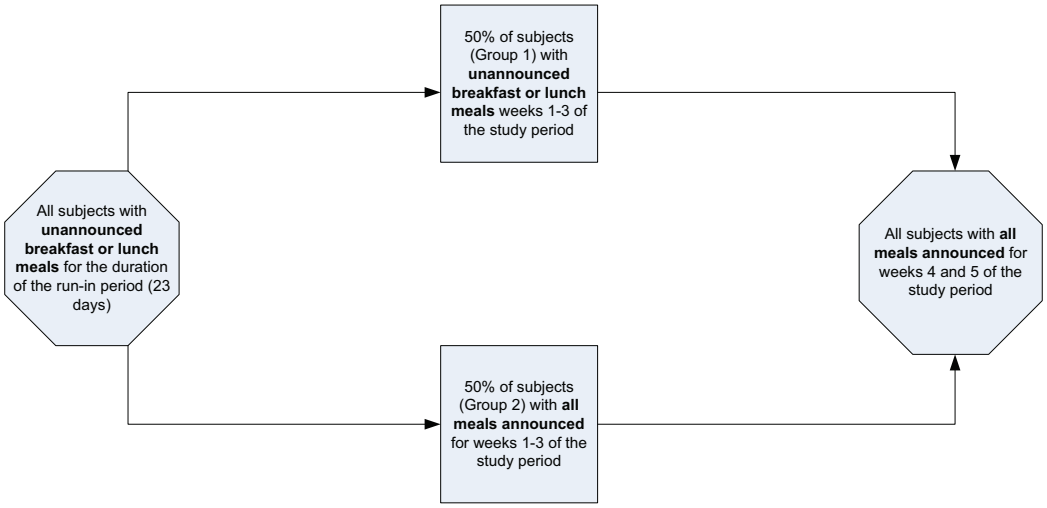
Device Setting

- At the start of the study period, insulin delivery settings based on data collected during the run-in period will be made available to the investigator.
    - If the investigator agrees with the new settings, they will be programmed into a subject's study pump.
    - If the investigator does not agree with the recommendations, they may be implemented gradually over a period of time, e.g. 1-2 weeks.
    - If the investigator does not agree with the recommendations and does not wish to implement them gradually, details about the disagreement will be noted on the applicable CRF
- After approximately 2 weeks of the study period, following a pump upload by subjects at home, new device settings will be made available.
    - If the investigator agrees with the new settings, they will be programmed into a subject's study pump.
    - If the investigator does not agree with the recommendations, the investigator will enter details about the disagreement on the applicable CRF.
- After approximately 3 weeks of the study period, following a pump upload by subjects at home, new device settings will be made available.
    - If the investigator agrees with the new settings, they will be programmed into a subject's study pump.
    - If the investigator does not agree with the recommendations, the investigator will enter details about the disagreement on the applicable CRF
- After approximately 4 weeks of the study period, following a pump upload by subjects at home, new device settings will be made available.
    - If the investigator agrees with the new settings, they will be programmed into a subject's study pump.
    - If the investigator does not agree with the recommendations, the investigator will enter details about the disagreement on the applicable CRF.

Note: The following list of reasons for rejecting device settings recommendations will be available to the investigator on the applicable CRF:

1. Device settings recommendations are being rejected in order to extend observation from the last device settings recommendations

2. Device settings recommendations are being rejected, because they are too aggressive, e.g. would cause low glucose
3. Device settings recommendations are being rejected, because they are too conservative, e.g. they would cause high glucose
4. Device settings recommendations are being rejected – Other: (Enter comment)



Cohort C: Meal Time Prediction Algorithm

The meal prediction algorithm will look at pump data collected during the run-in period and uploaded to the Medtronic Data Cloud, in order to determine the timing of meal-time predictions. Subjects will not use the App during the run-in period.

Due to a limitation with regard to the availability of the Medtronic PCL App to subjects under 13 years of age, who rely exclusively on the use of Apple products, i.e., iPhones, an Android phone may be provided for use during the study.

While there are ***no specific challenges*** for this cohort the following study procedures will be implemented:

Run-in Period Study Procedures Based on Therapy at Screening

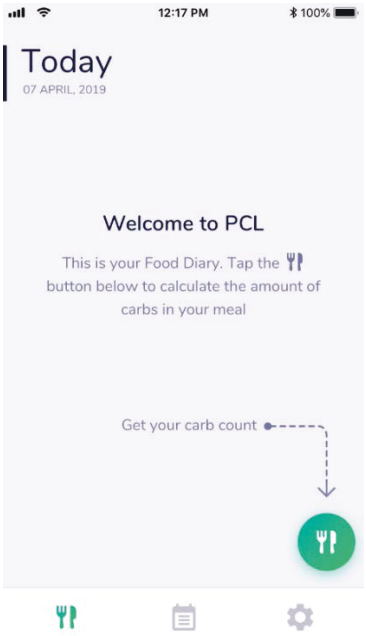
- Patients who come in using pump with CGM at Screening will spend a minimum of 30 days using the AHCL system during the run-in period. Device settings may be adjusted as needed
- Patients who are using MDI therapy or pump without CGM (CSII) at Screening will spend at least 2 additional weeks using the AHCL system during the run-in period. Part of the extra time will be used to collect blinded CGM data as a baseline. The rest of the time will be used to allow subjects get used to pump and CGM. Device settings may be adjusted as needed.
- With the AHCL system, the auto basal rate target should be set to 100mg/dL for the duration of the study, unless the investigator considers this setting to be a safety issue for a subject. At the investigator's discretion, the setpoint may be set to 120mg/dL.

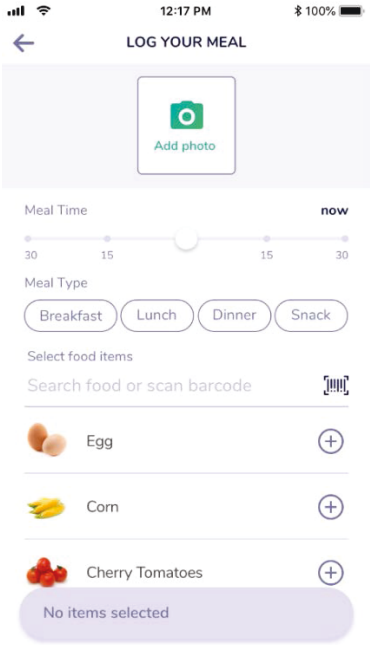
At selected centers, a limited number of subjects will undergo frequent sample testing (FST). The testing is **not** done in support of study data. Rather, the FST data is being collected as a means of gaining experience with a new testing method (ABL90 by Radiometer).

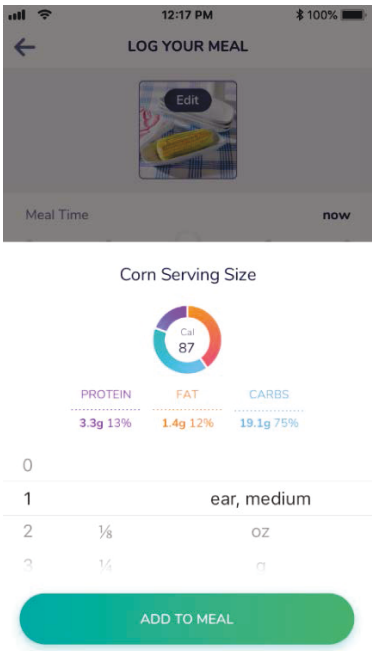
Subjects who are selected to participate in the FST procedures will undergo a hematocrit blood test prior to the start of the procedures. The passing criteria for this test are that subjects should not be more than 10% below the lower limit of normal Hct for the reference range of the local lab that is testing the sample. If a subject's medical record contains evidence that the test was taken, with the result as outlined above, within 6 months prior to screening, the blood draw and test during the study will not be required.

Study Period for the Meal Prediction Cohort:

During the approximately 42-day long study period, subjects in this cohort will use the PCL Mobile App to log meals and receive CHO estimates; they will not receive insulin delivery settings recommendations. They will enter the type of meal they wish to eat along with the serving size into the App (e.g. Pasta dish, Toast and eggs, etc.). This will prompt the App to calculate a CHO estimate that is based on the search criteria the subject entered (see example of sequence below).






12:17 PM
100%
LOG YOUR MEAL
Edit
Meal Time
now
Corn Serving Size
Cal
87
PROTEIN
FAT
CARBS
3.3g 13%
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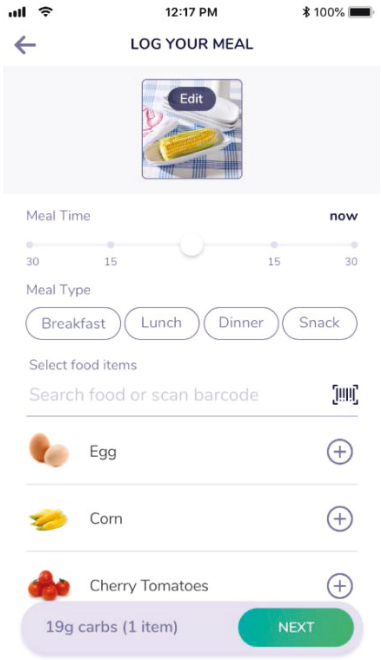
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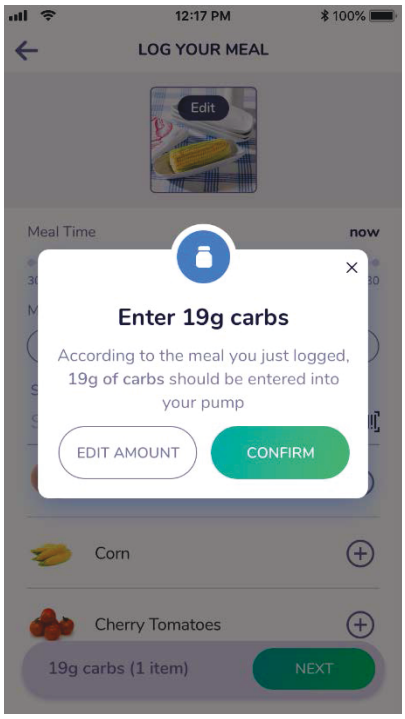
Edit
Meal Time
now
30
15
15
30
Meal Type
Breakfast
Lunch
Dinner
Snack
Select food items
Search food or scan barcode
Egg
Corn
Cherry Tomatoes
19g carbs (1 item)
NEXT


12:17 PM
100%
LOG YOUR MEAL
Edit
Meal Time
now
Enter 19g carbs
According to the meal you just logged, 19g of carbs should be entered into your pump
EDIT AMOUNT
CONFIRM
Corn
Cherry Tomatoes
19g carbs (1 item)
NEXT

Subjects will enter the CHO amount calculated and displayed on the App into the pump for bolus calculation and insulin delivery. The user may modify the amount of CHO estimated by the App prior to entering it manually into the bolus wizard.

Cohort C subjects will perform study procedures both in-clinic and at home during the Feasibility 2 study:

In-clinic:

- Diabetes Management as per investigator discretion, e.g. correction boluses
- The first two days of the study period will be spent in the clinic or in a hotel-type setting.
- If a visit to the clinic is not possible due to circumstances that would negatively impact the subjects, other subjects or Investigational center staff, e.g., COVID-19 exposure or illness, both days of Visit 11 may be conducted as Telemedicine visits.
    - Investigational center staff should be in contact with subjects via video connection to train them on the use of the App.
    - Investigational center staff should be in contact with subjects via video connection to observe use of the PCL app at appropriate times, i.e., during all meals where the App is used to collect meal information and BGs are required. BG checks are required for the 2 largest CHO content meals of the day. Subjects will be observed during meals where CHO estimates that are generated by the App's meal library are entered into the pump's bolus wizard prior to the main meals (Breakfast, Lunch, Dinner). Please note that the investigator may override CHO estimate and provide their own based on investigator's discretion.
- During clinic visits, subjects will be observed during meals where CHO estimates that are generated by the App's meal library are entered into the pump's bolus wizard prior to the main meals (Breakfast, Lunch, Dinner). Please note that investigator may override CHO estimate and provide their own based on investigator discretion.
- BG checks during the in-clinic visits will be performed at start of the 2 meals with the highest CHO content, as well as 2 hours after the start of those meals.
- FST with ABL-90 will take place at sites that are selected by the sponsor for one day of the in-clinic visit
- Testing frequency is at 30-minute intervals for approximately 8 hours.

At Home:

System will record information about meal time, CHO counting and BG checks. Subjects will follow the same process they followed during the in-clinic visit.

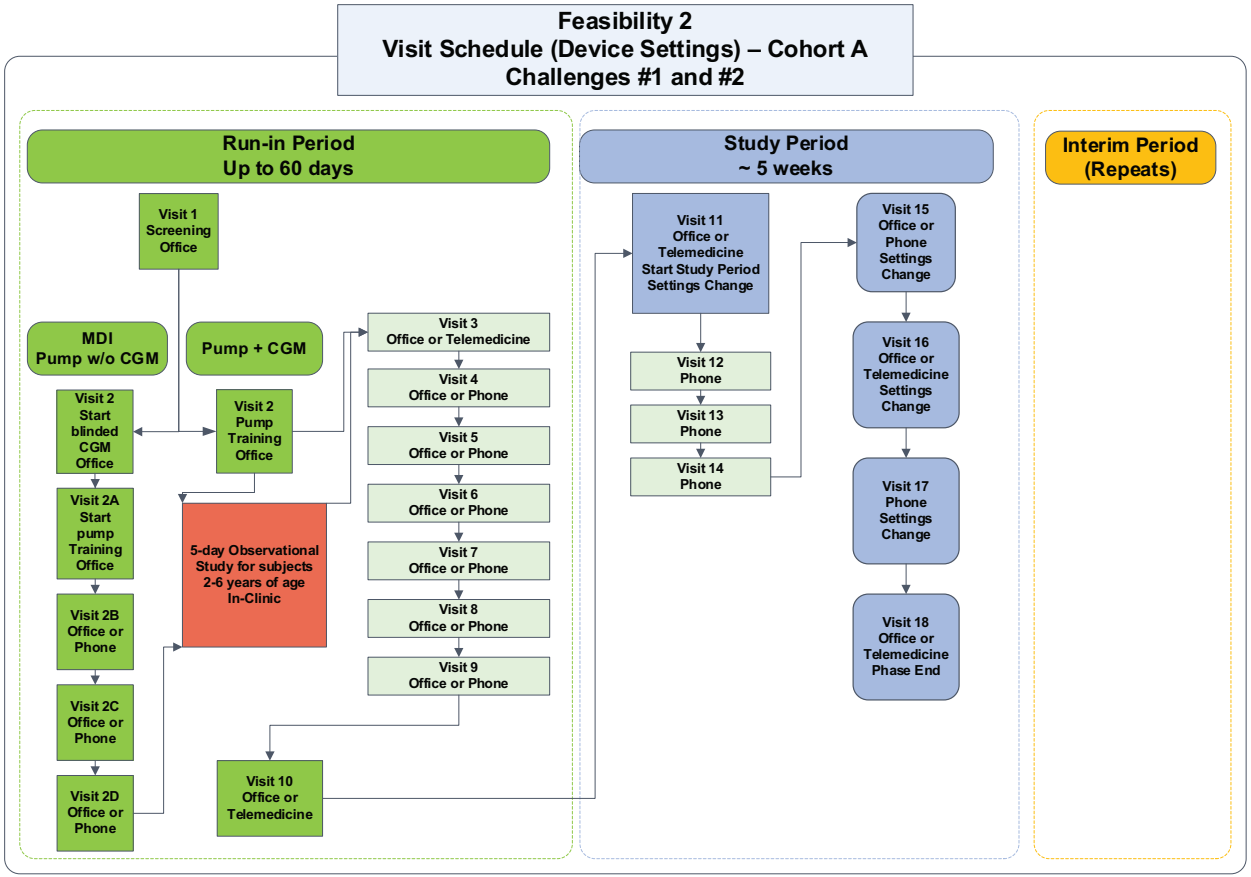
Study Procedures for subjects 2-6 years of age (In-Clinic Observational Study)

The In-Clinic observational study is intended for subjects 2-6 years of age and must be completed before they are allowed to proceed to Cohort A and Cohort C study procedures.

