Medtronic

**Clinical Investigation Plan**

| | |
|---|---|
| **Clinical Investigation Plan/Study Title** | Safety Evaluation of the Advanced Hybrid Closed Loop (AHCL) System in Type 1 Adult and Pediatric Subjects |
| **Clinical Investigation Plan Identifier** | 321 |
| **Study Product Name** | MiniMed™ 670G Insulin Pump System, version 4.0 AHCL<br>MiniMed™ 780G Insulin Pump System |
| **Sponsor** | USA:<br>Medtronic MiniMed, Inc.<br>("Medtronic")<br>18000 Devonshire St<br>Northridge, CA 91325<br>866.948.6633 |
| **Document Version** | D (Equivalent to FDA Version D.4) |
| **Document Version Date** | 22-APR-2021 |
| **Document Reference Number** | 10813115DOC |

**Confidentiality Statement**

# Table of Contents

# 1. Glossary

| Abbreviation | Definition |
|---|---|
| AE | Adverse Event |
| ADE | Adverse Device Effect |
| AHCL | Advanced Hybrid Closed Loop |
| ASIC | Application Specific Integrated Circuit |
| AUC | Area Under Curve |
| CEC | Clinical Events Committee |
| CFR | Code of Federal Regulations |
| CGM | Continuous Glucose Monitoring |
| CGMS | Continuous Glucose Monitoring System |
| 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 |
| GCP | Good Clinical Practice |
| HbA1c | Glycosylated hemoglobin |
| HIPAA | Health Insurance Portability and Accountability Act of 1996 |

| Abbreviation | Definition |
|---|---|
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| IDE | Investigational Device Exemption |
| IEC | Independent Ethic Committee |
| IFU | Instructions for Use |
| IRB | Institutional Review Board |
| IV | Intravenous |
| MC2 | Medtronic Core Clinical Solutions |
| NGSP | National Glycohemoglobin Standardization Program |
| OC-RDC | Oracle Clinical Remote Data Capture |
| PC | Personal Computer |
| QC | Quality Control |
| RF | Radio Frequency |
| SAE | Serious Adverse Event |
| SADE | Serious Adverse Device Events |
| SAP | Sensor Augmented Pump |
| SG | Sensor Glucose |
| SGV | Sensor Glucose Value |
| SMBG | Self-Monitoring of Blood Glucose |
| TAR | Time Above Range |
| TBR | Time Below Range |
| TDD | Total Daily Dose |
| TIR | Time in Target Range |

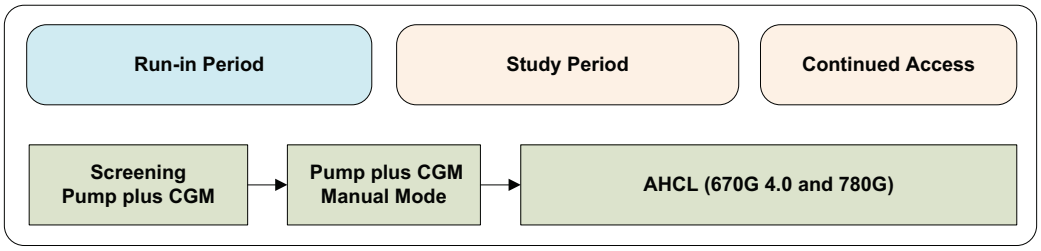
| Abbreviation | Definition |
|---|---|
| TLS | Transport Layer Security |
| TS | Technical Support |
| TSH | Thyroid-stimulating hormone |
| UADE | Unanticipated Adverse Device Effect |

## 2. Synopsis

| | |
|---|---|
| **Title** | Safety Evaluation of the Advanced Hybrid Closed Loop (AHCL) System in Type 1 Adult and Pediatric Subjects |
| **Investigational Device Exemption (IDE) Number** | G190075 |
| **Devices** | *Investigational devices*<br><br>**Hybrid Closed Loop (HCL) System:**<br>• MiniMed™ 670G Insulin Pump, version 4.0 AHCL (MMT-1740) - referred to as the study pump throughout this protocol<br>• MiniMed™ 780G Insulin Pump (MMT-1884)<br>• Guardian™ Sensor (4) Glucose Sensor (MMT-7040) - referred to as Guardian™ Sensor (4) throughout this protocol<br>• Guardian™ 4 Transmitter (MMT-7841)<br><br>*Non-Investigational/Exempt devices:*<br>• Guardian™ Sensor (3) Glucose Sensor (MMT-7020) - referred to as Guardian Sensor (3) throughout this protocol<br>• Guardian™ Link (3) Transmitter (MMT-7811)<br>• Guardian™ Link (3) Transmitter (MMT-7911)<br>• One-Press Serter (MMT-7512) - referred to as the Serter throughout this protocol<br>• Transmitter Charger (MMT-7715)<br>• Tester (MMT-7736L)<br>• Medtronic CareLink™ Personal software (MMT-7333) for clinical-– referred to as CareLink™ Personal software throughout this protocol; Class I exempt device<br>• Medtronic CareLink™ system software (MMT-7350) for clinical-referred to as CareLink™ system software; 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<br>• Abbott™* Precision Xtra™* Blood Glucose & Ketone Monitoring System to be used for blood ketone measurements only -referred to as the Precision Xtra™* ketone meter throughout this protocol<br>• Roche Accu-Chek™* Guide Link Blood Glucose Meter (08116083022M) - referred to as the Accu-Chek™ Guide Link study meter throughout this protocol<br>• MiniMed™ Clinical App (MMT-6103 Android; MMT-6104 IOS); Class II exempt device<br>• Medtronic CareLink™ Clinical App (MMT-6113 Android; MMT-6114 IOS); Class II exempt device<br>• Blue Adapter (ACC-1003911) |
| **Purpose** | The purpose of this study is to evaluate the safety of the Advanced Hybrid Closed Loop system (AHCL) in type 1 diabetes adult and pediatric subjects in a home setting. In addition, during the continued access period, all remaining subjects will receive the 780G insulin pump system to evaluate subject safety. |
| **Objective(s)** | The objective of the study is to collect in-home data using different versions of the AHCL system. For the initial part of the study, the 670G insulin pump system, version 4.0 AHCL, is being used; during the continued access period the 670G system will be replaced by the 780G insulin pump system. |
| **Study Design** | This study is a multi-center, single arm study in insulin-requiring adult and pediatric subjects with type 1 diabetes. The study period will be approximately 90 days long. It will be followed by a continued access period, during which subjects who have completed the entire study period will be given the opportunity to continue using investigational study devices until those devices are approved by the FDA for commercial use and are commercially available. They will be provided with a revised consent form and will sign it prior to continuing. Subjects who have already completed the study period will be given the opportunity to re-enter the study, if they elect to continue using the system. They will also sign the revised consent form, if required by IRB.<br><br>A total of up to 350 subjects (aged 7-75) will be enrolled at up to 30 investigational centers in the US in order to achieve the following:<br>• N=125 subjects 14-75 years of age with type 1 diabetes who will complete the study<br>• N=125 subjects 7-13 years of age with type 1 diabetes who will complete the study<br>Staged enrollment:<br>• Subjects 7-13 years of age may be enrolled after N=15 subjects 14 -75 years with type 1 diabetes have finished 30 days of the study period. The Data |

