Medtronic

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Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	Feasibility Study with Personalized Closed Loop (PCL)
Clinical Investigation Plan Identifier	CIP326
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Sponsor/Local Sponsor	USA: Medtronic MiniMed, Inc. ("Medtronic") 18000 Devonshire St Northridge, CA 91325 866.948.6633

Table of Contents

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0 02-DEC-2019	• Not Applicable, New Document	[redacted] Biostatistician
2.0 30-NOV-2020	• Updated for Feasibility 2	[redacted] Biostatistician
3.0	• Updated to 056-F286 Statistical Analysis Plan Template Rev C • Updated section 5 Investigation Plan according to protocol version E • Updated section 7.9.1 Effectiveness Endpoints	[redacted] Sr Statistician

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
AHCL	Advanced Hybrid Closed Loop
AI	Artificial Intelligence
BG	Blood Glucose
CGM	Continuous Glucose Monitoring
CHO	Carbohydrate
CRF	Case Report Form
CSII	Continuous Subcutaneous Insulin Infusion
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
FST	Frequent sample testing
MDI	Multiple Daily Injection
PCL	Personalized Closed Loop
SG	Sensor Glucose
SMBG	Self-Monitoring of Blood Glucose
TDD	Total Daily Dose

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. Study Objectives

4.1 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.

5. Investigation Plan

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 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.

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 Feasibility 1, 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
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 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™.

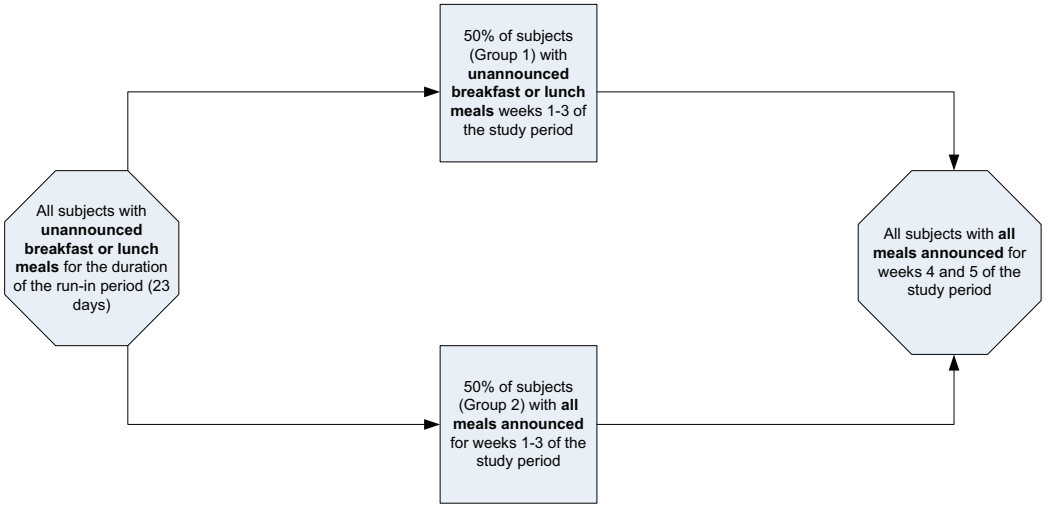
Subjects will be instructed to upload the pump and meter at specific time points during the study period. Device settings recommendations will be provided during this study period. Investigators should make every attempt to follow these recommendations, except if they do not agree with the device settings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

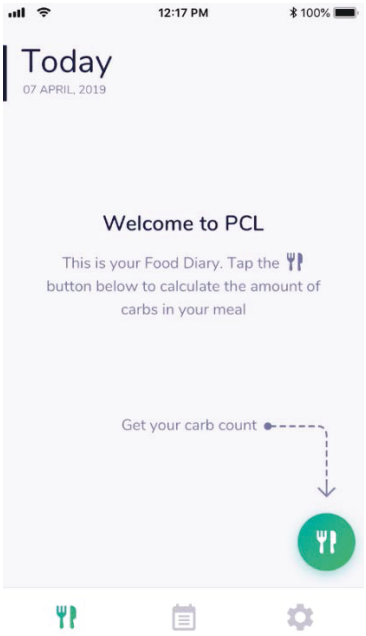
At selected centers, a limited number of subjects will undergo frequent sample testing (FST). The testing is **not** done in support of study data. Rather, the FST data is being collected as a means of gaining experience with a new testing method (ABL90 by Radiometer).