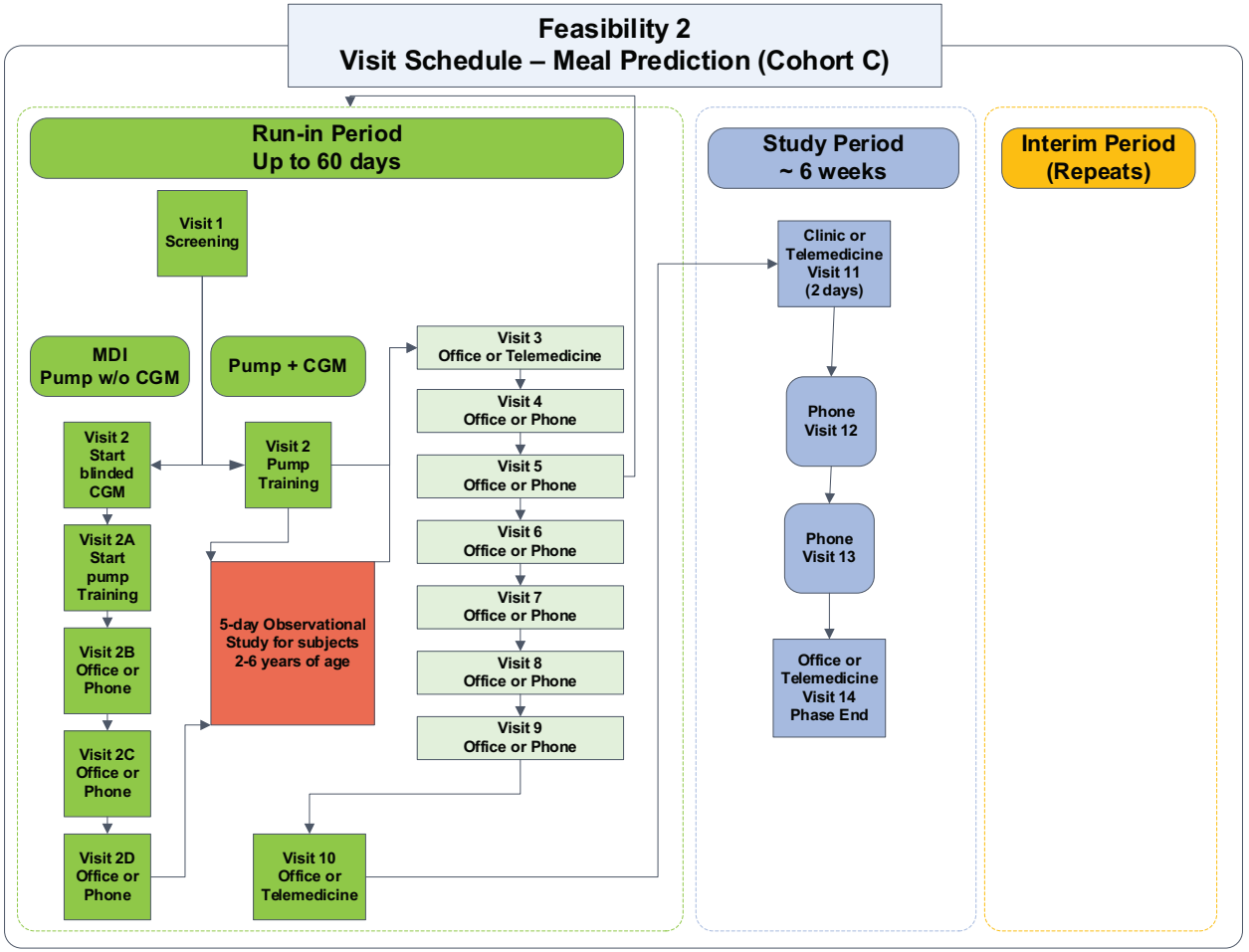
Study procedures for the observational study:

- After enrollment into the CIP326 study, subjects 2-6 years of age will initially use the AHCL system in Manual Mode. If subject was using 670G with Auto Mode at Screening, the subject may use Auto Mode with the Auto Correction feature off (i.e., not enabled).
- The in-clinic study will be conducted after completion of Visit 2 (see visit schedule).
- The in-clinic study for subjects 5-6 years of age and subjects 2-4 years of age may be conducted in parallel.
- During the 5-day in-clinic study, subjects will use the AHCL system in Auto Mode.
- After the completion of the in-clinic observation study, the Data Monitoring Committee (DMC) will convene to review the safety data.
- DMC will review in clinic data from subjects in the 5-6 year age group (N=8), in order to assess that it is safe for 5-6 year olds to perform Cohort A or Cohort C study procedures.
- DMC will review in-clinic data from both the 2-4 year age group (N=8) and the 5-6 year age group (N=8) in order to assess that it is safe for 2-4 year olds to perform Cohort A and Cohort C study procedures.
- While waiting for approval by the DMC after completing the in clinic observational study, subjects will use the AHCL system at home in Manual Mode. If subject was using 670G with Auto Mode at Screening, the subject may use Auto Mode with the Auto Correction feature off (i.e., not enabled).
- The observational study may be divided into two different weekends based on investigator discretion to provide improved flexibility for parents and child.
    - Friday to Sunday x 1
    - Saturday to Sunday x 1
- When not in clinic to perform the observational study, subjects should be in Manual Mode. If subject was using 670G with Auto Mode at Screening, the subject may use Auto Mode with the Auto Correction feature off (i.e., not enabled).
- Upon receiving approval to proceed from the DMC, subjects may return to using Auto Mode.

Visit Schedule for Cohort A: Device Settings Adaptation (Digital Twin) – Challenges #1 and #2



Visit Schedule for Cohort C: Meal Prediction



5.1. Duration

The anticipated study duration is no longer than 18 months for all three feasibility studies. Subjects will be in the study for approximately 3.5 months.

5.2. Rationale

The design of this study includes a series of 3 single-arm feasibility trials with safety and effectiveness endpoints that are not statistically powered. They represent the next step in the development of a personalized advanced closed loop insulin delivery system. Iterative changes in the cloud-based control algorithms, which will include advanced levels of automation, require a study design similar to the design that was approved in the studies of the predecessor MiniMed™ 670G system.

6. Product Description

6.1. Intended Population

A population of type 1 subjects will be studied. The study population will have a range for age, duration of diabetes, and glycemic control.

6.2. General Overview of MiniMed Insulin Pump Systems Used in Feasibility 2: System Components and Consumables

Table 3. MiniMed™ Insulin Pump Systems Used in this Study: System Components and consumable materials

Device name	MDT Model number/ part number	Device Status
Cloud-based Digital Twin Algorithm	N/A	Investigational
Cloud-based Meal Prediction Algorithm	N/A	Investigational
MiniMed™ 670G Insulin Pump, version 4.0 Tel D	MMT-1740	Investigational
PCL Mobile Application	N/A	Investigational
Guardian™ Sensor (3)	MMT-7020	Non-Investigational
Guardian™ Link (3) Transmitter	MMT-7811	Non-Investigational

Device name	MDT Model number/ part number	Device Status
One-Press Serter	MMT-7512	Non-Investigational
Charger	MMT-7715	Non-Investigational
Tester	MMT-7736L	Non-Investigational
Medtronic CareLink™ Personal For Clinical Research Software	MMT-7333	Non-Investigational
CONTOUR® NEXT LINK 2.4 Study Meter	MMT-1352	Non-Investigational

6.3. Investigational Devices

6.3.1. PCL System – Components Overview

The PCL system will be a fully-automated insulin delivery system that allows for personalization of therapy based on the user's historical data. Table 4 below lists the primary devices that make up the system and provides a brief description of each component.

Table 4. PCL System Components (Feasibility 2 study)

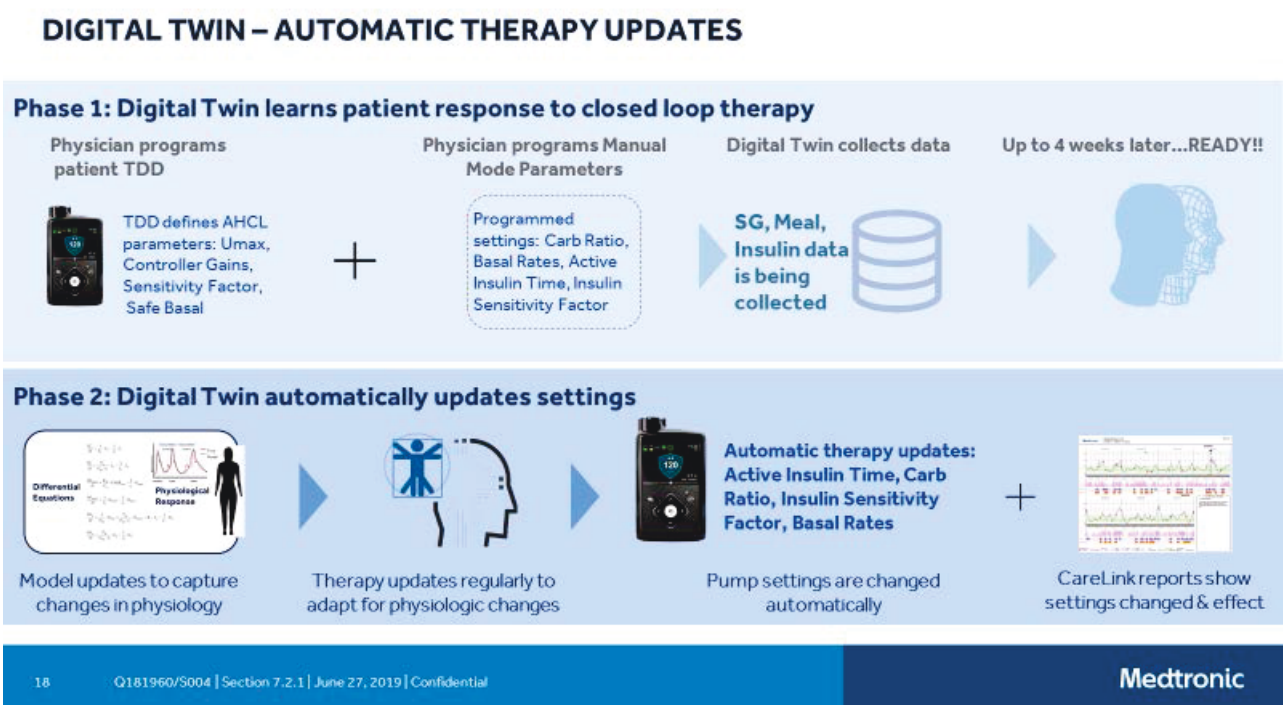
System Component	Description
Digital Twin AI Patient Model Algorithm (Medtronic Cloud)	• Individualized mathematical model of the patient's physiology, housed in the Medtronic Data Cloud, generated using patient's historical data and refined with each new data upload to the cloud or at pre-defined intervals • Used to determine personalized HCL parameters and therapy factors for the patient and HCP that are then sent to the PCL pump algorithm for implementation
Meal Prediction Algorithm (Medtronic Cloud)	• Individualized Model that estimates the most likely meal times to promote consistent, accurate meal announcements
Pump with: • Tel-D communication • Advanced Hybrid Closed Loop (AHCL) Algorithm	• Ambulatory, battery-operated, rate-programmable micro-infusion pump intended for delivery of basal/bolus insulin that also receives real-time SG values from a continuous glucose monitor (CGM) for display and storage.
CGM	• Measures glucose in user's interstitial fluid and transmits SG values to the pump
PCL Mobile Application on Smartphone	• Secondary user interface for the pump display • App will reside on each user's personal Smartphone
CareLink™ Personal Therapy Management Software	• Allows viewing and easy evaluation of device data by user/HCP • Provides live, customizable data dashboards and summaries of Digital Twin/meal prediction adaptations • Provides insights about user behavior that could lead to improved therapy

6.3.2. PCL System Function Overview

The PCL system is designed to facilitate immediate use by the patient after some basic training and after consultation with the Study Investigator. Basic training will include instructions such as insertion of infusion sets and sensors, use of Auto Mode and the association of a Smartphone as part of the system. Basic training will include instructions such as insertion of infusion sets and sensors, use of Auto Mode and the association of a Smartphone as a component of the final system. If the investigator does not elect to use the quick-start feature, the system will revert to the customary a 48-hour warmup. Insulin to CHO ratio, active insulin time, etc. need to be entered as they do in the current version of the system.

For the 48-hour warm-up, the PCL system will start to function in Auto Mode as soon as Sensor glucose values become available and after a BG entry is received. The Auto Mode features of the system are not available without sensor use. For meal handling, the PCL system will include user-configurable options for meal announcements: Entry of carb amounts or entry of meal size (small, medium, or large). Over time, the Meal Wizard will learn a user's meal patterns and will present a default carb amount or meal size that is most probable, based on meal time, location or other information available to the system. The user may also command meal bolus delivery from an associated Smartphone through a Meal Wizard screen on the App.

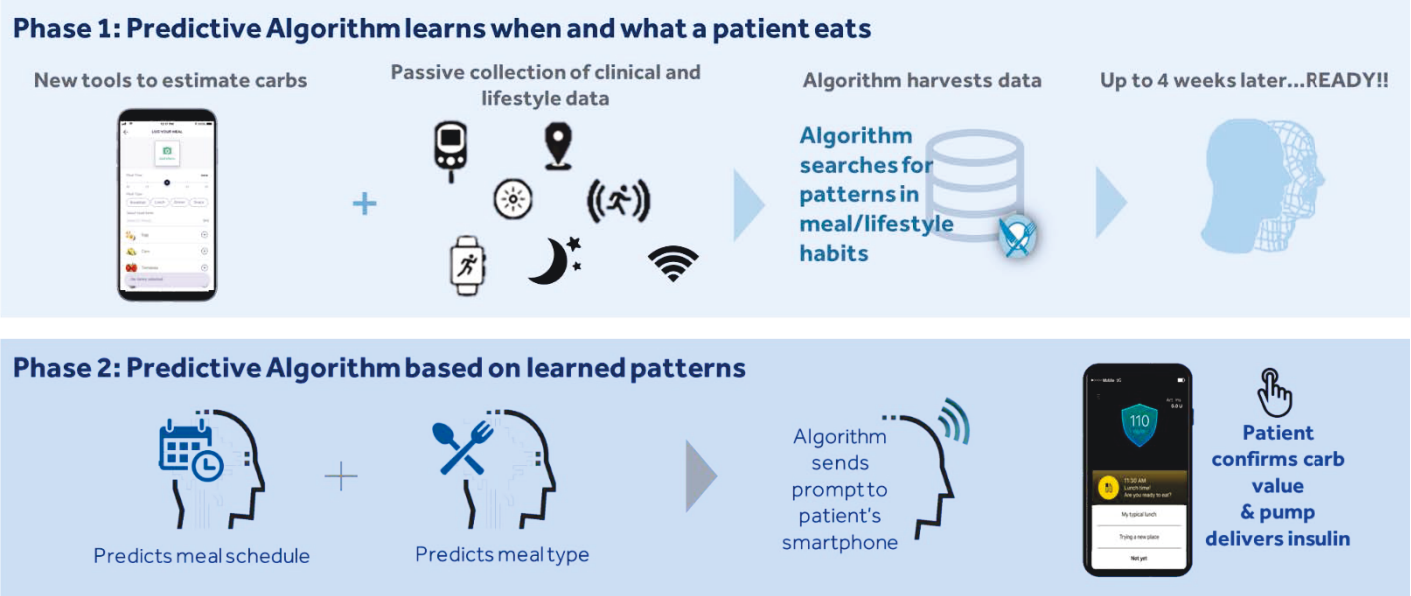
6.3.3. Cloud-based Digital Twin Algorithm



The Cloud-based Digital Twin algorithm is a mathematical model of an individual patient, based on the patient's historical data, that is used to compute optimized therapy settings for the patient's closed loop sensor-augmented pump system. It is based on Medtronic's virtual patient model in which a patient's historical information is processed through a series of differential equations to predict a patient's physiological response and to adapt insulin delivery, i.e. individualized HCL parameters and therapy factors, accordingly.

The algorithm resides in the Medtronic Data Cloud platform and communicates directly with the Medtronic Data Cloud. It begins to evaluate patient data as soon as he/she starts wearing the system, a period referred to as imprinting. This initial period lasts for approximately 3 weeks. During this time, the algorithm only identifies patterns in a patient's physiological responses and behaviors, but does not provide any therapy recommendations to the patient. Those patterns are then used to establish a virtual model that closely mimics each patient's physiology and behavior (hence the term "Digital Twin").

6.3.4. **Cloud-based Meal Prediction Algorithm**



The meal prediction algorithm leverages the capabilities of food-logging and nutrition information technology to predict the user's meal times, meal sizes and meal types based on each user's behavior history. The food logging resides in a Smartphone App while the meal prediction algorithm resides in the Medtronic Data Cloud.

The food logging tool allows the user to enter meals either as simple carbohydrate gram counts or as a more sophisticated set of selections from an extensive food library that contains images of food items along with nutritional information for each serving size. Users will also be provided the option to take photographs of their food to associate them with each meal entry. The Smartphone app will then send the meal log data to the Medtronic AI Data Cloud so that machine learning algorithms may begin learning the eating habits of the individual user. For Feasibility 2, both pump and CGM data will be gathered

through CareLink™, while meal logging data will be gathered through the App. This study will make only meal time predictions, but the user will be able to use the App's food library to log meals and estimate carbohydrates to enter into the pump's Bolus Wizard for meal bolusing.

6.3.5. MiniMed™ 670G Insulin Pump, Version 4.0 Tel-D

The MiniMed™ 670G Insulin Pump, version 4.0 AHCL is capable of continuous insulin delivery, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin. When used with the CGM components (Guardian™ Sensor [3] and Guardian™ Link [3] transmitter), the pump system is capable of continuous or periodic monitoring of glucose levels via a sensor that is inserted in the interstitial fluid under the skin, including the detection of possible low or high blood glucose episodes. The pump also displays glucose values, storing this data so that it can be retrospectively analyzed to track patterns and improve diabetes management.

The MiniMed™ 670G Insulin Pump, version 4.0 AHCL also includes the closed loop algorithm as part of the SmartGuard™ collection of features that may be enabled by the user. SmartGuard™ is comprised of Manual Mode Low Management, which includes the Suspend on low feature (suspends insulin delivery when a pre-set low SG threshold is reached), the Suspend before low feature (enables insulin to suspend 30 minutes before a pre-set low SG threshold is reached) and Auto Mode (hybrid closed loop) feature. The Auto Mode and Manual Mode Low Management features will not be active at the same time.