Monitoring Committee (DMC) will review the subjects' data. Enrollment of subjects 7-13 years of age may begin after DMC approval.




**Overview of the Run-in and Study Periods:**

## Run-in Period:

The run-in period will be used to allow subjects to become familiar with new study devices. During the run-in period study subjects will be using the Study Pump (MiniMed™ 670G, version 4.0 AHCL) with only the Sensor Augmented Pump function activated (i.e. SmartGuard™ Auto Mode is turned OFF). All subjects and their caregivers 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.

For study purposes, subjects will be instructed to perform SMBG if they are experiencing a severe hypoglycemic event, severe hyperglycemic event or Diabetic Ketoacidosis (DKA). 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. Reminders will be given to subjects at each office visit. Information about sensor insertions will be collected on an electronic case report form (eCRF) in the study database, i.e. insertion location.

**Regular Sized Dinner Challenge with Missed Meal Bolus**:

On the day prior to attending Visit 5, while subjects are in manual mode with CGM, they will be asked to consume dinner without administration of a Meal Bolus. The size of the meal should be their standard amount. Subjects will be asked to check BG at the start of the meal, as well as 2 hours and 4 hours after the meal and provide correction as necessary. Content and timing of the meal, along with BG values, will be recorded on the Meal Challenge log. This missed dinner bolus challenge should only start if the following conditions are met:

- SMBG at start of meal is $\leq$ 200 mg/dL

- Sensor glucose is available.

## Study Period:

Having met all criteria, subjects will proceed to the study period, which begins at Visit 5. All subjects will continue using the study pump and will use Auto Mode for 90 days during the study period.

Subjects should use the system in Auto Mode at all times. If subjects are exited from Auto Mode, they should try to mitigate and return to Auto Mode as soon as possible. During times when subjects are not able to use Auto Mode, they should use the remaining SmartGuard™ features (i.e. Suspend before Low).

**Setpoint in the study pump:**

The sponsor will provide guidance on the starting setpoint for subjects based on cohorts listed below:

- A minimum of 50 subjects 14 years of age and older will start the study with an Auto Basal setpoint of 100 mg/dL. They will switch to the 120 mg/dL setpoint after 45 days (± 5 days) of the study period.
- A minimum of 50 subjects 14 years of age and older will start the study with an Auto Basal setpoint of 120 mg/dL. They will switch to the 100 mg/dL setpoint after 45 days (± 5 days) of the study period.
- A minimum of 50 subjects 7-13 years of age will start the study with an Auto Basal setpoint of 100 mg/dL. They will switch to the 120 mg/dL setpoint after 45 days (± 5 days) of the study period.
- A minimum of 50 subjects 7-13 years of age will start the study with an Auto Basal setpoint of 120 mg/dL. They will switch to the 100 mg/dL setpoint after 45 days (± 5 days) of the study period

The investigator has the discretion to start subjects at either the 100 mg/dL or 120 mg/dL setpoints, while the Sponsor will ensure that the required minima for each setpoint are being met. Regardless of which setpoint is being set at the beginning of the study period, subjects should attempt to change the setpoint after 45 days (+/- 5 days) of the study period. For example: A subject who starts at the 100 mg/dL setpoint, should attempt to change the setpoint to 120 mg/dL after 45 days.

**Meal challenges (Run-in and Study period):**

The table below summarizes all meal challenges in the study.

- All meal challenges should only start if the following conditions are met:
  - SMBG at start of meal is $\leq$ 200 mg/dL

- Sensor glucose is available.

| Run-in period; Regular sized meal with missed Meal Bolus challenge | | | | |
|---|---|---|---|---|
| **Timing** | **Type of challenge** | **Day** | **Meal(s)** | **Notes** |
| Run-in | Missed Meal Bolus (regular sized meal) | Day prior to V5 | Regular sized Dinner | If the subject qualified to stay in Auto Mode during the Run-In Period, they must turn off Auto Mode for at least 6 hours prior to the start of the Missed Meal Bolus Challenge. |
| **Study period; Meal challenges** | | | | |
| **Setpoint** | **Type of challenge** | | **Meal(s)** | **Notes** |
| Study Period (100 mg/dL setpoint) | Large sized meals | Day 1 | Large sized Breakfast **and** Large sized Dinner | Meal composition, meal size and time of meal consumption should match meals at **Setpoint of 120 mg/dL.** |
| Study Period (100 mg/dL setpoint) | Large sized meals | Day 2 | Large sized Breakfast **and** Large sized Dinner | Meal composition, meal size and time of meal consumption should match meals at **Setpoint of 120 mg/dL.** |
| Study Period (100 mg/dL setpoint) | Large sized meal | Day 3 | Large sized Breakfast | Meal composition, meal size and time of meal consumption should match meal at **Setpoint of 120 mg/dL.** |
| | Missed Meal Bolus | | Regular sized dinner meal | Meal composition, meal size and time of meal consumption should match **Run-in period** meal |
| Study Period (100 mg/dL setpoint) | Missed Meal Bolus with Large sized meal | Day 4 | Large sized Dinner | Meal composition, meal size and time of meal consumption should match meal at **Setpoint of 120 mg/dL.** |
| Study Period (120 mg/dL setpoint) | Large sized meals | Day 1 | Large sized Breakfast **and** Large sized Dinner | Meal composition, meal size and time of meal consumption should match meals at **Setpoint of 100 mg/dL.** |