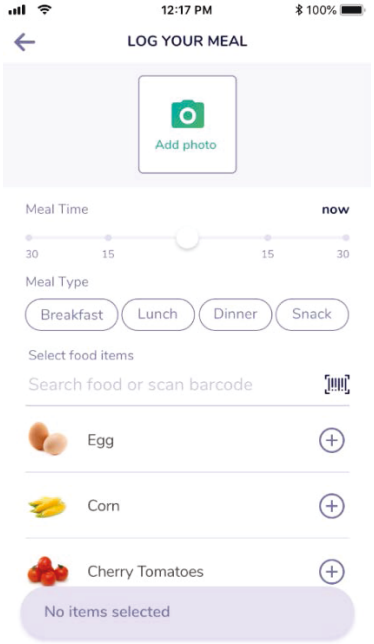
Subjects who are selected to participate in the FST procedures will undergo a hematocrit blood test prior to the start of the procedures. The passing criteria for this test are that subjects should not be more than 10% below the lower limit of normal Hct for the reference range of the local lab that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

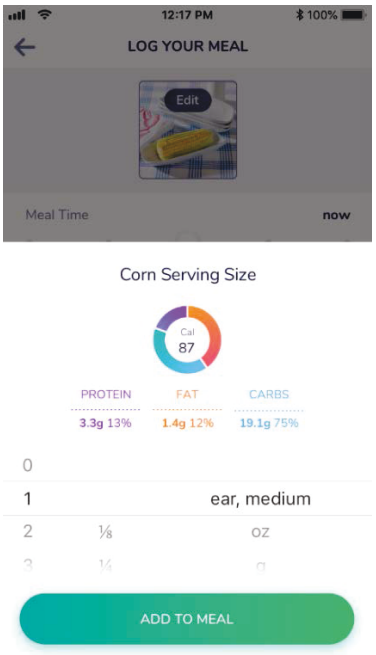
outlined above, within 6 months prior to screening, the blood draw and test during the study will not be required.

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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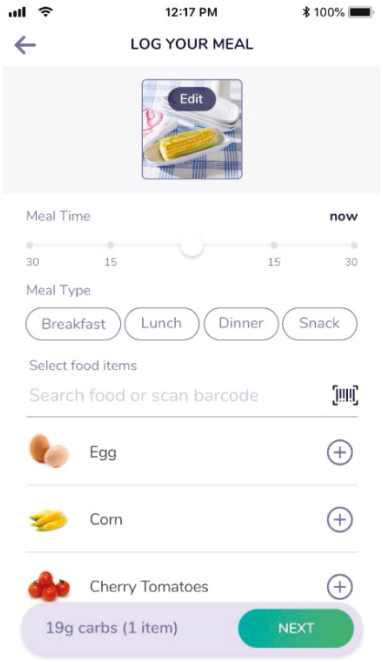
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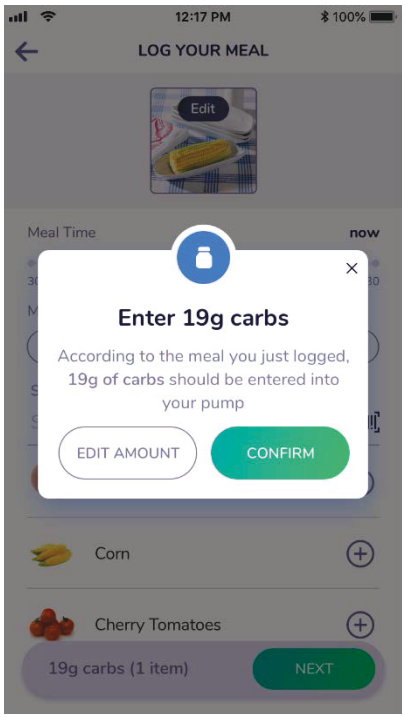
30
Meal Type
Breakfast
Lunch
Dinner
Snack
Select food items
Search food or scan barcode
Egg
Corn
Cherry Tomatoes
19g carbs (1 item)
NEXT


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 the investigator may override CHO estimate and provide their own based on investigator's 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)