In Auto Mode, the pump features selectable auto basal target setpoints (100 mg/dL and 120 mg/dL) as well as automatic correction bolus capability, based on sensor glucose.

6.3.6. PCL Mobile Application

A PCL Mobile Application, referred to as App, on each patient's own Smartphone will be used to facilitate 2-way data transfer between the pump and the Medtronic Data Cloud. It features a real-time secondary display of the pump as well as a food-logging interface that includes remote bolus command capability.

6.4. Non-Investigational/Exempt Devices

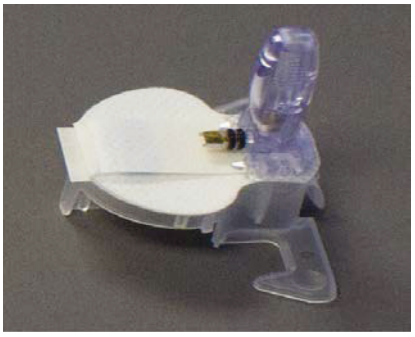
The following non-investigational/exempt devices designated for use in the study are described in this section.

6.4.1. Guardian™ Sensor (3)

The Guardian™ Sensor (3) glucose sensor, referred to as Guardian™ Sensor (3) in this protocol, is a sensor that contains one microelectrode with a thin coating of glucose oxidase beneath several layers of biocompatible membrane. The sensor is the latest generation of glucose sensor with design changes supporting improved accuracy. It is intended to penetrate the skin at a 90-degree angle. The sensor is tubeless and as a result has a smaller volume than previous Medtronic MiniMed sensors. An introducer needle penetrates the skin surface and provides support for the sensor microelectrode during insertion. The sensor continuously converts small amounts of glucose from the subject's interstitial fluid into an

electronic signal that is received by a transmitter or recorder, the strength of which is proportional to the amount of glucose present in the blood. The electrode is composed of embedding, signal-conducting and insulating layers.

Figure 1. Guardian™ Sensor (3)



6.4.2. Guardian™ Link (3) Transmitter

The Guardian™ Link (3) transmitter is a device that reads the electronic signal generated by the sensor. In addition, the transmitter contains a custom Application Specific Integrated Circuit (ASIC), which enables Electrochemical Impedance Spectroscopy (EIS). The EIS measurements are used as diagnostics for the sensor, which are incorporated into the sensor calibration logic.

In addition, the transmitter also contains the sensor calibration algorithm which converts the sensor signal to a SG value using calibration BG values from a meter relayed to the transmitter through the pump. The transmitter transmits the calculated glucose data to the pump via 2.4GHz RF technology (Tel-D communication protocol). Some elements of the calibration logic include prompting the user to calibrate when needed, referred to as "Smart Cal," instead of strictly scheduled time-based calibration requirements. The algorithm is designed to improve and optimize performance when paired with the sensors.

The approved Guardian™ Link (3) transmitter will be connected to the approved Guardian™ Sensor (3).

6.4.3. One-press Serter

The One-press Serter, referred to as the Serter (Figure 2) in this protocol, is an insertion device that is used to ensure correct placement of the Guardian™ Sensor (3) into the user's subcutaneous tissue. Insertion is triggered when the two spring loaded buttons on the sides of the Serter are pressed simultaneously. The Serter is intended as a single patient, non-sterile, multi-use device.

Figure 2. One-press Serter

6.4.4. Charger

The Charger is used to recharge the Guardian™ Link (3) Transmitter as needed. The charger operates using disposable batteries and will recharge the Guardian™ Link (3) Transmitter device according to the user guide.

Figure 3. Charger

6.4.5. Tester

The Tester operates as a sensor simulator creating signal current at a level that is within the range of an in-vivo sensor during normal operation. It is used to test and clean the Guardian™ Link (3) Transmitter.

Figure 4. Tester

6.4.6. CareLink™ Personal Therapy Management Software for Diabetes For Clinical Research Software

Medtronic CareLink™ Personal Therapy Management Software for Diabetes For Clinical Research is a web-based system which allows the device data to be viewed and easily evaluated by the subject and his/her physician. A PC links to the Medtronic CareLink™ system via the Internet, which then allows subjects and investigational center staff to upload data from Medtronic MiniMed insulin pumps and third-party BG meters. The clinical support version of Medtronic CareLink™ Personal Therapy Management Software for Diabetes For Clinical Research will be used by the investigational center staff and subjects. For the purposes of this study, all references to CareLink™ Personal For Clinical Research software in this document relate to the clinical support version of Medtronic CareLink™ Personal Therapy Management Software for Diabetes For Clinical Research. The data contained in CareLink™ Personal For Clinical Research software is accessible to users using a standard browser, i.e., Microsoft® Internet Explorer, on an Internet enabled PC.

The CareLink™ Personal For Clinical Research software system uses standard Transport Layer Security (TLS) technology. The TLS transmission protocol invokes encryption on both ends of the transmissions and is the standard for all security-based systems. The encryption remains in effect whether the data is moving to and from the client and server in the United States, or to and from a client in another country to the United States. The data is secure behind a three-tier industry standard architecture, which places the database behind three different firewalls, where each firewall separates a tier:

- The internet to the web server;
- Web server to the application server;
- Application server to the database server.

6.4.7. CONTOUR®NEXT LINK 2.4 Study Meter

A CONTOUR® NEXT LINK 2.4 BG meter, referred to as the CONTOUR® NEXT LINK 2.4 study meter in this protocol, will be provided to all subjects. The RF-enabled study meter measures a subject's capillary blood glucose level using the CONTOUR® NEXT Strips, which is then used to calibrate the glucose sensor. The result of the finger stick (capillary SMBG) reading is entered into the MiniMed™ 670G Insulin Pump and can be stored in its memory as a glucose data point. The MiniMed™ 670G Insulin Pump asks if the user wants to use the linked meter BG for calibration. If yes is selected, the glucose value will be stored in memory as a calibration data point.

6.4.8. Abbott™* Precision Xtra™* Blood Glucose & Ketone Monitoring System

The Abbott™* Precision Xtra™* Blood Glucose & Ketone Monitoring System, referred to as Precision Xtra™* ketone meter throughout this protocol, measures both blood glucose (sugar) and blood ß-Ketone. In this study, the meter will only be used to collect ß-Ketone data, which will be collected for reporting and review (see Investigator Site File for details) and as described in the body of this study protocol. This particular meter will be used because it is the only commercially available meter which allows quantification of blood ß-Ketone levels and is the preferred patient method of testing over urine testing.

Note: In the event the blood ketone meter is not used to collect ketone values, urine ketones must be measured and entered into CareLink™ Personal For Clinical Research software instead.

6.5. Consumable devices

Infusion sets, reservoirs, infusion set serter devices, glucose meter accessories and other consumable materials will be provided to subjects for use in the study.

6.6. Insulin

Subjects will use their own rapid-acting analogue insulin (Novolog™* or Humalog™*) during this study.

6.7. Smartphone

Subjects will use their own Smartphone during this study.

6.8. Anticipated Devices Change

Device change(s) may occur during the study. Therefore, a protocol amendment will be submitted in the event the device change(s) are made.

6.9. Product Accountability

Good clinical research practice requires that investigators and research teams ensure accurate accountability for any investigational device used in a research trial. It is expected that all investigational devices will be used in the manner intended during the study, that they will be stored under appropriately controlled conditions, and that they will be used only by (on) subjects who have consented to participate in the research study.

Any investigational device being used in clinical research must be strictly accounted for and will not be shipped to any site unless all of the necessary approvals (e.g. Regulatory, Institutional Review Board [IRB]) have been received. This includes keeping records of:

1. Center receipt and inventory management
2. Storage
3. Subject Disbursement
4. Return (by Subjects and Center) and/or disposal

During the conduct of the study the investigational center staff will account for and document the following:

Table 5 Device Accountability Requirements

Device	Record on Site Received eCRF	Record Disbursement, Returned or Not Returned from Subject on Device Identification eCRF	Subject Return Device to Investigational Center	Record Returned or Not Returned to Sponsor on Site Returned eCRF	Site Return Device to Sponsor at Conclusion of Study
MiniMed™ 670G Insulin Pump, version 4.0 Tel-D (MMT-1740)	Yes	Yes	Yes	Yes	Yes
Guardian™ Link (3) Transmitter	Yes	No	Yes	Yes	Yes (used and unused)
Guardian™ Sensor (3) (MMT-7020)	Yes	No	No	Yes	Dispose or return unused to sponsor
CONTOUR® NEXT LINK 2.4 Study Meter (MMT-1352)	Yes	Yes	Yes	Yes	Dispose or return unused to sponsor

The investigational center will promptly notify the sponsor of any device handling violation that might impact either the safety or welfare of subjects or data integrity.

6.9.1. Receipt and Inventory of Investigational Devices by Investigational Center

- Upon receipt of the study devices, investigational center staff take inventory of the shipment, making sure that information on the packing slips/invoices matches exactly the contents of the containers, as applicable, including:
    - Ship to Address
    - Reference Number
    - Device Type
    - Quantity

- Quantity per package
- Lot number (where applicable)
- Serial number (where applicable)

- Ensure that devices and supplies received have not reached or exceeded their expiration date
- Sign and date the packing slips/invoices, noting any discrepancies, and file in appropriate study binder
- Notify the study monitor of any discrepancies
- Enter the study device information on the appropriate eCRF in the study database.

6.9.2. Storage of Study Devices at Investigational Center

Study devices are to be stored in a secure environment with access limited to authorized research personnel. Study devices are stored in the proper environmental conditions as identified in the IFU/labeling.

6.9.3. Disbursement of Study Devices

Each time a study device is disbursed to a subject by the investigator or authorized member of the research team, all required eCRF and source documentation will be completed. Documentation may include:

- Date of disbursement
- Subject ID
- Lot number(s)
- Serial Number
- Reference Number
- Amount dispensed

6.9.4. Return or Disposal of Study Devices

After use by the subject, the investigational center is expected to accept and retain all devices as described in Table 5 and store them in a secure environment. If containers/units/devices are missing, the reasons should be documented in the applicable eCRF. If discrepancies between the amounts used by subjects and the amounts expected to be returned exist, the reasons should be documented in the applicable eCRF.

Requirements for return of devices by subjects to the investigational center and return of device by the investigational center to the sponsor are listed in Table 5. The devices that are being returned to the investigational center may be returned to the sponsor as subjects complete the study, at the EOS visit or upon sponsor request.

Other unused consumable devices (i.e., infusion sets, alcohol wipes, study meter supplies, tape, etc.), supplies or materials may be returned to the sponsor, they may be retained by investigational centers for

educational purposes only, or they may be disposed of properly by investigational center staff. Any used commercial study meter may be kept by subjects.

Disposable devices and supplies that have been ***used*** by a subject will be disposed of properly by the subject or the investigational center staff during the conduct of the study.

All study devices that are required to be entered into the study database must be accounted for as described above before they are returned to the sponsor.

7. Selection of Subjects

7.1. Study Population

A total of up to 200 subjects will be enrolled at up to 15 investigational centers across the US in order to have up to 150 subjects who complete the study.

It is expected that at least N=12-18 subjects will participate in each phase during Feasibility 2.

7.2. Subject Enrollment

Subjects will be considered enrolled in the study upon signing the Informed Consent Form (ICF)/Assent form.

A subject will be assigned a unique study subject ID (SID) via the eCRF, which is a 9-digit code (326XXXXXX). The first three numbers refer to the CIP number (326), the next three numbers refer to the investigational center number, and the last 3 numbers refer to the subject number assigned during Visit 1 (e.g., 326002001 is subject 001 from site 002).

The investigator will maintain a log of all subjects enrolled in the clinical study, assigning a SID linked to their names, alternative SID, and contact information.

7.3. Inclusion Criteria

General Inclusion Criteria

1. Subject is age 2-80 years at time of Visit 1.
   Note: See staged enrollment reference for adult and pediatric subjects in the Study Design section
2. Subject has a clinical diagnosis of type 1 diabetes.
   a. Subjects 7 years of age and older: Diagnosed at least 1 year prior to Visit 1
   b. Subjects 2-6 years of age: Diagnosed at least 3 months prior to Visit 1

Study-specific inclusion criteria

3. Subject must have a minimum daily insulin requirement (Total Daily Dose) of greater than or equal to 8 units.

4. If subject has a history of hypothyroidism, must have at least 1 documented normal thyroid-stimulating hormone (TSH) on historical labs within 12 months of Visit 1. A subject without a history of hyperthyroidism is not expected to have a TSH test.
5. Subjects and their parent(s)/guardian(s) must have Internet access , a computer system that meets the requirements for uploading the study pump and Smartphone that meets study requirements.
6. Subject must have a companion or caregiver available at night for the duration of the study period who resides (or will live) in in the same building (or home). This requirement may be verified by subject report at screening visit.
7. If subject has celiac disease, it has been adequately treated as determined by the investigator.
8. Subjects and their parent(s)/guardian(s) are willing to take one of the following insulins and can financially support the use of either of the 2 insulin preparations throughout the course of the study (i.e. co-payments for insulin with insurance or able to pay full amount)
    a. Humalog™* (insulin lispro injection)
    b. NovoLog™* (insulin aspart)

7.4. Exclusion Criteria

1. Subject has a history of 1 or more episodes of severe hypoglycemia, which resulted in any the following during the last 1 year prior to Visit 1
    a. Medical assistance (i.e. Paramedics, Emergency Room (ER) or Hospitalization)
    b. Coma
    c. Seizures
2. Subject is unable to tolerate tape adhesive in the area of sensor placement.
3. Subject has any unresolved adverse skin condition in the area of sensor placement (e.g., psoriasis, dermatitis herpetiformis, rash, Staphylococcus infection).
4. Women of child-bearing potential who have a positive pregnancy test at Visit 1 or plan to become pregnant during the course of the study
5. Females who are sexually active and able to conceive will be excluded if they are not using an effective method of contraception and do not agree to continue using an effective method of contraception for the duration of the study as determined by investigator.
6. Subject has a cardiovascular condition which the Study Investigator determines should exclude the subject, e.g. ventricular rhythm disturbance, hypertrophic cardiomyopathy, recent myocardial infarction in the last year prior to Visit 1.
7. Subject is being treated for hyperthyroidism at time of Visit 1.
8. Subject has a diagnosis of adrenal insufficiency.
9. Subject has had Diabetic Ketoacidosis (DKA) within 1 year prior to Visit 1.
10. Subject has taken any oral, injectable, or intravenous (IV) glucocorticoids within 8 weeks from time of visit 1, or plans to take any oral, injectable, or IV glucocorticoids during the course of the study.
11. Subject is actively participating in an investigational study (e.g., drug or device) wherein he/she has received treatment from an investigational study (drug or device) in the last 2 weeks prior to Visit 1. Please note participation in observational study is acceptable.
12. Subject has been hospitalized or has visited the ER in the 6 months prior to Visit 1 resulting in a **primary diagnosis** of uncontrolled diabetes.
13. Subject is currently abusing illicit drugs.
14. Subject is currently abusing alcohol.
15. Subject is using pramlintide (Symlin), DPP-4 inhibitor, liraglutide (Victoza or other GLP-1 agonists), metformin, canagliflozin (Invokana or other SGLT2 inhibitors) at time of Visit 1.

16. Subject has a history of visual impairment which would not allow subject to participate in the study and perform all study procedures safely, as determined by the investigator.
17. Subject has elective surgery planned that requires general anesthesia during the course of the study.
18. Subject diagnosed with current eating disorder such as anorexia or bulimia.
19. Subject has been diagnosed with chronic kidney disease that results in chronic anemia.
20. Subject is on dialysis.
21. Subject has serum creatinine of >2 mg/dL, as confirmed through historical labs within 1 year prior to Visit 1.
22. Subject is a member the research staff involved with the study.

8. Study Site Requirements

8.1. Study Site Activation

During the activation process (prior to subject enrollment), Medtronic will train investigational center staff. If new members join the study investigational center team, they will receive training on the applicable study requirements relevant to their role before contributing to the study.

Prior to performing study related activities, all regulatory requirements shall be fulfilled.

9. Study Procedures

9.1. Schedule of Events

Each subject's participation will be comprised of the scheduled visits listed in Section 9.2 during the run-in period and study period. Refer to the Appendices (Section 18.4) for Feasibility 2 Visit Details Table.

If subject exits the study early (i.e. before their last scheduled visit), all requirements that apply to the final visit should be completed.