| | | | | |
|---|---|---|---|---|
| Study Period (120 mg/dL setpoint) | Large sized meals | Day 2 | Large sized Breakfast **and** Large sized Dinner | Meal composition, meal size and time of meal consumption should match meals at **Setpoint of 100 mg/dL.** |
| Study Period (120 mg/dL setpoint) | Large sized meal | Day 3 | Large sized Breakfast | Meal composition, meal size and time of meal consumption should match meal at **Setpoint of 100 mg/dL.** |
| | Missed Meal Bolus | | Regular sized dinner meal | Meal composition, meal size and time of meal consumption should match **Run-in period** meal |
| Study Period (120 mg/dL setpoint) | Missed Meal Bolus with Large sized meal | Day 4 | Large sized Dinner | Meal composition, meal size and time of meal consumption should match meal at **Setpoint of 100 mg/dL.** |

- **Regular Sized Dinner Challenge with Missed Meal Bolus**

  During the study period, once at each Auto Basal setpoint (i.e. 120 mg/dL and 100 md/dL) on Day 3 of the multi-day meal challenge, subjects will be asked to consume the ***same regular sized dinner that they had during the run-in period***. For example, if the dinner meal was consumed without an insulin bolus for the meal at 5 pm during the run-in period, that same dinner meal should be consumed at approximately the same time on Day 3 at each setpoint during the study period. Subjects will be asked to check BG at the start of the meal, as well as 2 hours and 4 hours after the start of the meal and provide correction as necessary. Details should be recorded, along with BG values, on the Meal Challenge log.

- **Large sized Meal Challenges:**

  On large sized meal challenge days, all subjects will be instructed to eat at least 1 meal with at least 50% higher caloric intake including 50% more carbohydrates and 50% higher in fat than what the subject reports that he/she usually eats. It is recommended that subjects eat food at restaurants or consume prepared meals (e.g. things like turkey and stuffing), which have not been eaten during the last month. A log will be used to collect information about type of food, name of restaurant (if applicable), confirmation that the meal eaten was different from any meal eaten within the last month and confirmation that meal size was at least 50% more than when subjects usually consume in terms of calories, carbohydrates and fat. The log should also contain the time and date of the meal, as well as confirmation that a BG was taken at the start of the meal, 2 hours after the start of the meal and 4 hours after the start of the meal. The timing of the meal challenges will be at the investigator's discretion. The subject's companion must be physically present in the same building, home or location (if not at home) during the meal challenge (and for 4 hours

following the start of the meal), must be able to check SMBG (in case it is needed) and give glucose/administer glucagon as needed. This challenge will include a missed Meal Bolus on Day 4. See Table above.

**Exercise Challenges (Study Period):**

The following exercise challenges are required during the study period:

- 3 consecutive days of exercise challenge at setpoint of 100 mg/dL
- 3 consecutive days of exercise challenge at setpoint of 120 mg/dL

- **Exercise Challenges Details**

  On exercise challenge days, all subjects will be required to engage in 1-2 hours of physical exercise each day. During this time, subjects should use the Auto Basal setpoint target of 100 mg/dL or 120 mg/dL (depending on what is required at that time of the study period), unless a subject prefers to use the 150 mg/dL target before, during and immediately after the exercise challenges. For the remainder of days, the temporary target will be started at the Investigator's discretion. A log will be used to collect information about exercise type, date, time (start and finish of exercise), duration and name of the companion. The log should also contain confirmation that SMBG was done at the beginning of exercise, as well as 2 and 4 hours after the start of the exercise. The timing of the exercise challenge will be at the investigator's discretion. A photograph should be taken on each day of the exercise to indicate that exercise took place. Subjects may also use a Smart Phone application to document their exercise. The subject's companion must be physically present in the same building, home or location (if not at home) during the exercise challenge, must be able to check SMBG (in case it is needed) and give glucose/administer glucagon as needed. Examples of types of exercise include but are not limited to:

  - Running
  - Cycling
  - Swimming
  - Hiking
  - Walking
  - Games (e.g. Wii interactive video games)
  - Indoor/outdoor playground (Pediatric subjects)
  - Yoga/stretching
  - Any sport activity which involves ongoing physical movement (i.e., tennis, golf, basketball, tee ball or volleyball)
  - Dancing

- Zumba
- Aerobics
- Spinning

**Continued Access Period:**

At the end of the study period, subjects will have the opportunity to continue using the AHCL system at home until the Sponsor receives FDA approval to commercialize the products and the system is commercially available. During the continued access period, subjects will be asked to use the system as intended and to upload device data on a weekly basis. See Visit Schedule tables for frequency of device uploading. Office visits will be required at 3 month intervals.

**Continued Access Period expansion:**

During the continued access period, all participating subjects will transition from the 670G system, version 4.0 AHCL, to the 780G system which features Bluetooth® connectivity. The CGM used with 780G will be Guardian™ 4 Transmitter with the Guardian™ Sensor (4).

Subjects will continue to use the 780G system at home until the sponsor notifies sites to end subjects' study participation.

The MiniMed™ Clinical App and the Medtronic CareLink™ Clinical App will be used by subjects when they are available.

**SMBG recommendations for 670G system, version 4.0 AHCL**:
Typically, one SMBG is required every 12 hours for calibration. Routine SMBG is not required. 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 is not low) or high and if they are experiencing a severe hypoglycemic event, a severe hyperglycemic event or DKA.

**SMBG recommendations for 780G system:**
With the 780G system and the Guardian™ 4 transmitter, calibration is not required. However, a calibration is optional and will occur any time a BG is entered. 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 is not low) or high including a severe hypoglycemic event, a severe hyperglycemic event or DKA.