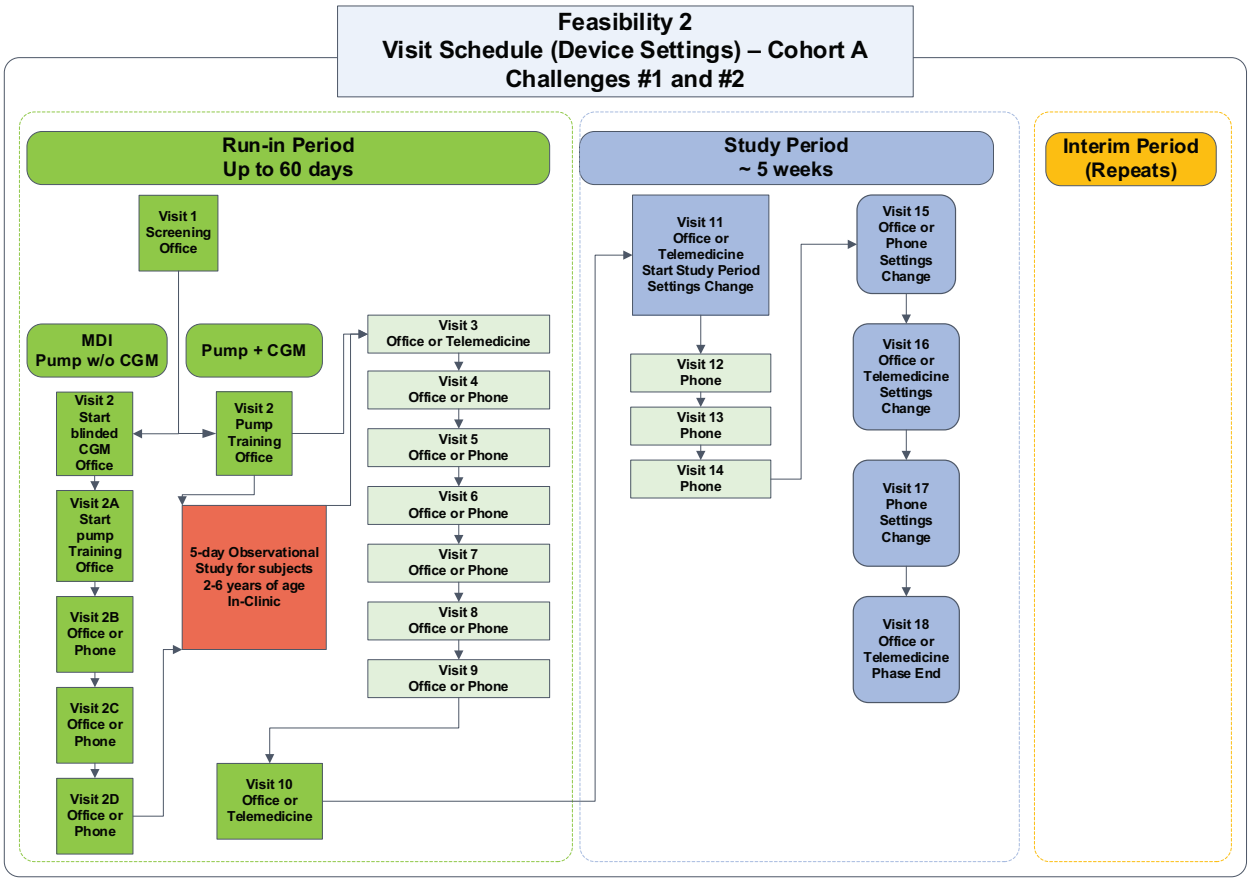
The In-Clinic observational study is intended for subjects 2-6 years of age and must be completed before they are allowed to proceed to Cohort A and Cohort C study procedures.

Study procedures for the observational study:

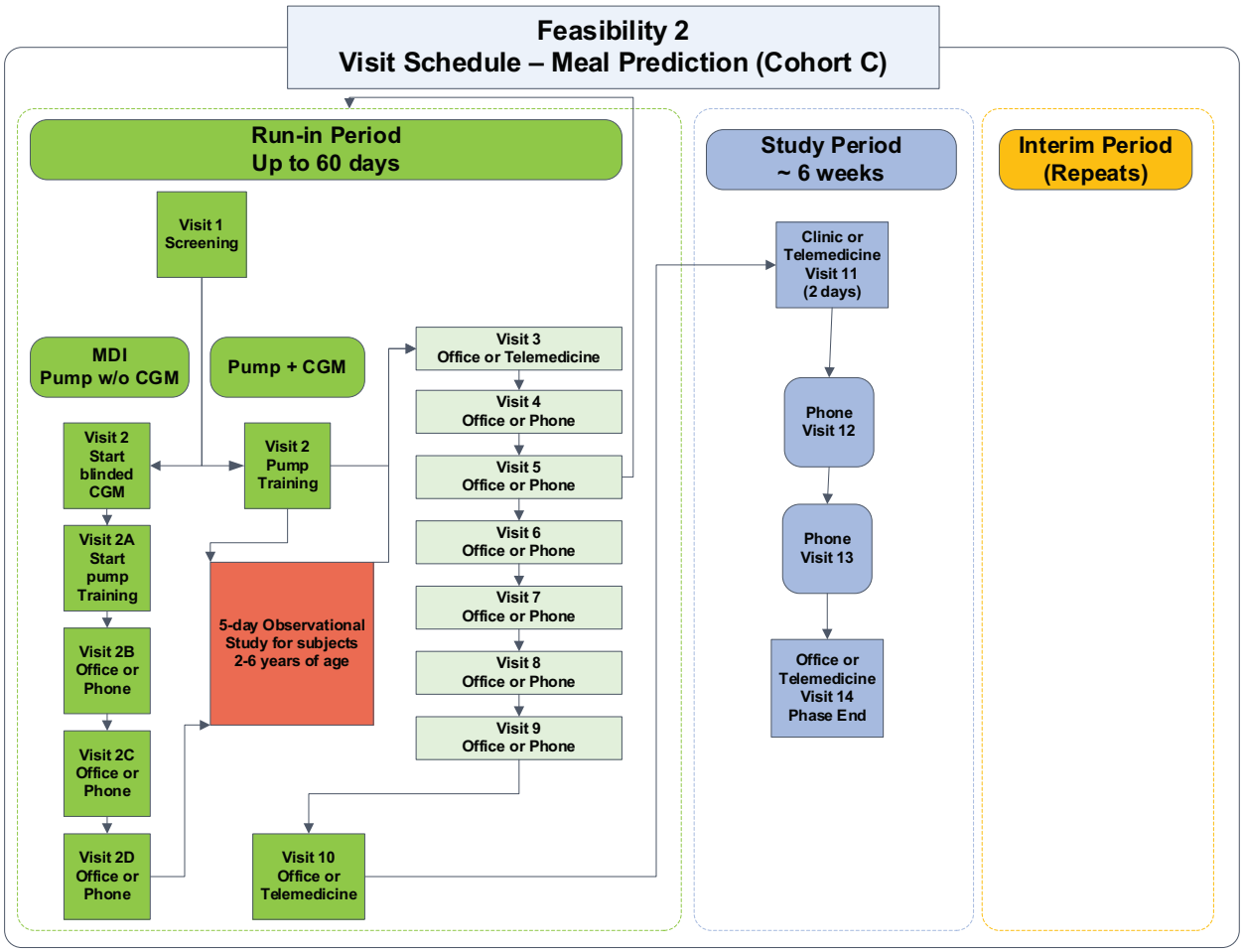
- After enrollment into the CIP326 study, subjects 2-6 years of age will initially use the AHCL system in Manual Mode. If subject was using 670G with Auto Mode at Screening, the subject may use Auto Mode with the Auto Correction feature off (i.e., not enabled).
- The in-clinic study will be conducted 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



6. Determination of Sample Size

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.

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.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

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

7.1.2 Clinical Investigation Plan (CIP) Deviations

All protocol deviations will be presented in the listings.

7.1.3 Analysis Sets

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.

7.2 General Methodology

No statistically powered analyses or hypothesis testing will be performed. Summary and descriptive statistics will be performed.

7.3 Center Pooling

Data will be pooled for analysis.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

All available data will be included in the data listings and tabulations. No imputation will be applied for the missing data.

7.5 Adjustments for Multiple Comparisons

Not applicable.

7.6 Demographic and Other 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.

7.7 Treatment Characteristics

Not applicable.

7.8 Interim Analyses

Not applicable.

7.9 Evaluation of Objectives

Descriptive Endpoints

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

7.9.1 Effectiveness Endpoints

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

Analyses in detail, if applicable:

- Overall percentage of time in severe hypoglycemia: SG <54 mg/dL
- Overall percentage of time in severe hyperglycemia: SG >250 mg/dL
- Overall mean SG and standard deviation of SG
- Postprandial analysis, up to 5h post-meal period
    - Postprandial SG mean, peak SG, SG nadir (post peak), AUC >180 mg/dL, and time in target (SG <70 mg/dL, SG <54 mg/dL, 70-180 mg/dL and > 180 mg/dL)

Descriptive subgroup analysis for the above analyses will be performed in the following cohorts:

Cohort A: Recommended Settings

Cohort C: Meal Prediction

7.9.2 ABL90

Descriptive statistics will be performed for ABL-90 glucose value vs. MBG and ABL-90 glucose value vs. SG after pairing. Metrics included 20/20% agreement (±20 mg/dL when MBG/SG less than (<) 80 mg/dL), bias and MARD.

7.10 Safety Evaluation

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

7.11 Health Outcomes Analyses

Not applicable.

7.12 Changes to Planned Analysis

Not applicable.

8. Validation Requirements

Level I or Level II validation are required for analysis output. Level I requires that the peer reviewer independently programs output and then compares the output with that generated by the original Statistical Programmer. Level II requires that the peer reviewer reviews the code; where appropriate, performs manual calculations or simple programming checks to verify the output.

9. References

Not Applicable.