9.2. Visit Schedule &Scheduled Follow-up Visit Windows

Each subject's participation will be comprised of the following scheduled visits listed below over the course of approximately 4.5 months during the run-in period and study period, and for 1 month during the interim period. With Sponsor and site approval, telemedicine (e.g., remote/virtual visit) may be performed for office visits that do not require any of the following:

- Collection of blood test samples
- Training
- Device related procedures that require staff assistance

The schedule is planned as follows:

9.2.1. Feasibility 2 Visit Schedule

Visit Schedule Details – Cohort A: Digital Twin Challenge #1

Run-in Period Visits: To be completed in 60 days

- Screening Visit 1 (Office): Consent and Screening
- Visit 2 (Office):
  - *Confirm Eligibility*
    Therapy at time of Screening: MDI/CSII (no CGM):
  - Study training and start of blinded CGM
  - Start run-in baseline data collection at home with own therapy (at least 7 days). Data loss may occur if a blinded CGM is worn for longer than 14 days. Sensor wear not recommended for more than 10 days.
  - **Next visit is Visit 2A**

    Therapy at time of Screening: Pump plus CGM:
  - Disburse study pump and transmitter (AHCL system)
  - Upload pump and meter
  - Verify CareLink™ credentials, complete registration
  - Provide study and device training
  - Start run-in baseline data collection at home with AHCL system (at least 7 days)
  - Auto Mode activation may occur if subjects were using Auto Mode at Screening (i.e., ok to use automated basal insulin delivery feature only)
  - **Next visit is Visit 3**

- Visit 2A (Office): Therapy at time of Screening: MDI/CSII (no CGM)
  - Return to clinic after blinded CGM data collection
  - Return blinded CGM
  - Disburse study pump and transmitter (AHCL system); use in Manual Mode
  - Upload pump and meter
  - Verify CareLink™ credentials, complete registration
  - Provide study and device training

- Visit 2B (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 1 after visit 2A
  - Review Manual Mode settings

- Visit 2C (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 2 after Visit 2A
  - Review Manual Mode settings

- Visit 2D (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 7 (+3 days) after Visit 2A
  - Review Manual Mode settings

- Visit 3 (Office or Telemedicine) – Auto Mode activation, i.e. automated basal and auto correction
  - Should occur at least 7-14 days after start of wearing AHCL system; 14 days may be preferable for those who were on MDI/CSII (no CGM) at time of screening

- Visit 4 (Telephone or office) – Day 1 after Visit 3

- Visit 5 (Telephone or office) – Day 2 after Visit 3
- Visit 6 (Telephone or office) – Day 3 after Visit 3
- Visit 7 (Telephone or office) – Day 4 after Visit 3
- Visit 8 (Telephone or office) – Day 5 after Visit 3
- Visit 9 (Telephone or office) – Day 6 after Visit 3
  - Upload pump and meter
- Visit 10 (Office or Telemedicine) – Day 14 (+7 days) after Visit 3
  - Upload pump and meter during visit
  - Review CareLink™ Upload
  - Instruct subjects to Upload pump and meter at home on Day 23 or 24 after Visit 3

Study Period Visits:

- Visit 11 (Office or Telemedicine): Day 30 (+7 days) after Visit 3
  - Start Study Period
  - Retrieve insulin delivery device settings recommendations
  - Review/approve settings before programming pump (please note that investigator discretion may be used as described above)
  - Upload pump and meter during visit
  - Review CareLink™ Upload
  - Instruct subjects regarding study procedures for Challenge #1
- Visit 12 (Telephone): Day 1 after Visit 11
  - Review CareLink Upload
- Visit 13 (Telephone): Day 2 after Visit 11
  - Review CareLink™ Upload
- Visit 14 (Telephone): Day 7 (+2 days) after Visit 11
  - Review CareLink™ Upload
  - Instruct subjects to upload on Day 6 after Visit 14
- Visit 15 (Office or Telephone): Day 8 (+3 days) after Visit 14
  - Upload pump and meter during visit
  - Review CareLink™ Upload
  - Retrieve insulin delivery device settings recommendations
  - Review/approve settings before programming pump (please note that investigator discretion may be used as described above)
  - Program pump with insulin delivery settings
  - Instruct subjects to upload on Day 6 after Visit 15

- Visit 16 (Office or Telemedicine): Day 8 (+3 days) after Visit 15
  - Review CareLink™ Upload
  - Retrieve insulin delivery device settings recommendations
  - Review/approve settings before programming pump (please note that investigator discretion may be used as described above)
  - Program pump with insulin delivery settings
  - Instruct subjects to upload on Day 6 after Visit 16

- Visit 17 (Telephone): Day 8 (+3 days) after Visit 16
  - Review CareLink™ Upload
  - Retrieve insulin delivery device settings recommendations
  - Review/approve settings before programming pump (please note that investigator discretion may be used as described above)
  - Program pump with insulin delivery settings

- Visit 18 (Office or Telemedicine): Day 7 (+3 days) after Visit 17
  - Review CareLink™ Upload
  - End of Phase
  - Return AHCL system unless phase is repeated Review CareLink™ Upload

Interim Period (as applicable):

Sponsor may request subjects to repeat this phase (up to 2 times)

Wash out period for a minimum of 23 days using the AHCL system in Auto Mode should be performed before phase is repeated

Subjects will be instructed to upload weekly during the interim period

Subjects who are repeating the phase will start at Visit 11 after wash-out period

Visit Schedule Details – Cohort A: Digital Twin Challenge #2

Run-in Period Visits: To be completed in 60 days

- Screening Visit 1 (Office): Consent and Screening

- Visit 2 (Office):
  - *Confirm Eligibility*
    Therapy at time of screening: MDI/CSII (no CGM)
  - Study training and start of blinded CGM
  - Start run-in baseline data collection at home with own therapy (at least 7 days). Data loss may occur if a blinded CGM is worn for longer than 14 days. Sensor wear not recommended for more than 10 days.
  - **Next visit is Visit 2A**

    Therapy at time of screening: Pump plus CGM
  - Disburse study pump and transmitter (AHCL system)
  - Upload pump and meter

  - Verify CareLink™ credentials, complete registration
  - Provide study and device training
  - Start run-in baseline data collection at home with AHCL system (at least 7 days)
  - Auto Mode activation may occur if subjects were using Auto Mode at Screening (i.e., ok to use automated basal insulin delivery feature only)
  - **Next visit is Visit 3**

- Visit 2A (Office): Therapy at time of Screening: MDI/CSII (no CGM)
  - Return blinded CGM
  - Disburse study pump and transmitter (AHCL system)
  - Upload pump and meter
  - Verify CareLink™ credentials, complete registration
  - Provide study and device training

- Visit 2B (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 1 after visit 2A
  - Review Manual Mode settings

- Visit 2C (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 2 after Visit 2A
  - Review Manual Mode settings

- Visit 2D (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 7 (+3 days) after Visit 2A
  - Review Manual Mode settings

- Visit 3 (Office or Telemedicine) – Auto Mode activation, i.e. automated basal and auto correction
  - Should occur at least 7-14 days after start of wearing AHCL system; 14 days may be preferable for those who were on MDI/CSII (no CGM) at time of screening

- Visit 4 (Telephone or office) – Day 1 after Visit 3

- Visit 5 (Telephone or office) – Day 2 after Visit 3

- Visit 6 (Telephone or office) – Day 3 after Visit 3

- Visit 7 (Telephone or office) – Day 4 after Visit 3

- Visit 8 (Telephone or office) – Day 5 after Visit 3

- Visit 9 (Telephone or office) – Day 6 after Visit 3
  - Upload pump and meter

- Visit 10 (Office or Telemedicine) – Day 14 (+7 days) after Visit 3

- Upload pump and meter during visit
- Review CareLink™ Upload
- Instruct subjects to Upload pump and meter at home at least 23 days after Visit 3

Study Period Visits:

- Visit 11 (Office or Telemedicine): Day 30 (+7 days) after Visit 3
  - Start Study Period
  - Retrieve insulin delivery device settings recommendations
  - Review/approve settings before programming pump (please note that investigator discretion may be used as described above)
  - Review CareLink™ Upload
  - Instruct subjects regarding study procedures for Challenge #2

- Visit 12 (Telephone): Day 1 after Visit 11
  - Review CareLink Upload

- Visit 13 (Telephone): Day 2 after Visit 11
  - Review CareLink™ Upload

- Visit 14 (Telephone): Day 7 (+2) after Visit 11
  - Review CareLink™ Upload
  - Instruct subjects to upload on Day 6 after Visit 14

- Visit 15 (Office or Telephone): Day 8 (+3 days) after Visit 14
  - Review CareLink™ Upload
  - Retrieve insulin delivery device settings recommendations
  - Review/approve settings before programming pump (please note that investigator discretion may be used as described above)
  - Program pump with insulin delivery settings
  - Instruct subjects to upload on Day 6 after Visit 15

- Visit 16 (Office or Telemedicine): Day 8 (+3 days) after Visit 15
  - Review CareLink™ Upload
  - Retrieve insulin delivery device settings recommendations
  - Review/approve settings before programming pump (please note that investigator discretion may be used as described above)
  - Program pump with insulin delivery settings
  - Instruct subjects to upload on Day 6 after Visit 16

- Visit 17 (Telephone): Day 8 (+3 days) after Visit 16
  - Review CareLink™ Upload
  - Retrieve insulin delivery device settings recommendations
  - Review/approve settings before programming pump (please note that investigator discretion may be used as described above)
  - Program pump with insulin delivery settings

- Visit 18 (Office or Telemedicine): Day 7(+3 days) after Visit 17
  - Review CareLink™ Upload

- End of Phase
- Return AHCL system unless phase is repeated Review CareLink™ Upload

Interim Period (as applicable):

Sponsor may request subjects to repeat this phase (up to 2 times)

Wash out period for a minimum of 23 days using the AHCL system in Auto Mode should be performed before phase is repeated

Subjects will be instructed to upload weekly during the interim period.

Subjects who are repeating the phase will start at Visit 11 after wash-out period

Visit Schedule Details – Cohort C: Meal Prediction:

Run-in Period Visits:

- Screening Visit 1 (Office): Consent and Screening

- Visit 2 (Office):
  - *Confirm Eligibility*
    Therapy at time of Screening: MDI/CSII (no CGM)
  - Study training and start of blinded CGM
  - Start run-in baseline data collection at home with own therapy (at least 7 days). Data loss may occur if a blinded CGM is worn for longer than 14 days. Sensor wear not recommended for more than 10 days.
  - **Next visit is Visit 2A**

    Therapy at time of Screening: Pump plus CGM
  - Disburse study pump and transmitter (AHCL system)
  - Upload pump and meter
  - Download App, verify CareLink™ credentials, complete registration
  - Provide study and device training
  - Start run-in baseline data collection at home with AHCL system (at least 7 days)
  - Auto Mode activation may occur if subjects were using Auto Mode at Screening (i.e., ok to use automated basal insulin delivery feature only)
  - **Next visit is Visit 3**

- Visit 2A (Office): **MDI/CSII (no CGM)**
  - Return blinded CGM
  - Disburse study pump and transmitter (AHCL system)
  - Upload pump and meter
  - Download App, verify CareLink™ credentials, complete registration
  - Provide study and device training

- Visit 2B (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 1 after visit 2A
  - Review Manual Mode settings

- Visit 2C (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 2 after Visit 2A
    - Review Manual Mode settings

- Visit 2D (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 7 (+3 days) after Visit 2A
    - Review Manual Mode settings

- Visit 3 (Office or Telemedicine) – Auto Mode activation, i.e. automated basal and auto correction
    - Should occur at least 7-14 days after start of wearing AHCL system (14 days may be preferable for those who were on MDI/CSII (no CGM) at time of screening.

- Visit 4 (Telephone or office) – Day 1 after Visit 3

- Visit 5 (Telephone or office) – Day 2 after Visit 3

- Visit 6 (Telephone or office) – Day 3 after Visit 3

- Visit 7 (Telephone or office) – Day 4 after Visit 3

- Visit 8 (Telephone or office) – Day 5 after Visit 3

- Visit 9 (Telephone or office) – Day 6 after Visit 3
    - Upload pump and meter

- Visit 10 (Office or Telemedicine) – Day 14 (+7 days) after Visit 3
    - Upload pump and meter during visit
    - Review CareLink™ Upload
    - Instruct subjects to Upload pump and meter at home at least 21 days after Visit 3

Study Period Visits:

- Visit 11 (Office or Telemedicine): Day 30 (+7 days) after Visit 3 is activated: 2-day supervised visit in clinic or remote
    - Start Study Period
    - Should occur at least 6 days after the last pump upload
    - Subject is trained and begins to use meal prediction App
    - Subject is being observed in clinic or remotely
    - Subjects may leave after day 1 and return the next day to complete the visit

  At applicable sites:
    - Eight-hour long FST will occur on one of the 2 in-clinic days at sites selected by Sponsor

- Visit 12 (Telephone): Day 14 (± 2 days) after Visit 11
    - Review CareLink™ Upload

- Visit 13 (Telephone): Day 21 (± 4 days) after Visit 11
  - Review CareLink™ Upload

- Visit 14 (Office or Telemedicine): Day 42 (+ 7 days) after Visit 11
  - Upload pump and meter during visit
  - Review CareLink™ Upload
  - End of Phase
  - Return AHCL system unless phase is repeated
  - Remove App from Smartphone

Interim Period (as applicable):

Sponsor may request subjects to repeat this phase (up to 2 times)

Wash out period for a minimum of 23 days using the AHCL system in Auto Mode should be performed before phase is repeated

Subjects will be instructed to upload weekly during the interim period.

Subjects who are repeating the phase will start at Visit 11 after wash-out period

Visit Schedule Details – Ages 2-6

Run-in Period Visits: To be completed in 90 days

- Screening Visit 1 (Office): Consent and Screening

- Visit 2 (Office):
  - *Confirm Eligibility*
    Therapy at time of Screening: MDI/CSII (no CGM):
  - Study training and start of blinded CGM
  - Start run-in baseline data collection at home with own therapy (at least 7 days). Data loss may occur if a blinded CGM is worn for longer than 14 days. Sensor wear not recommended for more than 10 days.
  - **Next visit is visit 2A**

    Therapy at time of Screening: Pump plus CGM:
  - Disburse study pump and transmitter (AHCL system)
  - Upload pump and meter
  - Verify CareLink™ credentials, complete registration
  - Provide study and device training
  - Start run-in baseline data collection at home with AHCL system (at least 7 days)
  - Auto Mode activation may occur if subjects were using Auto Mode at Screening (i.e., ok to use automated basal insulin delivery feature only)
  - **Next visit is the in-clinic Observational study**

- Visit 2A (Office): Therapy at time of Screening: MDI/CSII (no CGM)

- Return to clinic after blinded CGM data collection
- Return blinded CGM
- Disburse study pump and transmitter (AHCL system); use in Manual Mode
- Upload pump and meter
- Verify CareLink™ credentials, complete registration
- Provide study and device training

- Visit 2B (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 1 after visit 2A
  - Review Manual Mode settings

- Visit 2C (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 2 after Visit 2A
  - Review Manual Mode settings

- Visit 2D (Telephone or Office): **Therapy at time of Screening: MDI/CSII (no CGM)** – Day 7 (+3 days) after Visit 2A
  - Review Manual Mode settings
  - **Next visit is the in-clinic Observational Study**

In-Clinic Study for all subjects 2-6 years of age

- In Clinic Study Day 1 – Auto Mode activation, i.e. automated basal and auto correction, pump upload
  - Should occur at least 7-14 days after start of wearing AHCL system; 14 days may be preferable for those who were on MDI/CSII (no CGM) at time of screening
  - This is an in-clinic observational study to observe the safety of 2-6 year-olds using the AHCL system. No challenges will be performed.

- In Clinic Study Day 2

- In Clinic Study Day 3

- In Clinic Study Day 4

- In Clinic Study Day 5
  - End of In-Clinic Study
  - Instruct subjects to use the system in Manual Mode until they are notified about DMC approval to continue. If subject was using 670G with Auto Mode at Screening, the subject may use Auto Mode with the Auto Correction feature turned off (not enabled).
  - Once DMC approves, Subjects will participate in their assigned cohorts
    - Cohort A: See Cohort A visit schedule. Subject will begin with **Visit 3**
    - Cohort C: See Cohort C visit schedule. Subject will begin with **Visit 3**

9.3. Subject Consent

Informed Consent/Assent will be obtained in accordance with the Code of Federal Regulations (CFR) Title 21, Part 50. Prior to entry into the study, the California Experimental Subject Bill of Rights (if applicable), the IRB and Medtronic approved ICF/ Assent form and an Authorization Form required by the Health Insurance Portability and Accountability Act (HIPAA) will be presented to each subject to review and sign as applicable. The subject or parent/guardian will be offered the opportunity to review these documents away from the investigational center.

The following will be provided to or explained to the subject or parent/guardian by the investigator or designee: The purpose of the study, the duration of the study, the requirements expected to be adhered to by the subject during the study and the potential risks /possible benefits associated with participation in the study. Every attempt will be made to answer the subject or parent/guardian's questions during the informed consent/assent process. The language used shall be as non-technical as possible and must be understandable to the subject or parent/guardian.

Neither the investigator, nor the investigation site staff shall coerce or unduly influence a subject or parent/guardian to participate or to continue to participate in the clinical study. The informed consent/assent process shall not waive or appear to waive the subject's rights.

Subjects will complete California Experimental Subject's Bill of Rights (if applicable), the HIPAA Form, and the ICF/ Assent form. The consenting process must be documented in the subject's source files. The subject or parent/guardian will receive copies of the fully executed documents. A subject's participation in study procedures cannot begin before the consent process has been properly executed.

Medtronic will inform the investigators whenever information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The investigator or his/her authorized designee should inform the subject or parent/guardian in a timely manner.

Medtronic will revise the written ICF/ Assent form whenever new information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The revised information will be sent to the investigator for approval by the IRB. After approval by the IRB, a copy of this information must be provided to the participating subjects, and the informed consent/assent process as described above needs to be repeated.

If the ICF/ Assent form is amended during the course of the study, the IRB will determine:

- Whether or not active subjects should be re-consented at their next visit and
- Whether or not subjects who have completed the study at the time of the amendment should repeat the informed consent/assent process.