**Companions:**
Subjects will be required to have a companion who resides (or will live) in the same building (or home) during the proposed study at night, and also to be physically present in the same building, home or location (if not at home) during the exercise and meal challenges. A companion should be present during meal challenges and for 4 hours following the start of the meal. Companions should be able to check SMBG (in case it is needed), give glucose or administer glucagon.

| | |
|---|---|
| **Sample Size and Investigational Sites** | A total of up to 350 subjects will be enrolled at up to 30 investigational centers across the US in order to have 250 subjects who complete the study period. The number of subjects enrolled in the continued access period depends on the subjects' desire to continue. |
| **Duration** | The study is anticipated to last no longer than 36 months from investigational center initiation to completion of all data entry and monitoring procedures. The study will target 6 months to complete subject enrollment. Subjects can expect to participate for approximately 4-5 months between the run-in period and study period. The continued access period may lengthen the overall duration of the study considerably. |
| **Inclusion Criteria** | *General Inclusion Criteria*<br>1. Subject is age 7-75 years at time of Screening<br>2. Subjects 14-75 years of age: A clinical diagnosis of type 1 diabetes for 2 years or more as determined via medical record or source documentation by an individual qualified to make a medical diagnosis<br>3. Subjects 7-13 years of age: A clinical diagnosis of type 1 diabetes for 1 year or more as determined via medical record or source documentation by an individual qualified to make a medical diagnosis<br>4. Individual of legal age is capable of providing consent.<br>*Study-specific inclusion criteria*<br>5. Subject is willing to perform $\geqslant$ 4 finger stick blood glucose measurements daily<br>6. Subject is willing to perform required sensor calibrations<br>7. Subject is willing to wear the system continuously throughout the study<br>8. Subject must have a minimum daily insulin requirement (Total Daily Dose) of greater than or equal to 8 units<br>9. Subject has a Glycosylated hemoglobin (HbA1c) less than 10% (as processed by Central Lab) at time of Screening visit<br>**Note: All HbA1c blood specimens will be sent to and tested by a NGSP certified Central Laboratory. HbA1c testing must follow National Glycohemoglobin Standardization Program (NGSP) standards.**<br>10. Subject has TSH in the normal range OR if the TSH is out of normal reference range the Free T3 is below or within the lab's reference range and Free T4 is within the normal reference range.<br>11. Pump therapy for greater than 6 months prior to screening (with or without CGM experience)<br>12. 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). A companion or caregiver should also be available during exercise challenges in the same building, home or location (if not at home). This requirement may be verified by subject report at screening visit.<br>13. Subject willing to upload data from the study pump, must have Internet access and a computer system that meets the requirements for uploading the study pump<br>14. If subject has celiac disease, it has been adequately treated as determined by the investigator |

| | |
|---|---|
| | 15. Subject is 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)<br>○ Humalog™* (insulin lispro injection)<br>○ NovoLog™* (insulin aspart)<br>16. Subjects with history of cardiovascular event 1 year or more from the time of screening must have an EKG within 6 months prior to screening or during screening. If subject has an abnormal EKG, participation is allowed if there is clearance from a cardiologist<br>17. Subjects with the 3 or more cardiovascular risk factors listed below must have an EKG within 6 months prior to screening or during screening. If subject has an abnormal EKG, participation is allowed if there is clearance from a cardiologist<br>a. Cardiovascular risk factors include:<br>○ Age >35 years<br>○ Type 1 diabetes of >15 years' duration<br>○ Presence of any additional risk factor for coronary artery disease<br>○ Presence of microvascular disease (proliferative retinopathy or nephropathy, including microalbuminuria)<br>○ Presence of peripheral vascular disease<br>○ Presence of autonomic neuropathy<br>18. Subjects with history of cardiovascular event 1 year or more from the time of screening must have a stress test within 6 months prior to screening or during run in period. If subject fails stress test, participation is allowed if there is clearance from a cardiologist |
| **Exclusion Criteria** | 1. Subject has a history of 1 or more episodes of severe hypoglycemia, which resulted in any the following during the 6 months prior to Screening:<br>a. Medical assistance (i.e. Paramedics, Emergency Room (ER) or Hospitalization)<br>b. Coma<br>c. Seizures<br>2. Subject has been hospitalized or has visited the ER in the 6 months prior to Screening resulting in a **primary diagnosis** of uncontrolled diabetes<br>3. Subject has had Diabetic Ketoacidosis (DKA) in the 6 months prior to Screening.<br>4. Subject has Hypoglycemia Unawareness, measured by the Gold questionnaire as ≥4 (Gold, MacLeod et al. 1994) at Screening<br>5. Subject is unable to tolerate tape adhesive in the area of sensor placement<br>6. Subject has any unresolved adverse skin condition in the area of sensor placement (e.g., psoriasis, dermatitis herpetiformis, rash, Staphylococcus infection)<br>7. Women of child-bearing potential who have a positive pregnancy test at Screening or plan to become pregnant during the course of the study<br>8. 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.<br>9. Subject has had any of the following cardiovascular events within 1 year of screening: myocardial infarction, unstable angina, coronary artery bypass surgery, |

| | |
|---|---|
| | coronary artery stenting, transient ischemic attack, cerebrovascular accident, angina, congestive heart failure, ventricular rhythm disturbances or thromboembolic disease<br>10. Subject is being treated for hyperthyroidism at time of Screening<br>11. Subject has a diagnosis of adrenal insufficiency<br>12. Subject has taken any oral, injectable, or intravenous (IV) glucocorticoids within 8 weeks from time of Screening, or plans to take any oral, injectable, or IV glucocorticoids during the course of the study<br>13. Subject is actively participating in an investigational study (drug or device) wherein he/she has received treatment from an investigational study drug or investigational study device in the last 2 weeks<br>14. Subject is currently abusing illicit drugs<br>15. Subject is currently abusing marijuana<br>16. Subject is currently abusing prescription drugs<br>17. Subject is currently abusing alcohol<br>18. 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 Screening<br>19. 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<br>20. Subject has elective surgery planned that requires general anesthesia during the course of the study<br>21. Subject has a sickle cell disease, hemoglobinopathy; or has received red blood cell transfusion or erythropoietin within 3 months prior to time of Screening<br>22. Subject plans to receive red blood cell transfusion or erythropoietin over the course of study participation<br>23. Subject diagnosed with current eating disorder such as anorexia or bulimia<br>24. Subject has been diagnosed with chronic kidney disease that results in chronic anemia<br>25. Subject has a hematocrit that is below the normal reference range of lab used.<br>26. Subject is on dialysis<br>27. Subject has serum creatinine of >2 mg/dL.<br>28. Research staff involved with the study. |
| **Study Visit Schedule** | **<u>Run-in Period Visits: To be completed in 45 days</u>**<br>• Screening Visit 1 (Office): Consent and Screening<br>• Run-in Visit 2 (Office): Day 7 after Visit 1 (+3 days)<br>○ ***Eligibility has been confirmed***<br>○ Start Study Pump<br>▪ Pump Training<br>○ Start CGM (if using SAP prior to Screening)<br>▪ If SAP using Suspend on Low/Predictive Suspend before Low prior to Screening, those features may be used from Visit 2<br>▪ CGM Training, if applicable |