Subjects will be informed that qualified personnel from the investigational center, the sponsor (Medtronic), agencies such as the FDA and/or the IRB, may have access to the clinic records that reveal their identity and health care information.

The investigational center must report the following informed consent/assent violations to their IRB and sponsor:

- Failure to obtain informed consent/assent from subject.
- Failure to obtain informed consent/assent prior to performing one or more study procedures.
- Failure to maintain ICFs/ Assent forms on file for all subjects who have provided informed consent/assent.
- Use of an ICF/ Assent form that has not received approval from the IRB.

- Use of an incorrect version of the ICF/ Assent form.

9.4. Assessment of Safety

AE information is collected in this study. See Section 11 for further information regarding the collection of AEs and safety information.

9.5. Medical Oversight

Investigator/ Investigational site selection

All clinical investigators managing the subject's Type 1 Diabetes, CGM, and insulin pump therapy must be qualified practitioners and have experience in the diagnosis and treatment of subjects with Type 1 Diabetes. All Primary investigators must be experience with and/or trained as an Endocrinologist to treat diabetic emergencies.

The role of the principal investigator is to implement and manage day-to-day conduct of the clinical trial as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical study.

9.5.1. Medical Staff

The principal investigator shall:

- Be qualified by education, training and experience to assume responsibility for the proper conduct of the clinical study.
- Be experienced in the field of managing subjects with insulin carbohydrates and insulin sensitivity ratios

The principal investigator shall be able to demonstrate that the investigational site:

- Has the required number of eligible subjects
- Has one or more qualified sub-investigators, qualified study team and adequate facilities for the foreseen duration of the clinical study

9.5.2. Qualification

The investigator (or designee) will need to have one of the following qualifications: Endocrinology fellowship or management in patients with diabetes in a clinical practice. The provider must be qualified to treat diabetic emergencies. All site personnel training and delegation will be completed prior to participation in this clinical study.

9.5.3. Experience

The principal investigator is licensed to practice medicine, has experience conducting a clinical trial and has a minimum of one-year managing subjects with Type 1 Diabetes.

9.6. Safety Monitoring/Risk Analysis

9.6.1. Glucose Monitoring Risk

- Subjects will be instructed to make sure they have clean fingers when performing finger stick glucose testing.
- Subjects will have training on diabetes self-management principles.

9.6.2. Hypoglycemic/Hyperglycemic Risk

Intervention and treatment for hypoglycemia and hyperglycemia are addressed in Section 10.

9.6.3. Calibration of CGM Risk

When an erroneous glucose value is used to calibrate a CGM, the bias is carried through until the next opportunity to calibrate the CGM. This can result in an incorrect bias. Subjects will be trained to appropriate calibration.

9.6.4. Reuse Risk

All study devices will be single patient use.

9.6.5. Sterilization Risk

The following devices will be supplied sterilized:

- Infusion sets
- Insulin reservoirs
- Glucose sensors

9.6.6. Misuse Risk

Comprehensive training will take place at the initiation visit for investigational center staff for all the devices being used, to include all of its functional components and all other study devices to be used during the study at the investigational center.

9.6.7. Risk of Blood Sample Collection, Contamination from Sampling Techniques

Detailed mitigations to blood sampling risk are provided in Section 10.

9.7. Glucose and Glycemia Measurements

During the course of the study, the subjects' BG levels, SG levels, and blood ketones will be assessed using the methods outlined in this section.

9.7.1. Daily Blood Glucose

Values will be assessed during the study by all subjects using the CONTOUR® NEXT LINK 2.4 study meter. The control solution test will be performed following the manufacturer's user guide. Subjects will be trained on the use of the CONTOUR® NEXT LINK 2.4 study meter per the manufacturer's instructions.

9.7.2. Sensor Glucose Values

SG data will be collected by subject's study insulin pump and calibrated by each subject's CONTOUR® NEXT LINK 2.4 study meter.

9.8. Recording Data

Data will be captured on eCRFs using OC-RDC module. Original eCRFs will not be considered as source data and supporting documentation will be required.

Electronic device data will be collected from the study pump using CareLink™ Personal For Clinical Research software. The system uses TLS technology, which encrypts all data it stores (21 CFR Part 11 compliant). Certain data points stored in the downloaded information may also be captured on the appropriate eCRF.

The investigator will ensure that all eCRFs are completed promptly, completely, and accurately. Medtronic will provide detailed instructions to assist with eCRF completion. In the event of data discrepancies, investigational centers will be asked to resolve queries electronically in the OC-RDC system; otherwise, irresolvable data-related issues will be routed to the sponsor for review and final disposition. An audit trail is maintained in OC-RDC to capture any corrections or changes of the eCRFs. System backups for data stored in the Oracle Clinical system will be consistent with Medtronic Standard Operating Procedures (SOPs).

Medtronic will only consider eCRFs to be complete when all discrepancies between source data and eCRF have been resolved and eCRF content has been reviewed by a study monitor. In addition, specific eCRFs must also be reviewed and electronically signed by the investigator, indicating his/her agreement with the accuracy of all recorded data. It is expected that the investigator and his/her staff will cooperate with the monitoring team and provide any missing data in a timely manner.

9.9. Deviation Handling

A deviation is any instance(s) of failure to follow, intentionally or unintentionally, the requirements of the CIP. It is expected that the investigator will conduct this clinical trial in compliance with the CIP and all applicable regulations governing the conduct of clinical research involving human subjects. Failure to do so could result in one or all of the following:

- Investigational center disqualification
- Notification to the regulatory authorities/IRB depending on the severity of the deviation and reporting requirements

The investigator should not implement any deviation from, or changes to, the CIP without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB, except where

necessary to eliminate an immediate hazard(s) to trial subjects or when the change does not affect the scientific soundness of the plan or the rights, safety, and welfare of the subjects.

The following are deviations related to study procedures:

- If subjects do not follow the fingerstick recommendations, no study deviation will be given unless the site staff did not train the subject on SMBG study procedures.
- If subjects do not upload devices perfectly, no study deviation will be given unless the site staff did not train the subject on upload procedures.
- As it can occur that subjects do not follow study instructions perfectly, such as uploading their pumps, changing between Auto Mode and Manual Mode, no study deviation will be given unless site staff did not provide sufficient instructions to subjects regarding study requirements.
- If subject does not collect enough blinded CGM data during the run-in period, no study deviation will be given as long as subject made effort to wear the blinded CGM.

FST Sample:

Deviations for missing ABL-90 FST samples will be issued for the following reason: If there are 3 or more total ABL-90 FST samples missing per subject per SMBG FST (unless they were missed for safety issues, IV or FST device issues).

9.9.1. Unplanned CIP Deviations

The investigator may encounter the need to deviate from the CIP when necessary to protect the safety, rights or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g. subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness).

All deviation from the CIP, regardless of the reason should be documented as soon as possible, after the deviation occurs or is identified. This documentation should include deviation date, description of the deviation, and the reason for deviation.

CIP deviations should be reported as follows:

a) To the IRB for notification/acknowledgement, if required;
b) To the sponsor and, if required;
c) To the applicable regulatory agency(reported by the sponsor)

For medically justifiable conditions that preempt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation that will apply to all visits going forward. This may also apply to other unforeseen situations (e.g. the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary end point analysis). However, prior approval from sponsor is required for such situations.

9.9.2. Minor or Administrative CIP deviations

Minor or administrative deviations are those that do not "affect the scientific soundness of the research plan or the rights, safety, or welfare of human subjects."

Deviations that do not meet the criteria for expedited notification or prior regulatory/IRB approval, may be reported at the time of eCRF completion or separately upon discovery such as during monitoring visits.

If a CIP deviation occurs which meets this definition, the deviation should be reported to the IRB at the time the continuing review application is submitted.

9.9.3. Reporting Requirements for Study Deviations

All study deviations must be reported on the eCRF regardless of whether medically justifiable, an inadvertent occurrence, or taken to protect the subject in an emergency. The date and reason for each deviation will be documented (21 CFR 812.140 Records). In the occurrence of a corrupted device interrogation file, Sponsor may request a deviation to document that a readable interrogation file is unavailable.

In order to protect the rights and interests, safety and health of subjects, the deviation occurred under emergency situations that cannot be timely reported shall be reported in written form afterwards in accordance with relevant regulations as soon as possible.

The following examples are deviations that could impact subject safety, affect the integrity of study data and/or affect subject's willingness to participate in the study. These deviations are significant and require immediate sponsor notification upon investigator awareness.:

- Failure to obtain informed consent/assent, i.e., there is no documentation of informed consent/assent
- Informed consent/assent obtained after initiation of study procedures
- Continuation of a subject who did not meet all inclusion/exclusion criteria
- Performing study procedure not approved by the IRB
- Failure to inform IRB and sponsor of reportable AEs (see Section 11)
- Investigational study device dispensed without obtaining informed consent/assent

In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the IRB as well as Medtronic within five (5) working days.

Reporting of all other study deviations should comply with IRB policies and/or local laws and must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation. Reporting of deviations must comply with IRB policies, local laws, and/or regulatory agency requirements. Refer to Investigator Reports, Table 7, for specific deviation reporting requirements and timeframes for reporting to Medtronic, IRB, and/or regulatory agency (if applicable).

9.9.4. Analyzing Deviations

Medtronic is responsible for reviewing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, conduct additional training, terminate the investigation). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and investigational center, and in some cases, necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study.

9.10. Subject Exit, Withdrawal or Discontinuation

Subjects may choose to withdraw from the study at any time by notifying investigational center staff of their intent.

If a subject chooses to end his or her study participation or if the subject is removed from the study at the Investigator's discretion or for failure to meet the study requirements, the reason for withdrawal must be documented. All study devices and supplies must be returned (as applicable) and documented both in source documents and on an eCRF.

Subjects may also be withdrawn from the study at the discretion of the Investigator. A subject will be withdrawn from the study if:

- In the opinion of the investigator, the subject's health or safety would be compromised by continuing in the study
- In the opinion of the investigator, it is in the subject's best interest to discontinue participation in the study
- During the course of the study, subject begins participation in another investigational study (drug or device).
- Subject participates in a phase that requires a Smartphone as part of the study requirements and subject does not have a Smartphone.
- During the course of the study, subject begins abusing illicit drugs.
- During the course of the study, subject begins abusing alcohol.
- During the course of the study, subject begins using pramlintide (Symlin), DPP-4 inhibitors, liraglutide (Victoza or other GLP-1 agonists), metformin, canagliflozin (Invokana or other SGLT2 inhibitors).
- During the course of the study, the subject demonstrates that he/she is not able to comprehend instructions for study procedures, as evaluated by the appropriate research staff.
- During the course of the study, subject is taking oral, injectable, or IV glucocorticoids
- During the study, (female) subject becomes pregnant.
- During the study, the subject experiences one severe hypoglycemic episode
- During the study, the subject experiences one episode of DKA
- During the study, subject has a cardiovascular event or any vascular event such as stroke.

Documentation of the reason(s) leading to subject withdrawal will be kept in the subject's source documentation.

For **Study Exit** visits for reason other than subject lost to follow-up, the following information is required:

- Assess and document any reportable AEs (refer to section 10 Adverse Events)
- For study exit visits occurring in the clinic, perform a CareLink™ upload
- If the study exit visit occurs via telephone, ensure the subject has completed a CareLink™ upload prior to the telephone follow-up

9.11. Subject Stopping Rules

Any episode of DKA or severe hypoglycemia will result in withdrawal of subject from study.

9.12. Stopping Rules for Entire Study

During the study period, the following steps will be taken for:

- Unanticipated Adverse Device Effects (UADE)
- Algorithm-related Diabetic Ketoacidosis (DKA)
- Algorithm-related Severe hypoglycemia

1. Site will notify the sponsor within approximately 24 hours of receiving knowledge of the event.
2. Sponsor will notify Food and Drug Administration (FDA) within approximately 72 hours of knowledge of the event and provide updates to those agencies as information becomes available.
3. Clinical Events Committee (CEC) is to review the event within 10 days from the time that the sponsor is notified.
4. CEC will provide recommendation to the sponsor on the following:
    a) If enrollment and study may continue
    b) If enrollment should be stopped; enrolled subjects are still allowed to continue in study
    c) If the entire study must be stopped, including subjects who have already received study devices
5. The study will be suspended if 2 or more algorithm-related DKA events OR 4 or more algorithm-related Severe Hypoglycemia events occur

9.13. Success Criteria for Feasibility 2 (Digital Twin and Meal Prediction)

The following criteria will be used to evaluate success of the Feasibility 2:

No occurrence of severe hypoglycemia or DKA due to device algorithm during the feasibility studies

1. Average time with SG below 70 mg/dL of 47 minutes or less (i.e. ≤ 3.3%) as in CER294DOC

10. Risks and Benefits

10.1. Potential Risks

Table 6. Risks, Prevention and Mitigation

Risks with Infusion Sets	Prevention and Mitigation
Risks with infusion sets may include: • Localized infection • Skin irritation/redness • Bruising • Discomfort/pain • Bleeding • Irritation • Rash • Hyperglycemia secondary to infusion set occlusion or infusion site failure including DKA • Hyperglycemia secondary to site falling off including DKA • Anxiety associated with insertion	Prevention and mitigation include: • Follow the provided user guides for insertions and care of infusion sets. • If an infusion site becomes irritated or inflamed, the infusion set will be removed and another placed in a new location. • In case of hyperglycemia secondary to infusion set occlusion, remove current infusion set and replace with new infusion set and give correction insulin if needed with syringe. • Follow the provided user guides for insulin pump management. • Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems.
Risks with Insulin Administration and Pumps	**Prevention and Mitigation**
Risks with the use of an insulin infusion pump may include the risk of malfunction of the components of the system (pump, software, infusion set and reservoir) as well as the risk of use error during use of the system. Device deficiencies or use errors can result in administration of too much or too little insulin which can lead to the following clinical consequences: • Hypoglycemia • Hyperglycemia • Diabetic ketoacidosis • Severe hypoglycemia with or without associated seizure, coma or death • Kinked cannula leading to hyperglycemia • Infusion set disconnection from pump leading to hyperglycemia • Subject removes the reservoir from the pump but forgets to disconnect the infusion set from the body which results in hypoglycemia or severe hypoglycemia • Dislodged cannula leading to hyperglycemia • A pump error may lead to under delivery or over-delivery of insulin • Battery failure – no insulin delivered	Prevention and mitigation include: • Follow the provided user guides& instructions for insulin pump management which includes information on infusion set change. • Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems. • Check SMBG 4-6 times a day and also before driving (as applicable). • Instruct to have glucose on hand for hypoglycemia • Instruct to change infusion set if suspected catheter occlusion or administer insulin with syringe for persistent hyperglycemia especially if ketones develop. • Parent(s)/guardian(s)/companion(s) will be present at night with subjects and will be trained on study device and diabetes management principles and instructed to call investigator with problems.

• Insulin deterioration leading to hyperglycemia • Incomplete priming; fails to prime tubing and/or cannula, leading to hyperglycemia • Remove a reservoir, without suspending and reconnecting after a while resulting in a Hypoglycemia • Patient not filling pump reservoir when needed leading to hyperglycemia • Magnetic Resonance Imaging resulting in pump/transmitter malfunction • Inaccurate insulin delivery due to sudden altitude changes. • Hypoglycemia or hyperglycemia from manual bolus • Hypoglycemia or hyperglycemia from computer hacking	
Risks with hyperglycemia may include • Diabetic ketoacidosis • Symptomatic ketosis • Cardiovascular event • Dehydration • Potassium and sodium imbalance • Shock • Altered mental status • Coma • Acidosis	Prevention and mitigation include: • Follow the provided user guides for insulin pump management. • Parent(s)/guardian(s)/companion(s) will be present at night with subjects and will be trained on study device and diabetes management principles and instructed to call investigator with problems. • Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems. • Check SMBG 4-6 times a day. • Alternative method of managing glucose levels will be available (insulin and syringe for example)
Risks with hypoglycemia may include: • Seizure • Coma • Altered mental status • Loss of consciousness • Cardiovascular event • Death • Risk of rebound hyperglycemia with ketosis	Prevention and mitigation include: • Follow the provided user guides for insulin pump management. • Parent(s)/guardian(s)/companion(s) will be present at night with subjects and will be trained on study device and diabetes management principles and instructed to call investigator with problems. • Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems. • Check SMBG 4-6 times a day. • Instruct to have glucose on hand for hypoglycemia
Risk with Sensors	**Prevention and Mitigation**
Risks with Sensors may include: • Skin irritation or reaction to adhesives • Bruising	Prevention and mitigation include: • Follow the provided user guides for insertions and care of sensors.

• Discomfort • Redness • Bleeding • Excessive bleeding due to anticoagulants • Pain • Rash • Infection • Irritation from tapes used with glucose-sensing products • Raised bump • Appearance of a small "freckle-like" dot where needle was inserted • Allergic reaction • Syncopal episode secondary to needle insertion • Soreness or tenderness • Swelling at insertion site • Sensor fracture, breakage or damage • Minimal blood splatter associated with sensor needle removal • Residual redness associated with adhesive and or tapes • Scarring • Scab • Blister • Itchiness • Inflammation • Anxiety • Incorrect sensor glucose reading results in incorrect diabetes management • Subject over-treating secondary to alarms which can result in hyperglycemia or hypoglycemia • Anxiety associated with insertion	• If a sensor site becomes infected or inflamed, the sensor will be removed and another placed in a new location • Base diabetes management on fingerstick readings and not sensor glucose values.
Risks with Transmitter	**Prevention and Mitigation**
Risks with Transmitter may include: • Skin irritation or reaction to adhesives • Bruising • Discomfort • Redness • Pain • Rash • Infection • Irritation from tapes used with glucose-sensing products • Raised bump • Allergic reaction • Soreness or tenderness • Residual redness associated with adhesive and/ or tapes • Scarring • Scab	Prevention and mitigation include: • Follow the provided user guides. • Train on the proper use of the transmitters.