- Run-in Visit 3 (Office): Day 0 after Visit 2 (+7 days)
  - Start CGM (if not already started at Visit 2)
  - Start 2 weeks of measured sensor wear period
    - System is used in manual Mode by subjects who are not using Auto Mode with 670G at Screening
      - SmartGuard™ features (Suspend on Low, Predictive Suspend before Low) may be activated
    - SAP subjects using Auto Mode with 670G at Screening may use Auto Mode:
      - Auto Correction must be turned off
      - Auto Basal setpoint must be set to 120 mg/dL

- Run-in Visit 4: Office Visit Day 14 after Visit 3 (+7 days)
  - Confirm run-in CGM data:
    - Subject demonstrates sensor compliance (i.e. 3,225 glucose sensor data points equivalent to 11.2 days of sensor wear)
  - Continue using study pump with CGM
      - SmartGuard™ features (Suspend on Low, Predictive Suspend before Low) may be activated
    - SAP subjects using Auto Mode with 670G at Screening may use Auto Mode:
      - Auto Correction must be turned off
      - Auto Basal setpoint must be set to 120 mg/dL

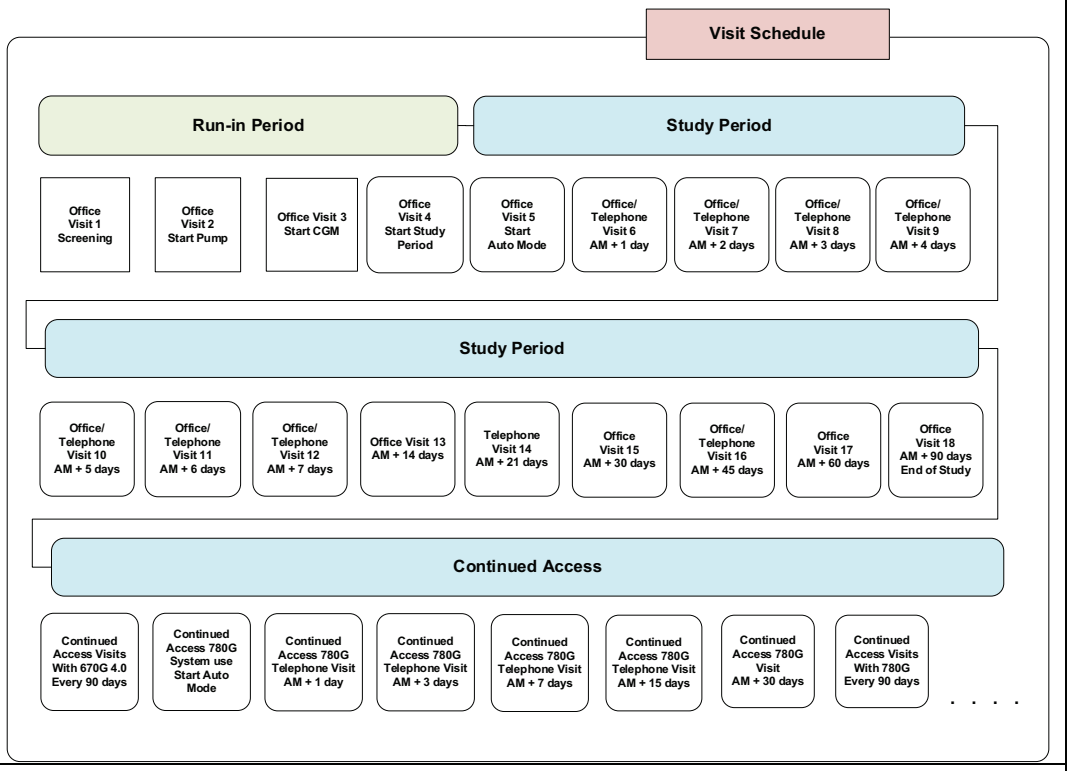
**Study Period Visits:**

- Visit 5: Office Visit 7-14 days after Visit 4
  - Start AHCL (e.g. Auto Mode feature turned ON with auto-correction)
- Visit 6: Telephone Visit (option of office visit) – Day 1 after Visit 5
- Visit 7: Telephone Visit (option of office visit) – Day 2 after Visit 5
- Visit 8: Telephone Visit (option of office visit) – Day 3 after Visit 5
- Visit 9: Telephone Visit (option of office visit) – Day 4 after Visit 5
- Visit 10: Telephone Visit (option of office visit) – Day 5 after Visit 5
- Visit 11: Telephone Visit (option of office visit) – Day 6 after Visit 5
- Visit 12: Telephone Visit (option of office visit) – Day 7 after Visit 5
- Visit 13: Office Visit - Day 14 after Visit 5 (± 3 days)
- Visit 14: Telephone Visit Day 21 after Visit 5 (± 3 days)
- Visit 15: Office Visit - Day 30 after Visit 5 (± 5 days)
- Visit 16: Telephone Visit (option of office visit) – Day 45 after Visit 5 (± 5 days)
  - Change Glucose Target
- Visit 17: Office Visit – Day 60 after Visit 5 (± 7 days)
- Visit 18: Office Visit - Day 90 after Visit 5 (± 7 days)
  - End of Study (EOS) Period

**Continued Access Period Visits:**

- Continued access visits will take place at 90 day (± 14 days) intervals from the last study period visit (Visit 18) – Office or Telemedicine Visit.
  - If the subject is entering continued access directly from the study period, Visit 18 and the first continued access visit may occur on the same day.
  - If the subject has previously completed the study period and exited the study, continued access visits will begin following the signing of the current ICF/Assent.
  - Subjects are instructed to continue uploading study device data weekly
    - It is recommended that an HbA1c sample is drawn and tested at each quarterly visit. If drawn, the test must be run by the Central lab.

- 780G system use Start - Office Visit or Telemedicine Visit
  - Start of 780G system use
  - Dispense 780G system
  - Train subjects on 780G system use
  - Start SmartGuard™ (Auto Mode) with all features turned on
- 780G - Telephone Visit –
  Day 1 after 780G System use Start Visit
  - Check for adverse events
  - Check for device deficiencies
  - Review CareLink data
- 780G - Telephone Visit –
  Day 3 after 780G System use Start Visit
  - Check for adverse events
  - Check for device deficiencies
  - Review CareLink data
- 780G - Telephone Visit –
  Day 7 after 780G System use Start Visit (± 2 days)
  - Check for adverse events
  - Check for device deficiencies
  - Review CareLink data
- 780G - Telephone Visit –
  Day 15 after 780G System use Start Visit (± 3 days)
  - Check for adverse events
  - Check for device deficiencies
- 780G - Office or Telemedicine Visit –
  Day 30 after 780G System use Start Visit (+ 7 days)
  - Check for adverse events
  - Check for device deficiencies
- Subsequent visits following receipt of the 780G system will take place at 90 day intervals (± 14 days) from the initial 780G visit (780G system use start) until Sponsor announces the end of the study. The subject will remain on the 780G system for the remainder of the Continued Access Period. These visits can be Office or Telemedicine Visits.

| | |
|---|---|
| | ○ Subjects are instructed to continue uploading study device data weekly<br>▪ It is recommended that an HbA1c sample is drawn and tested at each quarterly visit. If drawn, the test must be run by the Central lab.<br>  |
| **Safety Monitoring/ Risk Analysis** | Safety monitoring/risk analysis details are outlined in Section 9.7. |
| **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. |
| **Study Stopping Rules for Entire Study** | During the study period, the following steps will be taken for:<br>• Unanticipated Adverse Device Effects (UADE)<br>• Device related Diabetic Ketoacidosis (DKA)<br>• Device related Severe hypoglycemia |

| | |
|---|---|
| | 1. Site will notify the sponsor within approximately 24 hours of receiving knowledge of the event.<br>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.<br>3. Clinical Events Committee (CEC) is to review the event within 7 days from the time that the sponsor is notified.<br>4. CEC will provide recommendation to the sponsor on the following:<br>a) If enrollment and study may continue<br>b) If enrollment should be stopped; enrolled subjects are still allowed to continue in study<br>c) If the entire study must be stopped, including subjects who have already received study devices. |
| **Subject Stopping Rules** | Any event of DKA or severe hypoglycemia will result in withdrawal of subject from study, if it is related to the use of AHCL Auto Mode. |
| **Statistical Analysis for Endpoints and Hypothesis** | *During Study Period*<br>**Descriptive Endpoints**<br>• The mean change in HbA1c will be presented from baseline to EOS Period<br>• Change of Total Daily Dose (TDD) of insulin from baseline to EOS Period<br>• Change of weight from baseline to EOS Period<br>• Time spent in Auto Mode versus time spent in Manual Mode<br>• Time in different range (% of SG): SG < 50, 54, 60, 70 mg/dL, SG > 140, 180, 250 mg/dL, 350 mg/dL<br>• Number of Events, Area Under Curve (AUC) and Time in the hyperglycemic range: sensor glucose (SG) > 140, 180, 250, 350 mg/dL<br>• Number of Events, AUC and Time in the hypoglycemic range: SG < 50, 54, 60, and 70 mg/dL<br>○ Change in BG values during meal challenge (BG prior and BG 2 hours after meal)<br>○ Change in % of time in euglycemia (70-180 mg/dL) during meal challenge, prior and 2 hours after meal<br>○ Difference in AUC during meal challenge prior and 2 hours after meal<br>• Subgroup analysis will be performed for:<br>○ Age<br>▪ 7-13<br>▪ 14-75<br>○ Setpoint<br>▪ 100 mg/dL<br>▪ 120 mg/dL<br>○ Temp Target usage<br>▪ Yes<br>▪ No |

*During Study Period and Continued Access*

**Safety Data Summarized**

- Serious Adverse Events (SAE)
- Serious Adverse Device Effects (SADE)
- Unanticipated Adverse Device Effects (UADE)
- Incidence of Severe Hypoglycemia
- Incidence of DKA

*During Continued Access Period*

**Descriptive Endpoints for Continued Access**

- Time in Target Range (TIR, 70 – 180 mg/dL)
- Time Below Range (TBR, SG < 70 mg/dL)
- Time Above Range (TAR, SG > 180 mg/dL)
- Time in different range (% of SG): SG < 54, 60 mg/dL, SG > 140, 250 mg/dL, 350 mg/dL
- Number of Events, Area Under Curve (AUC) and Time in the hyperglycemic range: sensor glucose (SG) > 140, 180, 250, 350 mg/dL
- Number of Events, AUC and Time in the hypoglycemic range: SG < 54, 60, and 70 mg/dL
- Time spent in Auto Mode versus time spent in Manual Mode
- The mean change in HbA1c , if applicable
- Change of Total Daily Dose (TDD) of insulin

*Subject Feedback*

Descriptive summary will be used to characterize study questionnaire results. Refer to CIP321 AHCL Questionnaire Guide for administration details.

*Exploratory Analysis for Study Period*

**Analysis of Primary Safety Endpoint**

The overall mean difference of the change in HbA1c from baseline to end of 3-month study period. The goal is to show simple superiority in reducing HbA1c from baseline to end of 3-month study period.