• Blister • Itchiness • Inflammation	
Risks with Serter	**Prevention and Mitigation**
Risks with serters may include: • Improper insertion may lead to device performance issue or hyperglycemia	Prevention and mitigation include: • Follow the provided user guides for insertions and care of device. • Train on the proper use of the serter and skin preparation prior to insertion.
Risks with Finger Sticks	**Prevention and Mitigation**
Risks with frequent finger stick testing may include: • Potential risks associated with frequent meter testing of blood glucose and blood ketones include discomfort and ecchymosis at tips of fingers • Potential risks associated with finger stick testing include discomfort and bruising	Prevention and mitigation include: • Follow the provided user guides for use of the study meter with fingerstick testing. • Train on the proper use of the study meter and fingerstick testing.

Risk with Closed Loop Therapy	Prevention and Mitigation

Risks with Closed Loop may include:
• Hypoglycemia
• Severe hypoglycemia
• Hyperglycemia
• Diabetic ketoacidosis
• User Entry Error
  ○ Patient administering boluses by entering false carb doses leading to hypoglycemia or hyperglycemia
  ○ Patient entering false glucose values for any reason leading to hypoglycemia and hyperglycemia
  ○ Patient entering false BG values for calibration leading to hypoglycemia or hyperglycemia
• Sensor failure resulting from patient failure to calibrate leading to hypoglycemia or hyperglycemia
• Sensor over-reading resulting in hypoglycemia
• Sensor under-reading resulting in hyperglycemia
• Sensor missed transmission, or any other fault resulting in no SG value, leading to hyperglycemia or hypoglycemia
• Voluntary insulin delivery (with the pump or with a syringe) immediately prior to entering Auto Mode may result in severe hypoglycemia despite shutting down insulin delivery by the algorithm
• Meal prediction algorithm CHO recommendations may be too high or too low, potentially leading to hypoglycemia or hyperglycemia
• Hypoglycemia related to patient taking insulin via injection while in Closed Loop (Auto Mode)
	Prevention and mitigation include:
	• Follow the provided user guides for insulin pump management.
	• Train prior to study device on appropriate device use and diabetes management principles and instruct to call investigators with problems.
	• Check SMBG 4-6 times a day.
	• Instruct to have glucose on hand for hypoglycemia
	• Instruct to avoid the use of products containing acetaminophen
	• If acetaminophen is taken, subjects will be instructed to use additional BG meter readings (they are not to calibrate with those readings) to verify their glucose levels.
	• If acetaminophen is taken, subjects will exit Auto Mode
	• Pump has cybersecurity encryptions to prevent hacking.

• Hypoglycemia or hyperglycemia related to entering or exiting Closed Loop (Auto Mode) • Insulin over-delivery due to acetaminophen • Cyber security hacking into pump	
Risks with hyperglycemia may include • Diabetic ketoacidosis • Symptomatic ketosis • Cardiovascular event • Dehydration • Potassium and sodium imbalance • Shock • Altered mental status • Coma Acidosis	Prevention and mitigation include: • Follow the provided user guides for insulin pump management. • Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems. • Check SMBG 4-6 times a day.
Risks with hypoglycemia may include: • Seizure • Coma • Altered mental status • Loss of consciousness • Cardiovascular event • Death • Risk of rebound hyperglycemia with ketosis	Prevention and mitigation include: • Follow the provided user guides for insulin pump management. • Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems. • Check SMBG 4-6 times a day. • Instruct to have glucose on hand for hypoglycemia
Risk with Acetaminophen Use	**Prevention and Mitigation**
Potential risks with acetaminophen may include: • False elevation of sensor glucose readings. The level of inaccuracy depends on the amount of acetaminophen active in subject's body and may be different for each subject • Liver damage, liver failure and/or rare but fatal liver failure can occur • Skin rash and/or serious and potentially fatal skin reactions have been reported • Allergic reactions including those which are serious and potentially fatal can occur • Kidney disease • Lowered blood counts (red cells, and white cells)	Prevention and mitigation include: • Follow the user guide • Instruct to avoid the use of products containing acetaminophen • If acetaminophen is taken, subjects will be instructed to use additional BG meter readings (they are not to calibrate with those readings) to verify their glucose levels • Subjects will exit Auto Mode

Risk related to Algorithms	Prevention and Mitigation
Digital Twin Algorithm: • Frequent transition between Manual Mode and Auto Mode could introduce bias in the algorithm adaptations. • Lifestyle and physiological changes • Unannounced meals could introduce error in carb ratio estimation by the algorithm	• User historical data from system use in both pump modes (Auto Mode and Manual Mode) are used to generate a user's digital twin. • The amount of historical data (insulin delivery, SG values, meals/carb estimates) must be sufficient for a digital twin to be generated. • The Digital Twin algorithm is designed to absorb drastic lifestyle changes by providing therapy adaptations that are constrained by common insulin therapy heuristics or by safeguards of the pump's advanced hybrid closed loop (AHCL) insulin delivery algorithms • The Digital Twin algorithm simulates the total daily insulin delivery (TDD) after generating each adaptation of pump settings. If the simulated TDD is more than 50% greater or less than the TDD recorded in CareLink, the algorithm will not provide any therapy adaptations • The algorithm can detect meal events from historical data, even if the meals are not announced. If there are fewer than 2 meal events per day, on average, in the historical data set, whether the meals were announced or detected within the data, the Digital Twin algorithm does not generate a digital twin. When no digital twin of the patient is generated, no new adaptations to pump settings will be generated. • The primary mitigation is that the physician must review and approve all device setting recommendations.
Meal Prediction Algorithm: • Inaccurate carb estimate predictions (either higher or lower than the amount of CHO to be consumed) could lead to under- or over-delivery of insulin • Inaccurate meal time predictions could lead to nuisance or promotion of pre-mature meal bolus delivery	• The user will approve the amount of carbohydrate recommended by the meal prediction algorithm • No automated boluses are given. The user will approve all insulin given with meal.

10.2. Risk Minimization

Refer to "Prevention and Mitigation" column in the table under Section 10.1.

10.3. Potential Benefits

Subjects may experience improved glucose control. However, subjects may not benefit from participation in this study; they may gain increased awareness of emerging technologies for diabetes management as a result of their participation.

10.4. Risk-Benefit Rationale

The main benefit of this study is that patients are likely to experience improved glucose control. The primary risk, as with all automated insulin delivery systems, is the possibility of an increase in hypoglycemia. To address this risk, many scenarios have been modeled and, the risk is effectively minimized by a variety of safety checks that are an integral part of the new cloud algorithms and the revised insulin delivery algorithm.

10.5. Risk Determination

In the opinion of the sponsor, this study is considered a significant risk (SR) study. Subjects in the study will use the MiniMed 670G 4.0 Pump, an investigational device that is intended for use of substantial importance in treating diabetes and presents a potential for serious risk to the health, safety, or welfare of a subject. Per 21 CFR 812.3(m)(3), this device is a significant risk device.

Other investigational devices in the study include the cloud-based Digital Twin and Meal Prediction algorithms and the App. The Digital Twin algorithm is intended to provide pump settings recommendations based on individual patient data, which will be reviewed and approved by the investigator prior to implementation on a subject's pump. The Meal Prediction algorithm is intended to provide meal time notifications to the subject via the mobile application on the subject's Smartphone. The App is intended for meal logging and acknowledgment of meal time notifications by the subject. In this study, these 3 investigational devices function as accessories to, but do not communicate directly with, the MiniMed 670G 4.0 Pump.

All other devices used during this investigation have been previously approved by FDA for commercial distribution in the United States.

Considering the above discussion, and per 21 CFR 812.2, the devices above require application for an investigational device exemption.

11. Adverse Events Assessments

11.1. Adverse Events

Throughout the course of the study, investigational centers will make all efforts to remain alert to possible reportable adverse events (AEs) or untoward findings. The study personnel will elicit reports of AEs from the subject at each visit (including phone calls) starting at the time of signing the informed consent documenting the medical diagnosis, date of event start and end, causality (relationship to device or procedure), treatment, outcome, and description that includes the details of the event.

11.2. Definitions and Classification of Adverse Events

Medtronic uses the definitions provided in ISO 14155:2020 and 21 CFR 812 for AE definitions. Where the definition indicates "device", it refers to any device used in the study. This might be the device under investigation, or any market released component of the system.

Severe Hypoglycemia is an event requiring assistance of another person due to altered consciousness to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the subject was impaired cognitively to the point that he/she was unable to treat himself or herself, was unable to verbalize his or her needs, and was incoherent, disoriented and/or combative.

These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration. **(Adapted from American Diabetes Association Workgroup on Hypoglycemia, Diabetes Care 28:1245-1249, 2005)**

Severe Hyperglycemia is defined as hyperglycemia (blood glucose greater than (>) 300 mg/dL or 16.7 mmol/L) with blood glucose ketones greater than (>) 1.5 mmol/L, urine ketones moderate or large, or accompanied by symptoms of nausea, vomiting or abdominal pain.

Diabetic Ketoacidosis/DKA diagnostic criteria: blood glucose greater than (>) 250 mg/dL or greater than (>) 13.9 mmol/L, arterial pH less than (<) 7.3, bicarbonate less than (<) 15 mEq/L, moderate ketonuria or ketonemia and requiring treatment within a health care facility. (**American Diabetes Association-Diabetes Care, Volume 27, Supplement 1, January 2004; S94-S102**)

Hyperglycemic events will be recorded as DKA if the event includes the presence of all of the following:

- Arterial blood pH less than (<) 7.30 or serum bicarbonate less than (<) 15 mEq/L
- Blood glucose greater than (>) 250 mg/dL or greater than (>) 13.9 mmol/L
- Serum ketones or large/moderate urine ketones
- Symptoms such as polyuria, polydipsia, nausea, or vomiting
- Treatment provided in a health care facility

Adverse Event (AE) (ISO 14155:2020)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

Note 1 to entry: This definition includes events related to the investigational medical device or the comparator.

Note 2 to entry: This definition includes events related to the procedures involved.

Note 3 to entry: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

Adverse Device Effect (ADE) (ISO 14155:2020)

Adverse event related to the use of an investigational medical device.

Note 1 to entry: 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.

Note 2 to entry: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Note 3 to entry: This includes 'comparator' if the comparator is a medical device.

Serious Adverse Event (SAE) (ISO 14155:2020)

Adverse event that led to any of the following

a) death,
b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
    1. a life- threatening illness or injury, or
    2. a permanent impairment of a body structure or a body function including chronic diseases, or
    3. in-patient* or prolonged hospitalization, or
    4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
c) foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment

Note 1 to entry: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

** For the purpose of this study, Inpatient Hospitalization is defined as: admission to the hospital for a period of 24 hours or more based on urgent medical need rather than elective admission.*

For the purpose of this study, the term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. (ICH Topic E 2 A Clinical Safety Data Management: Definitions & Standards for Expedited Reporting. EMEA 2006)

Serious Adverse Device Effect (SADE) (ISO 14155:2020)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Adverse Device Effect (UADE) (21 CFR 812.3(s))

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 subjects.

11.3. Reporting of Adverse Events

The investigator or designee will record ALL AEs while the subject is enrolled in the clinical study.

Each AE needs to be assessed for its device or procedure relatedness. A device related AE is associated with the use of the study device (e.g. infection of sensor site or infusion set occlusion resulting in DKA). A procedure related AE is associated with testing related to the study procedures specified in the CIP (e.g. IV insertion pain).

Examples of device or procedure related AEs include:

- ***Device*** related (ADE): insertion site infection
- Serious adverse ***device effect*** (SADE): cellulitis at device insertion site requiring hospitalization
- ***Procedure*** related AE: bruising at IV insertion site

Subjects participating in the study have diabetes and are expected to experience hypoglycemia and or hyperglycemia. These normal events are not expected to be reported to sponsor as this is not considered an untoward event, but rather an expected occurrence. Any glycemic excursion that meets the protocol definition of Severe Hypoglycemia, Severe Hyperglycemia or DKA is considered an untoward event and a worsening from the subject's baseline and would be reported to sponsor on an AE eCRF.

Baseline medical conditions should only be reported to sponsor on an AE eCRF if there is a worsening from the subject's baseline. For example, a subject previously diagnosed with Asthma is hospitalized for severe asthma attack would be a reportable event.

Adverse events will be documented in the subject source file and reported to sponsor on an eCRF. The investigational center is responsible for documentation of AEs including obtaining source documents related to the event, such as emergency medical technician/paramedic reports, hospital records (admission summary; lab results, test results, discharge summary) or device uploads to support the

event. Source documents will be reviewed to determine if additional AEs have occurred and require reporting.

Adverse events that have not resolved at the time of the subject's discontinuation or completion of the study should have an "outcome" of Not Recovered/Not Resolved at study end in subject source and on an eCRF. The investigator should ensure that subject is aware of any follow-up or additional treatment that is required for any ongoing AE at end of study participation; however, there will be no eCRF entry for the ongoing follow-up.

11.4. Notification of Adverse Events

Sponsor Notification:

The investigational center staff must report all reportable AEs to Medtronic in a timely manner. All Severe Hypoglycemia, DKA, SAE, and SADE should be reported as soon as possible (desired within 24 hours of investigator or study coordinator awareness) to Medtronic. For the previously mentioned events, the AE eCRF will be completed with all known details as soon as possible, this will serve as notification to Medtronic. If the study database cannot be accessed due to technical problems, contact the sponsor via email at dl.diabetesclinicalresearchsafety@medtronic.com and provide the known details of the event. Once the access issue has been corrected, the event should be entered onto an AE eCRF.

Source documents that support the event (e.g. clinic notes, hospital admission and discharge records, lab reports, EMT reports, ER/Urgent Care) should be provided to the sponsor via the Medtronic BOX safety folder. All source documents/medical records should be redacted of patient identifiers (full name, address, etc.) prior to providing to the sponsor. Each source page should be identified with the subject ID.

11.5. Expedited Safety Reporting Requirements

For device studies, investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (812.150(a)(1)).

The sponsor will notify the investigator and IRB of any event that results in a safety report per regulations to the FDA. Documentation of IRB notification of any safety event must be kept at the investigational center and a copy sent to the sponsor.

It is the responsibility of the investigator to follow their IRB reporting requirements.

11.6. Causality Assessment

An AE is not automatically related to the study device or procedure simply because the subject is wearing the device and participating in the study. The event should be reviewed to determine if the device or study procedure could have possibly caused the event and therefore is related to the study device or procedure.

Causality assessment is the determination of the relationship between an AE and the device being studied. It is expected that the investigational center will review all elements surrounding the AE to properly assess the causality of the event to the study device or to a study procedure.

This review would include the subjects' description of the event, study device uploads and medical records (if applicable) from the treating facility. These records will be made available to sponsor.

Investigators should classify the relationship between the AE and the study device or study procedures using one of the five possible causality categories listed below:

- **Not related:** relationship to the device or procedures can be excluded when:
  - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures
  - the event has no temporal relationship with the use of the investigational device or the procedures;
  - the event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
  - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
  - the event involves a body-site or an organ not expected to be affected by the device or procedure;
  - the event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
  - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
  - harms to the subject are not clearly due to use error;
  - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

- **Unlikely:** the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but a relationship to the device cannot be completely ruled out.

- **Possible:** the relationship with the use of the investigational device is weak. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed should also be classified as possible.

- **Probable:** the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause.

- **Causal relationship:** the event is associated with the investigational device or with procedures beyond reasonable doubt when:
  - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
  - the event has a temporal relationship with investigational device use/application or procedures;
  - the event involves a body-site or organ that
    - the investigational device or procedures are applied to;
    - the investigational device or procedures have an effect on;
  - the event follows a known response pattern to the medical device (if the response

pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Example: A severe hyperglycemia AE with the following event description would have the following causality assessment for device relatedness:	
Improved glucose without an infusion set/site change	**Not related**
Changed infusion set with glucose improvement	**Possible**
Infusion set fell out, bent cannula, occlusion alarm	**Causal relationship**

11.7. Anticipated or Unanticipated

If an AE is determined to be related to the study device, the sponsor will then assess the event to determine if it is anticipated or unanticipated.

- **Anticipated:** the event is identified in the CIP; labeling; report of priors/ Investigator's Brochure (IB) or user guide.
- **Unanticipated:** the event has not been previously identified in the CIP; labeling; report of priors/IB or user guide.

12. Data Review Committees

12.1. Clinical Events Committee

A clinical events committee (CEC) consisting of external physicians with an expertise in endocrinology and the management of diabetes including insulin pumps and CGM will be convened. The CEC will review AEs as required per protocol, which include reports of:

- Serious Adverse Event
- Serious Adverse Device Effect
- Unanticipated Adverse Device Effect
- Severe Hypoglycemia
- Diabetic Ketoacidosis
- Severe Hyperglycemia

The CEC will assess events to determine agreement or disagreement with the investigator classification of an event. The CEC will only provide three causality assessments for device and procedure relatedness: Not Related, Possible, and Causal relationship.