**Analysis of Primary Effectiveness Endpoint**

| | |
|---|---|
| | The primary effectiveness endpoint is change in % of time in euglycemia (70 – 180 mg/dL).<br><br>The overall mean change in % of time in euglycemia (70-180 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).<br><br>**Analysis of Secondary Effectiveness Endpoint**<br><br>The secondary effectiveness endpoints are hierarchically ordered and will be evaluated in the fixed sequence from endpoint 1 to 3 during the study period.<br><br>• Secondary Endpoint: % of Time in Hyperglycemia (> 180 mg/dL)<br><br>The overall mean change in % of time in hyperglycemia (> 180 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).<br><br>• Secondary Endpoint: % of Time in Hyperglycemia (> 140 mg/dL)<br><br>The overall mean change in % of time in hyperglycemia (> 140 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).<br><br>• Secondary Endpoint: % of Time in Hypoglycemia (< 70 mg/dL)<br><br>The overall mean change in % time in hypoglycemia (< 70 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided). |
| **Final Report** | **<u>Study Phase Final Report for Subjects 14-75 Years Old</u>**<br><br>A study phase final report will be generated once the 14-75 years old cohort have completed the study period. Descriptive and exploratory endpoints and safety data for 14-75 years old subjects will be summarized and presented in the final report. This report will be sent to FDA as part of the Pre-Market Application before the report for pediatric subjects 7-13 years of age will be submitted.<br><br>**<u>Continued Access Phase Final Report for Subjects 14-75 Years Old</u>**<br><br>An addendum continuation phase final report will be generated once the 14-75 year old cohort have completed the continuation phase visits. Descriptive endpoints, subject |

| | |
|---|---|
| | feedback, and safety data for the continuation phase will be summarized and presented in the final report.<br><br>**Study Phase Final Report for Subjects 7-13 Years Old**<br><br>A separate study phase final report will be generated once the 7-13 years old cohort have completed the study period. Descriptive and exploratory endpoints and safety data for 7-13 years old subjects will be summarized and presented in the final report. This report will be sent to FDA as part of the Pre-Market Application after the report for subjects 14-75 years has been submitted.<br><br>**Continued Access Phase Final Report for Subjects 7-13 Years Old**<br><br>An addendum continuation phase final report will be generated once the 7-13 year old cohort have completed the continuation phase visits. Descriptive endpoints, subject feedback, and safety data for the continuation phase will be summarized and presented in the final report. |

# 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, 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.

Medtronic has conducted numerous studies to evaluate hybrid closed loop technology. After completing a variety of feasibility studies with the hybrid closed loop algorithm, 2 separate pivotal trials were initiated to show that the use of hybrid closed loop technology (MiniMed™ 670G system) is safe in both adults and children over the age of 2.

In the young adult/adult pivotal study, patients aged 14 to 75 years with type 1 diabetes were recruited from 10 centers (9 in the United States, 1 in Israel)

The pediatric pivotal study was conducted as an at-home, multi-center study, which enrolled 162 participants ages 2-13 years of age. Patients were recruited at 11 centers (10 in the United States, 1 in Israel). The study was identical in design to the young adult/adult pivotal study.

Study results in the pediatric study mirrored data from the pivotal trial of the system in adults and adolescents (14 and above), showing patients spent more time in euglycemic range, experienced less glycemic variability, had less exposure to hypoglycemia and hyperglycemia and significantly reduced HbA1c compared to baseline data where they used sensor-augmented pumps. No episodes of severe hypoglycemia or diabetic ketoacidosis and no serious device-related adverse events were reported.

The Advanced Hybrid Closed Loop system (AHCL) is based on the MiniMed™ 670G hybrid closed loop system currently in commercial distribution in the United States, Canada and Europe but includes enhancements intended to reduce the frequency of Auto Mode exits and decrease the time spent in hyperglycemia relative to the current MiniMed™ 670G system. Additionally, patients using the AHCL system will not be required to confirm sensor glucose using SMBG measurement before making therapy adjustments based on displayed sensor glucose values. This investigation is designed to confirm that

these enhancements to the system's closed loop algorithm and the elimination of the requirement for confirmatory SMBG measurements do not have any adverse impact on safety and efficacy.

During the continued access period, subjects will be using the 780G insulin pump, which may include a new transmitter (Guardian™ 4 transmitter) that contains a new sensor algorithm that converts raw signals into sensor glucose values without the need for entry of fingerstick calibration values. The accuracy of the sensor glucose values provided using this new algorithm was characterized by applying the algorithm to raw data collected during a prospective investigation that included frequent sample testing with either YSI or SMBG reference values. In silico modeling confirmed that glycemic outcomes during 780G Auto Mode operation using sensor values produced by the new sensor algorithm were similar to the outcomes when using the current algorithm which requires at least two calibrations per day.

The algorithm in the 780G insulin pump is functionally equivalent to the algorithm in the 670G, version 4.0 AHCL, insulin pump. Aside from a number of differences in the user interface, the method of telemetry is different in the 780G system, because it utilizes Bluetooth communication between devices and to upload pump data to CareLink™ via a smartphone device. The user experience is enhanced through the availability of smartphone apps that allow for uploading of pump data to CareLink™ and the remote monitoring of data that has been uploaded to CareLink™.

## 3.2. Purpose

The purpose of this study is to evaluate the safety of the Advanced Hybrid Closed Loop system (AHCL) in type 1 diabetes adult and pediatric subjects in a home setting. In addition, during the continued access period, all remaining subjects will receive the 780G insulin pump system to evaluate subject safety.

# 4. Objectives and Endpoints

## 4.1. Objectives

### 4.1.1. Primary Objective(s)

The objective of the study is to collect in-home data using different versions of the AHCL system. For the initial part of the study, the 670G insulin pump system, version 4.0 AHCL, is being used; during the continued access period the 670G system will be replaced by the 780G insulin pump system.

## 4.2. Endpoints

### 4.2.1. Descriptive Endpoints – During Study Period

- The mean change in HbA1c will be presented from baseline to EOS Period
- Change of Total Daily Dose (TDD) of insulin from baseline to EOS Period
- Change of weight from baseline to EOS Period
- Time spent in Auto Mode versus time spent in Manual Mode

- Time in different range (% of SG): SG < 50, 54, 60, 70 mg/dL, SG > 140, 180, 250 mg/dL, 350 mg/dL
- Number of Events, Area Under Curve (AUC) and Time in the hyperglycemic range: sensor glucose (SG) > 140, 180, 250, 350 mg/dL
- Number of Events, AUC and Time in the hypoglycemic range: SG < 50, 54, 60, and 70 mg/dL
    - Change in BG values during meal challenge (BG prior and BG 2 hours after meal)
    - Change in % of time in euglycemia (70-180 mg/dL) during meal challenge, prior and 2 hours after meal
    - Difference in AUC during meal challenge prior and 2 hours after meal
- Subgroup analysis will be performed for:
    - Age
        - 7-13
        - 14-75
    - Setpoint
        - 100 mg/dL
        - 120 mg/dL
    - Temp Target usage
        - Yes
        - No