If the CEC disagrees with the investigator's classification of the event, the rationale will be provided to the investigator. If the investigator agrees with the CEC's adjudication, the CRF documenting the AE will be updated accordingly.

If the investigator does not agree with the CEC's adjudication classification, both determinations will be provided within the final report; however, the CEC's adjudication will be used for data analysis. The disagreement will also be included in reporting to ECs and regulatory authorities, if required.

Causality Categories for Investigational Center	**Causality Categories for CEC:**
• Not Related • Unlikely • Possible • Probable • Causal relationship	• Not Related • Possible • Causal relationship

The sponsor will notify the investigator of any disagreement in assessment of an event by the CEC.

Refer to Section 9.12for Stopping Rules for Entire Study and 10 day review requirements.

The CEC may review applicable information for device related AEs which may include:

- Whether or not the event was unanticipated
- Review of sensor data from CareLink™ Personal For Clinical Research software report (when applicable)
- Review of pump data from CareLink™ Personal For Clinical Research software report (when applicable)
- Misuse of the device by the user

Review of events may require the following information. Final disposition may be delayed based on obtaining this information:

- Monitoring by sponsor at site
- Device return and failure analysis
- CareLink™ Personal For Clinical Research upload and review of CareLink™ Personal For Clinical Research software reports
- Subject clarification to site regarding details about the event

- Source documents that support event: Paramedic records; ER records; Lab records; Hospital admission and discharge summary

The following factors should be carefully considered in the CEC's recommendation to sponsor:

1. Was the severe hypoglycemia or DKA related to the AHCL algorithm, or was it related to a known insulin pump risk? For example, a question that may be considered in DKA would be whether the event was related to an infusion set issue or caused by the AHCL algorithm.

2. Another important consideration would be if the severe hypoglycemia, severe hyperglycemia or DKA event was related to a device malfunction versus patient non-compliance. For example, if a software anomaly leading to an under-delivery of insulin is discovered versus the subject repeatedly ignoring alarms prompting the subject to take action.

3. Severe hypoglycemia, severe hyperglycemia or DKA caused directly by an infusion set issue when the study pump is functioning as intended would likely result in acceptance to proceed with the study versus severe hypoglycemia or DKA that are directly caused by the AHCL algorithm or a device malfunction might stop study enrollment or entire study altogether.

4. It should be noted that the final determination of causality related to AHCL System that is made by the CEC may include additional factors which the members consider to be clinically relevant and important.

12.2. Data Monitoring Committee

A data monitoring committee (DMC) consisting of external physicians with an expertise in Endocrinology and the management of insulin-requiring diabetes including CGM, along with an external statistician will be convened to review study safety. The Board will also meet when ad hoc review is required.

The DMC will review Safety data and provide a recommendation to the sponsor regarding staged enrollment of pediatric subjects:

- Enrollment of pediatric subjects 2-13 years of age into a specific phase may not proceed until N=10 subjects 14 years and older have completed the corresponding phase and safety data has been reviewed by the DMC.
- Study subjects 2-6 years of age will be enrolled in Cohort A and Cohort C only after completing an in clinic observational study using the AHCL system and safety data has been reviewed by the DMC.
- DMC will review in clinic data from subjects in the 5-6 year age group (N=8), in order to assess that it is safe for 5-6 year olds to perform Cohort A or Cohort C study procedures.
- DMC will review in-clinic data from both the 2-4 year age group (N=8) and the 5-6 year age group (N=8) in order to assess that it is safe for 2-4 year olds to perform Cohort A and Cohort C study procedures.

General guidance for DMC's recommendations to sponsor should be based on the following:

In general, a DMC recommendation regarding study stoppage or resumption of enrollment should be made to the sponsor within 1 week of the DMC meeting where the determination is made. However, if more data is needed, the DMC may meet again to re-assess their decision within 2 weeks or when required data becomes available.

13. Device Deficiencies and Troubleshooting

The Medtronic 24-Hour Technical Support (TS) will be consulted for device troubleshooting (e.g. assistance is needed by subject to operate their device(s)). When subjects call the TS, they are instructed to notify the TS operator that they are currently participating in a clinical research study. All device deficiencies that are reported to the TS will be documented by the TS staff.

The investigational center will be provided with a copy of all TS calls for their subjects. The TS call reports should be reviewed for investigational center staff awareness and assessment for the possibility of an AE. If an AE is detected the investigational center staff will complete the appropriate eCRF(s).

All device deficiencies reported directly to the investigational center staff by a subject should either be reported to the TS by the subject or investigational center staff. Any device deficiency the investigational center may have should be reported to the TS. A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance. NOTE: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling. This definition includes device deficiencies related to the investigational medical device or the comparator. (ISO14155:2020)

To return a study device as part of a device deficiency, the investigational center staff and/or subject are required to call the 24-Hour TS. Following the call to TS, the investigational center staff should then follow the study procedures for returning products with device deficiencies.

It is the responsibility of the investigator to follow their IRB reporting requirements.

14. Statistical Design and Methods

14.1. General Aspects of Analysis

All data collected from the time of screening until the end of the study will be collected either on eCRFs, subject questionnaires or electronically by downloading the various devices. Data and analysis will be summarized in a Clinical Study Report.

Any deviations from original statistical plan and the rationale will be described in the Clinical Study Report

14.2. Subject Disposition

The number of subjects enrolled in the study will be presented. The reasons for subject discontinuation prior to study completion will be summarized.

14.3. Subject Demographics and Baseline Characteristics

Subject characteristics, including age, gender, race, ethnicity, height, weight, and BMI will be summarized by descriptive statistics (mean, standard deviation, minimum, median, and maximum) for continuous variables and by counts and percentages for categorical variables.

14.4. Endpoints and Hypotheses

14.4.1. Descriptive Endpoints

There are no statistically powered endpoints or hypothesis testing but there are descriptive endpoints.

14.4.2. Safety Endpoints

- Severe glycemic events: (i.e., severe hypoglycemia, DKA)
- Collection of ALL adverse events (i.e. Summary of device related adverse events)

14.4.3. Effectiveness Endpoints

- Percentage of time in target: SG <70 mg/dL, 70-180 mg/dL and > 180 mg/dL

In each phase, data will be summarized and documented to evaluate the safety and effectiveness of the algorithm changes.

14.5. Sample Size Considerations

A total of up to 200 subjects will be enrolled at up to 15 investigational centers across the US in order to have up to 150 subjects who complete the study.

It is expected that at least N=12-18 subjects will participate in each phase during Feasibility 2.

14.6. General Considerations for Data Analysis

14.6.1. Analysis Populations

All enrolled subjects who have participated in the study will be included in the efficacy analysis population per each phase analysis. All enrolled subjects will be included in the safety analysis population.

14.7. Sample Size Justification

Given that this study is not statistically powered, no sample size calculation was performed. Up to 200 subjects will be enrolled to demonstrate a feasibility of an outpatient study using the Medtronic insulin pump system.

15. Ethics

15.1. Statement(s) of Compliance

IRB

This CIP, any subsequent amendments to this CIP, the ICF/ Assent form, subject materials, and any form of subject recruitment information (e.g. advertisements) relating to this study will be approved by the responsible IRB in accordance with 21 CFR Part 56.

The investigational center will not initiate any subject activities until IRB approval has been granted, the sponsor has cleared the investigational center to begin the study, and the investigational center staff has been appropriately trained to conduct the study.

Regulatory Compliance

This clinical study will be conducted in compliance with CIP, the Clinical Investigation Agreement; United

States CFR Title 21 Part 11 (Electronic Records; Electronic Signatures), Part 50 (Informed consents), Part 54 (Financial Disclosure by Clinical Investigators), Part 56 (IRBs), Part 812 (Investigational Device Exemptions), and all other applicable federal and local regulatory requirements.

The study will also be conducted in compliance with the principles of good clinical practice (GCP) meaning that the study design, conduct, performance, monitoring, auditing, recording, analysis and reporting will assure that the data and results are credible and accurate and that the rights, safety and well-being of subjects are protected. GCP includes review and approval by an independent ethic committee (IEC)/ IRB before initiating the investigation, ongoing review of the investigation by an IEC/IRB and obtaining and documenting the freely given informed consent/assent of the subject (or the subject's legally authorized representative) before their participation in the investigation.

The ethical principles that have their origin in the Declaration of Helsinki have been implemented in this clinical study by means of the informed consent/assent process, IRB approval, study training, clinical trial registration, preclinical testing, risk benefit assessment, publication policy, etc.

If the subject is below 18 years of age, he/she should be informed about the study to the extent compatible with the subject's understanding. If the subject could give consent to decisions about participation in research, the investigator must obtain that consent in addition to the consent of their legally authorized representative or guardian.

Sponsor's Support

The sponsor shall avoid improper influence on, or inducement to, the subject, monitor, any investigator(s) or other parties participating in or contributing to this study.

Sponsor representatives may provide support as required for the study, including technical support at investigational center. Sponsor representatives may provide technical support as required for the study under supervision of the PI, including:

1) Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities.
2) Technical support will be provided during study period.
3) Technical support will be under the supervision of a study investigator, but no data entry on the eCRF shall be performed by Medtronic personnel or their representatives at investigational centers.
4) Technical support to conduct device interrogations.

15.2. Investigator's Responsibilities

This study will be conducted at the investigational centers where all study-related activities will be performed and will be led by a Principal Investigator (PI). Per 21 CFR 56.102, an investigator means "an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject) or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team."

The investigator's responsibilities include but are not limited to:

- Conduct of the investigation in accordance with the signed Investigator Statement for clinical investigations of medical devices, the CIP applicable regulations set forth in 21 CFR Part 812 and all other applicable and other applicable regulations, and any conditions of approval imposed by the reviewing IRB or FDA regulatory requirements

- Conduct of investigation in accordance to draft guidance from FDA, "Protecting the Rights, Safety, and Welfare of Study Subjects - Supervisory Responsibilities of Investigators", to meet responsibilities with respect to protect human subjects and ensuring the integrity of the data from clinical investigations. This guidance is also intended to clarify FDA's expectations concerning the investigator's responsibility:
    1) to supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other third parties, and
    2) to protect the rights, safety, and welfare of study subjects.
- Controlling devices under investigation (21 CFR 812.100)
- Ensuring that the requirements for obtaining informed consent/assent are met in accordance with 21 CFR 50
- Supervising the use of investigational device. An investigator shall permit an investigational device to be used only with subjects under the investigator's supervision. An investigator shall not supply an investigational device to any person not authorized under 21 CFR Part 812 to receive it. The cloud algorithms cannot be accessed by investigational centers or subjects. Therefore, they do not meet the requirements to be tracked.
- Disposing of device properly. Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.
- Allowing study devices to be used only with subjects under the investigator's supervision and to supply study devices only to persons authorized to receive it
- Ensuring that investigational center staff are adequately trained to perform their assigned duties
- Maintenance of accurate, complete, and current records relating to the investigator's part of an investigation (21 CFR 812.140),, to include:
    - all relevant correspondence with another investigator (if applicable), Medtronic, an IRB, a monitor, or FDA (if applicable), including required reports.
    - records of each subject's case history and exposure to the device
    - the CIP, with documents showing the dates of and reasons for each deviation from the CIP
    - Any other records the FDA requires to be maintained by regulations or by specific requirement for a category of investigations or a particular investigation
- Preparation and submission to Medtronic and, when required, the reviewing IRB, the following complete, accurate, and timely reports:
    - any reportable AEs (see Section 11) occurring during an investigation
    - progress reports on the investigation as required by the IRB
    - any deviation from the CIP made to protect the life or physical well-being of a subject in an emergency
    - any use of the device without obtaining informed consent/assent

- any further information requested by the IRB about any aspect of the investigation
- Permitting FDA or other regulatory authorities to inspect and copy any records pertaining to the investigation including, in certain situations, those which identify subjects (21 CFR 812.145)
- Meeting with the monitor to discuss study progress and findings
- Ensuring that investigational center resources are adequate to fulfill the obligations of the study
- Ensuring completion of eCRF to include entry and addressing discrepancies in a timely fashion and approving selected eCRFs.

Only authorized study personnel as listed on the Delegation of Authority Log/ Delegated Task List are permitted to consent subjects, receive, dispense, dispose of and return investigational products, conduct subject visits, insert devices, and enter data on eCRFs. These tasks may be delegated by the investigator. However, the investigator is ultimately responsible to ensure investigational center-staff are qualified and perform the tasks that have been delegated to them correctly. In addition, the investigator is responsible for the conduct of investigational center in the execution of the clinical trial.

The investigator's signature on the Investigator Statement confirms that the investigator is familiar with the CIP in its entirety and agrees to conduct this study in accordance with the provisions of the CIP and all applicable regulations. The investigator, prior to the initiation of any study related activity, will sign the Investigator Statement. If the sponsor discovers that an investigator is not complying with the Investigator Statement, CIP, or other regulatory requirements, the sponsor shall promptly secure compliance or discontinue that investigator's participation in the study.

16. Study Administration

16.1. Training of Clinical Staff

Training of the investigational center staff on the conduct of the study and system being studied will be initiated before the CIP is implemented. All participating physicians and coordinators will be familiarized with the system. Other members of the investigational center staff may require training depending on their role listing in the Delegation of Authority Log/ Delegated Task List. Training may contain both lecture and hands-on experience.

The PI is responsible for ensuring that investigational center staff are trained to perform their assigned duties per Delegation of Authority Log/ Delegated Task List. Individual investigational center staff must be appropriately trained prior to performing study related tasks.

16.2. Monitoring

Monitoring visits may be conducted at the start, during and at the closure of the clinical study in accordance with Medtronic SOPs and the Monitoring Plan. Visits may be conducted remotely. At minimum, it will be verified whether signed and dated ICFs/ Assent forms have been obtained from each subject at the point of enrollment and that AEs discussed in Section 11.3 were reported via completion of the AE eCRFs. More details regarding the monitoring activities (frequency of monitoring visits, planned extent of source data verification) are described in the Monitoring Plan.

16.2.1. Accessibility of Investigational Center Staff and Study Materials

The PI(s), his/her delegate(s) and the study coordinator(s) shall be accessible to Medtronic field personnel, regulatory agency personnel and the Clinical Study Manager. This accessibility is of particular importance for reviewing data in the eCRF. Direct access to subject medical files for source data verification will need to be granted and prepared prior to any monitoring visits.

16.2.2. Audits and Investigational Center Inspections

In addition to regular monitoring visits, the sponsor may conduct audits at participating investigational centers. The purpose of an audit is to verify the adequate performance of the clinical study related activities independent of the employees involved in the clinical study. Regulatory agencies may also perform inspections at participating investigational centers. Any regulatory authority inspection announcements shall be forwarded immediately to the Clinical Study Manager.

The investigator and/or institution shall permit sponsor and regulatory agencies direct access to source data and documents, taking into account any restrictions due to local law, to perform clinical study-related monitoring, audits, IRB review, and regulatory inspections.

16.2.3. Investigational Center Disqualification

Sponsor and/or the IRB retain the right to disqualify an investigational center and remove all study materials at any time. Specific instances that may precipitate investigational center disqualification include but are not limited to:

- Unsatisfactory subject enrollment with regards to quantity.
- Persistent non-compliance to protocol procedures on the part of an investigator/investigational center
- Inaccurate, incomplete, and/or untimely data recording on a recurrent basis.
- The incidence and/or severity of adverse experiences in this or other studies indicating a potential health hazard caused by the device.
- Unsatisfactory accountability of investigational devices.

A written statement fully documenting the reasons for such a termination will be provided to sponsor, the IRB, investigational center(s) and other regulatory authorities, as required.

16.3. Data Management

16.3.1. Data collection

All device data will be obtained from the various study devices.

16.3.1.1. Electronic Case Report Forms (eCRFs)

The investigator must ensure accuracy, completeness and timeliness of the data reported in the eCRFs and in all other required reports. Data reported on the eCRFs, which are derived from source documents,

such as subject medical records, must be consistent with the source documents and the discrepancies need to be justified in a documented rationale.

Only authorized persons can complete eCRFs. eCRFs shall be signed by investigational center staff as specified on the Delegation of Authority Log/ Delegated Task List included in the Investigator Site File. The OC-RDC system maintains an audit trail on entries, changes, and corrections in eCRFs.

A copy of the eCRFs to be used in this clinical study is available under a separate cover upon request to the sponsor and in the Investigator Site File.

Investigational center will be trained to the use of the eCRFs. Access to final eCRFs for study conduct will be granted after training is performed and prior to patient's enrollment.

16.3.1.2. CareLink™ Personal For Clinical Research Software

During the course of the study, subject's BG values may be assessed from the CONTOUR® NEXT LINK 2.4 study meter. The SG values may be assessed from the study pumps. The study pumps will be uploaded in CareLink™ Personal For Clinical Research software by the investigator or designated investigational center staff and subjects at home. The system uses TLS technology, which encrypts all data it stores (21 CFR Part 11 compliant). The data in the different databases are linked to each other via the SIDs to prevent subject's identification by the sponsor.

16.3.2. Time windows for completion and submission of Case Report Forms

It is expected that eCRFs are completed in a timely manner with the exception of the reportable adverse events (see Section 11.4). After data entry, eCRFs should be submitted (i.e. saved) so that Monitors can proceed with data verification without delay.

16.3.3. Data review and processing

Data management will be done according to sponsor SOPs and the Data Management Plan for this clinical study.

Collected data will be reviewed for completeness, correctness, and consistency, as per the monitoring plan. In case of issues, queries will be entered on the respective eCRF for the investigator to complete, correct, or comment on the data.

16.4. Direct Access to Source Data/Documents

The subject's clinic file, CareLink™ Personal For Clinical Research software data, and source documents are handled as source data.

Medtronic clinical representatives or delegates will be granted access by the investigational center to all source documents including electronic source documents or copies of electronic source documents, if applicable, for the purposes of monitoring, audit, or inspection

16.4.1. Quality Audits

Sponsor reserves the right to conduct quality audits at the investigational center in order to verify adherence to external regulations and internal policies and procedures; assess adequacy and effectiveness of clinical policies and procedures; assure compliance with critical study document requirements; confirm integrity and accuracy of clinical study data; and protect the safety, rights and welfare of study subjects.

16.5. Confidentiality

The investigator will ensure that the subject's anonymity is maintained. Subjects will not be identified in any publicly released reports of this study. All records will be kept confidential to the extent provided by federal, state and local law. The study monitors and other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records. The investigator will inform the subjects that the above-named representatives will review their study-related records without violating the confidentiality of the subjects. All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified only by the subject ID code in order to maintain subject confidentiality. All records will be kept locked and all computer entry and networking programs will be done with coded numbers only.

16.6. Liability

Subjects will be paid for participation. Refer to the ICF on the details of the subject's compensation.

16.7. CIP Amendments

An investigator or study team member can propose any appropriate modification(s) of the CIP or study device/product or study device/product use. Medtronic will review this proposal and decide whether the modification(s) will be implemented.

Sponsor can decide to review the CIP based on new information (i.e. from an investigator, the CEC or the study team) and will submit any significant amendment to the CIP, including a justification for this amendment, to the appropriate regulatory agency (if applicable) and to the investigators to obtain approval from their IRB. The investigator will only implement the amendment after approval from the IRB, regulatory agency (if applicable), and sponsor. Administrative amendments to the CIP will be submitted to the IRB for notification.

16.8. Records and reports

16.8.1. Investigator Records

At a minimum, the following records must be kept by the investigator:

- All essential study documents and correspondence that pertains to the clinical study
- CIP and, if applicable, any amendments
- Report of Prior Investigations and/or user guide
- Medtronic and IRB-approved Subject ICF/ Assent form
- IRB and Regulatory authority approval or notification
- Fully signed clinical study agreements (i.e. including Investigator Statement and Signature Page, Clinical Trial Agreement and Confidential Disclosure Agreement)
- Completed Delegation of Authority Log/ Delegated Task List
- Training documentation of all investigational center staff
- Subject Screening log and/or SID log
- Signed, dated and fully executed Subject ICFs/ Assent forms
- Source documentation
- Fully executed eCRFs and corrections
- Report of AEs and Device Deficiencies
- Device accountability records
- CIP Deviation/ CIP Non-Compliance, if any
- Clinical Bulletins (if applicable)- A brief official update or summary of current study news on a matter of immediate interest and high importance to investigational center surrounding the CIP.
- Current signed and dated curriculum vitae (CV) of PI (and key study team members if required per local requirements)
- Study reports

16.8.2. Investigator reporting responsibilities

Table 7. Investigator Reporting Requirements

Report	Submit to	Description/Constraints
AEs	Sponsor, IRB, and local regulatory authority, where applicable	Refer to section 11.3,11.4,11.5, and 13 for reporting requirements.
Withdrawal of IRB approval (either suspension or termination)	Sponsor	An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
Progress report	Sponsor and IRB	The investigator must submit this report to the sponsor and IRB at regular intervals but in no event less than yearly.

Report	Submit to	Description/Constraints
Study deviations	Sponsor and IRB	Notice of deviations from the CIP to protect the life or physical wellbeing of a subject in an emergency shall be given as soon as possible but no later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by sponsor is required for changes in or deviations from the plan, and if these deviations may affect the scientific soundness of the plan or the rights, safety and welfare of human subjects, FDA and IRB in accordance with 812.35(a) also is required.
Failure to obtain informed consent prior to investigational device use	Sponsor and IRBs	If an investigator uses a device without obtaining informed consent/assent, the investigator shall report such use within 5 working days after device use.
Final report	Sponsor IRBs Relevant Authorities	This report must be submitted within 3 months after termination or completion of the investigation or the investigator's part of the investigation.
Other	Sponsor, IRB and FDA	An investigator shall, upon request by a reviewing IRB, FDA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation.

16.9. Record Retention

The sponsor and investigator will retain all records and documents pertaining to this study. They will be available for inspection by the appropriate regulatory agencies. In addition, the investigator will retain the source documents from which the information entered on the eCRF was derived. These records are to be retained in a secure storage facility maintained by the investigational center until 2 years (or longer if local laws require) after approval of the above-listed study devices or termination of the study, whichever is longer. The investigator should not dispose of these records without the approval of the sponsor.

16.10. Suspension or Early Termination

Sponsor or a Regulatory Authority may decide to suspend or prematurely terminate the clinical study (e.g. if information becomes available that the risk to study subject is higher than initially indicated, lack of enrollment, or because of a business decision). If the clinical study is terminated prematurely or suspended, sponsor shall promptly inform the investigators of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing IRB and the study subjects.

16.10.1. Early Investigational Center suspension or termination

Sponsor, IRB or a Regulatory Authority may decide to suspend or prematurely terminate an investigational center (e.g. in case of expiring approval of the reviewing IRB, non-compliance to the CIP, or lack of enrollment). Suspended clinical studies cannot be resumed without permission from IRB. If an investigational center is suspended or prematurely terminated, sponsor shall promptly inform the investigator(s) of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing IRB and the study subjects.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definite outcomes, investigators must assess whether to continue, modify, or immediately stop the clinical study in the respective investigational center and immediately inform the sponsor and IRB, if applicable.

16.10.2. Subject follow-up in case of termination

In case of early investigational center suspension or termination, all subjects should be contacted to plan an early Termination visit at the investigational center. All efforts will be made to complete and report all study observations at the time of termination. The subject will return the study devices to the investigational center.

16.11. Study Close Out

At the time of a study close-out, the investigators will be notified by sponsor. Appropriate notification/report to IRB and Regulatory Authority will be provided if required per local laws and regulations.

16.12. Publication and Use of Information

The contents of this CIP, documentation, and results pertaining to this study are confidential and may not be published or disclosed without the written consent of Medtronic.

The identity of the subjects may not be disclosed, unless required by law, to any persons not immediately involved in the study or the study procedures. The results for this study will be published on ClinicalTrials.Gov.

17. References

American Diabetes Association. Hyperglycemic Crises in Diabetes. Diabetes Care. 2004; 27(1):S94-S102.

American Diabetes Association Workgroup on Hypoglycemia. Defining and Reporting Hypoglycemia in Diabetes, Diabetes Care. 2005; 28: 1245-1249

Medtronic, Inc. CEP294 Final Clinical Study Report. CER294DOC, 2019.

Medtronic, Inc. Personalized Closed Loop Patient Questionnaire for Meal Prediction, Market Research Personalized Closed Loop. 2019

Medtronic, Inc. Personalized Closed Loop Patient Questionnaire for Device Settings, Market Research Personalized Closed Loop 2019

18. Appendices

18.1. Names and addresses

18.1.1. Investigational Centers and IRBs

The table below provides a list of the investigators and investigational centers currently approved to participate in the study.

Site No.	Principal Investigator Name	Investigational Center's Name & Address	IRB Name	IRB Chairperson* and Address	Investigational Center Status
001	Ronald Brazg	Rainier Clinical Research 800 SW 39th St, Ste 110 Renton, WA 98057	Advarra	1501 Fourth Avenue Suite 800 Seattle, WA 98101	Active
002	Mark Christiansen	Diablo Clinical Research 2255 Ygnacio Valley Road, Suite M Walnut Creek, CA 94598, USA	Advarra	1501 Fourth Avenue Suite 800 Seattle, WA 98101	Active
004	Satish Garg	Barbara Davis Center for Diabetes 1775 Aurora Court, A1321, Aurora, CO 80045	WIRB	Bonnie Love (Chairperson) Susan Abramson, MD (Vice Chairperson) 1019 39th Avenue SE Suite 120 Puyallup, WA 98374-2115	Active
005	Dorothy Shulman	University of South Florida Diabetes Center Faculty Offices 13220 USF Laurel Dr., suite 1100 Tampa, FL 33612, USA	Advarra	1501 Fourth Avenue Suite 800 Seattle, WA 98101	Active
006	Robert Slover	Barbara Davis Center for Diabetes	Western Institutional Review Board	Bonnie Love (Chairperson)	Active

Site No.	Principal Investigator Name	Investigational Center's Name & Address	IRB Name	IRB Chairperson* and Address	Investigational Center Status
		1775 Aurora Court, A140, Aurora, CO 80045		Susan Abramson, MD (Vice Chairperson) 1019 39th Avenue SE Suite 120 Puyallup, WA 98374-2115	
007	Anders Carlson	Park Nicollet International Diabetes Center 3800 Park Nicollet Blvd 6th N. Saint Louis Park, MN 55416, USA	Healthpartners IRB	Elie Gertner, MD, FRCP(C) FACP HealthPartners Institute PO Box 1524 Minneapolis, MN 55440	Active
011	John Reed	Endocrine Research Solutions 1475 Holcomb Bridge Rd., Suite129 Roswell, GA 30076, USA	Advarra	1501 Fourth Avenue Suite 800 Seattle, WA 98101	Active
012	Yogish Kudva	Mayo Clinic Rochester 200 1st St SW Rochester, MN 55902	Advarra	1501 Fourth Avenue Suite 800 Seattle, WA 98101	Active
013	David Liljenquist	Rocky Mountain Diabetes and Osteoporosis Center 3910 Washington Pkwy Idaho Falls, ID 83404, USA	Advarra	1501 Fourth Avenue Suite 800 Seattle, WA 98101	Active
015	Kashif Latif	AM Diabetes and Endocrinology Center Insulin Pump Center 3025 Kate Bond Rd Bartlett, TN 38133, USA	Advarra	1501 Fourth Avenue Suite 800 Seattle, WA 98101	Active

Site No.	Principal Investigator Name	Investigational Center's Name & Address	IRB Name	IRB Chairperson* and Address	Investigational Center Status
019	Bruce Bode	Atlanta Diabetes Associates 1800 Howell Mill Road, Suite 450, Atlanta, GA 30318	Advarra	1501 Fourth Avenue Suite 800 Seattle, WA 98101	Active
020	Kevin Codorniz	Loma Linda University Medical Center Diabetes Treatment Center 11175 Campus Street, Suite A-1108 Loma Linda, CA 92350	Advarra	1501 Fourth Avenue Suite 800 Seattle, WA 98101	Active

*For Advarra's IRB Chairperson, see current IRB Membership Roster.

Additional Investigational Centers at which the investigation will be conducted have not been identified at the time of this CIP was finalized.

18.1.2. Monitors Contact Information

The study will be monitored by the Medtronic Core Clinical Solutions (MC2) Global Monitoring and monitoring duties to be entrusted under:

[redacted]

Clinical Monitoring Manager, MC2 Global Monitoring

Medtronic

710 Medtronic Parkway

Minneapolis, MN 55432

At the time of this CIP was finalized, the names and address of the monitor(s) were not identified. The names and address of the monitors will be provided to the investigators under separate cover.

18.2. Labeling and IFUs of Devices

The current labeling and IFU for the investigational study devices (except the App) will be provided to the investigators in a separate cover.

18.3. Sample Consent Materials

Samples of the following consent forms/materials will be provided in a separate cover which includes the California Experimental Subject's Bill of Rights (if applicable), ICF/ Assent form, and the HIPAA Authorization.

18.4. CIP326 Visit Details Tables

For visit details, refer to excel sheets labeled as CIP326 Visit Details Table for Feasibility 2.

[redacted]

19. Version History

Version	Summary of Changes	Author(s)/Title
A.1	• Initial release	[redacted] Principal Medical Writer
B.1	• Updated for Feasibility 2	[redacted] Principal Medical Writer
B.2	• Added IDE number • Added in the study phase descriptions when subjects are using Auto Mode with the AHCL system, the automatic basal insulin delivery target should be set to 100 mg/dL during Auto Mode. In addition, updated the visit schedule at Visit 2 to reflect this update to Cohort A and Cohort C. • Added the review "by the DMC" during staged enrollment. In addition, we have added the	[redacted] Principal Medical Writer

	minimum of subjects 14 years and older to be reviewed by DMC before the 2-13 years can proceed. • We have added details about the role of the Data Monitoring Committee during the study. The DMC will review Safety data and provide a recommendation to the sponsor regarding staged enrollment of pediatric subjects 5-6 and 2-4 years of age. • Based on FDA feedback, modified the protocol to note that subjects 2-6 years of age will only be able to participate in Cohort A or Cohort C study procedures after they complete a 5 day long in-clinic observational study (see Study Design). Added DMC who will be reviewing the safety data from the in-clinic study before subject ages 2-6 years old will be enrolled in the outpatient portion. • We have added specific study procedures for 2-6 year-old subjects to follow before and during the observational study. • Based on FDA feedback, added inclusion criterion which specifies the role of companion/caregiver with respect to being present as a means of mitigating risk during the study. • Added "Review Manual Mode settings" at Visit 2D under Cohort A and Cohort C visit schedules. • Added a separate visit schedule for subjects 2-6 years of age and updated 5 day observational study for subjects in Visit Schedule Figures for Cohort A and C. • Corrected Challenge #1 to Challenge #2 for instructions under Visit 11 for Cohort A: Digital Twin Challenge #2	

	• Based on FDA feedback, updated protocol to include a pre-specified number of algorithm-related Severe Hypoglycemia and DKA events (see Study Stopping Rules). • Updated Notification of Adverse Events section on addition of provision of source documents to support AE events and addition of use of the MDT BOX for receipt of source documents. • Added the DMC section since we now have a DMC to convene to review the safety data after the completion of the in-clinic observation studies.	
B (Equivalent to FDA Version B.3)	• Revised Study stopping rules to clarify	[redacted] Sr. Program Manager

C (Equivalent to FDA C.1)	• Updated current year in copyright statement
	• Updated Feasibility 2 non-investigational devices
	• Updated Study Design for Feasibility 2
	  ○ Updated Cohort A: Insulin Delivery Recommendations Derived from the Digital Twin Algorithm
	  ○ Updated Run-in Period Study Procedures under Digital Twin Challenge #1 and #2:
	• Updated Background
	• Updated Schedule of Events
	• Updated Study Timeline, Visit Schedule diagram, Visit Details Table for Feasibility 2 (excel) (includes adding optional telemedicine visits under Feasibility 2 Visit Schedule)
		[redacted] Sr. Program Manager

	• Added that used commercial study meter can be retained by the subject. • Removed duplicate Digital Twin Challenge #1 Visit Schedule under Assessment of Safety section • Added remote monitoring • Updated Visit Details Table for Feasibility 2 (excel): ○ CIP version and date to reflect CIP amendment in footer ○ Added "Collect/Assist with Questionnaires" at Visit 14 (Cohort C) and Visit 18 (Cohort A, Digital Twin #2).	
D	• Increased study period for Cohort C to approximately 42 day long, includes update to the Visit Schedule figure and Visit Details Table for Feasibility 2 (excel) • Corrected model number of MiniMed™ 670G Insulin Pump	[redacted] Sr. Program Manager
E	• Updated Glossary section • Updated Study Design, Study Visit Schedule and its associated figures, and CIP326 Visit Details Table) to: ○ Provide additional flexibility for method of receipt of device setting changes by removing via RDC. ○ Expand additional time between visits for both Cohorts A. ○ Add information about providing Android phones to pediatric patients under certain circumstances in Cohort C ○ Provide additional flexibility for study visits by allowing for telemedicine visits.	[redacted] Sr. Program Manager

	○ Adjust Cohort A visit schedules to allow for additional time for sponsor to provide device settings recommendations ○ For Cohort C, BG checks at start of and after meals instructions was updated to clarify BG requirement of 2 largest CHO content meals of the day. • Updated device classification for devices which exempt • Updated inclusion criteria#4 • Potential Risks section: ○ Added a title and number for table listed under this section ○ Updated section to align with Medtronic • Adverse Events Assessments section updated to align with safety template. The update includes all ISO definitions to align with ISO 14155:2020. • Updated following sections to align with safety template: ○ Risk Minimization ○ Clinical Event Committees ○ Device Deficiencies and Troubleshooting • Updated the following subsections under Deviation Handling: ○ Reporting Requirements for Study Deviations ○ Unplanned CIP Deviations • Updated Ethics section • Updated Accessibility of Investigational Center Staff and Study Materials section • Updated Investigational Center Disqualification section	

	• Updated CIP Amendments section
	• Updated Suspension or Early Termination section
	• Updated Early Investigational Center Suspension or Termination section
	• Updated Investigational Centers and IRBs section
	• Updated the following clinical document names:
	  ○ Delegation of Authority Log/ Delegated Task List
	  ○ Investigator Statement
	  ○ Investigator Site File
	• Updated excel sheet labeled as "CIP326_ Visit Details Table for Feasibility 2"	