### 4.2.2. Descriptive Endpoints – During Continued Access Period

**Descriptive Endpoints for Continued Access**

- Time in Target Range (TIR, 70 – 180 mg/dL)
- Time Below Range (TBR, SG < 70 mg/dL)
- Time Above Range (TAR, SG > 180 mg/dL)
- Time in different range (% of SG): SG < 54, 60 mg/dL, SG > 140, 250 mg/dL, 350 mg/dL
- Number of Events, Area Under Curve (AUC) and Time in the hyperglycemic range: sensor glucose (SG) > 140, 180, 250, 350 mg/dL
- Number of Events, AUC and Time in the hypoglycemic range: SG < 54, 60, and 70 mg/dL
- Time spent in Auto Mode versus time spent in Manual Mode
- The mean change in HbA1c , if applicable
- Change of Total Daily Dose (TDD) of insulin

### 4.2.3. Safety Endpoint – During Study Period and Continued Access

- Serious Adverse Events (SAE)
- Serious Adverse Device Effects (SADE)
- Unanticipated Adverse Device Effects (UADE)
- Incidence of Severe Hypoglycemia
- Incidence of DKA

### 4.2.4. Device Deficiencies – During Study Period and Continued Access

Descriptive summary will be used to characterize device deficiencies:

- All reports of device issues.

### 4.2.5. Subject Feedback

Descriptive summary will be used to characterize study questionnaire results. Refer to CIP321 AHCL Questionnaire Guide for administration details.

## 4.3. Exploratory Analysis for Study Period

### 4.3.1. Analysis of Primary Safety Endpoint

The overall mean difference of the change in HbA1c from baseline to end of 3-month study period. The goal is to show simple superiority in reducing HbA1c from baseline to end of 3-month study period.

### 4.3.2. Analysis of Primary Effectiveness Endpoint

The primary effectiveness endpoint is change in % of time in euglycemia (70 – 180 mg/dL).

The overall mean change in % of time in euglycemia (70-180 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

### 4.3.3. Analysis of Secondary Effectiveness Endpoint

The secondary effectiveness endpoints are hierarchically ordered and will be evaluated in the fixed sequence from endpoint 1 to 3 during the study period.

- Secondary Endpoint: % of Time in Hyperglycemia (> 180 mg/dL)

The overall mean change in % of time in hyperglycemia (> 180 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

- Secondary Endpoint: % of Time in Hyperglycemia (> 140 mg/dL)

The overall mean change in % of time in hyperglycemia (> 140 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

- Secondary Endpoint: % of Time in Hypoglycemia (< 70 mg/dL)

The overall mean change in % time in hypoglycemia (< 70 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

# 5. Study Design

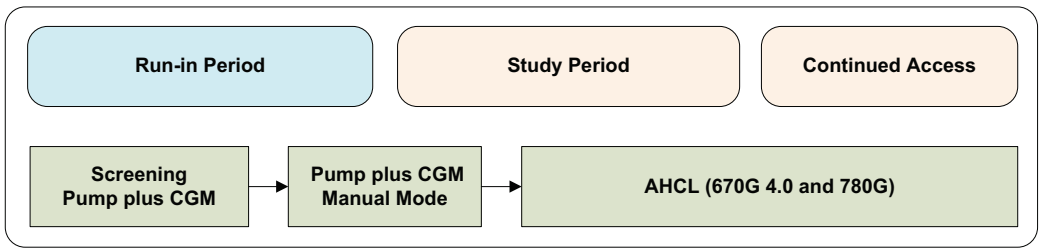
This study is a multi-center, single arm study in insulin-requiring adult and pediatric subjects with type 1 diabetes. The study period will be approximately 90 days long. It will be followed by a continued access period, during which subjects who have completed the entire study period will be given the opportunity to continue using investigational study devices until those devices are approved by the FDA for commercial use and are commercially available. They will be provided with a revised consent form and will sign it prior to continuing. Subjects who have already completed the study period will be given the opportunity to re-enter the study, if they elect to continue using the system. They will also sign the revised consent form, if required by IRB.

A total of up to 350 subjects (aged 7-75) will be enrolled at up to 30 investigational centers in the US in order to achieve the following:

- N=125 subjects 14-75 years of age with type 1 diabetes who will complete the study
- N=125 subjects 7-13 years of age with type 1 diabetes who will complete the study

Staged enrollment:

- Subjects 7-13 years of age may be enrolled after N=15 subjects 14 -75 years with type 1 diabetes have finished 30 days of the study period. The Data Monitoring Committee (DMC) will review the subjects' data. Enrollment of subjects 7-13 years of age may begin after DMC approval.




**Overview of the Run-in and Study Periods:**

## Run-in Period:

The run-in period will be used to allow subjects to become familiar with new study devices. During the run-in period study subjects will be using the Study Pump (MiniMed™ 670G, version 4.0 AHCL) with only the Sensor Augmented Pump function activated (i.e. SmartGuard™ Auto Mode is turned OFF). All subjects and their caregivers 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.

For study purposes, subjects will be instructed to perform SMBG if they are experiencing a severe hypoglycemic event, severe hyperglycemic event or Diabetic Ketoacidosis (DKA). 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. Reminders will be given to subjects at each office visit. Information about sensor insertions will be collected on an electronic case report form (eCRF) in the study database, i.e. insertion location.

**Regular Sized Dinner Challenge with Missed Meal Bolus**:

On the day prior to attending Visit 5, while subjects are in manual mode with CGM, they will be asked to consume dinner without administration of a Meal Bolus. The size of the meal should be their standard amount. Subjects will be asked to check BG at the start of the meal, as well as 2 hours and 4 hours after the meal and provide correction as necessary. Content and timing of the meal, along with BG values, will be recorded on the Meal Challenge log. This missed dinner bolus challenge should only start if the following conditions are met:

- SMBG at start of meal is $\leq$ 200 mg/dL
- Sensor glucose is available.

## Study Period:

Having met all criteria, subjects will proceed to the study period, which begins at Visit 5. All subjects will continue using the study pump and will use Auto Mode for 90 days during the study period.

Subjects should use the system in Auto Mode at all times. If subjects are exited from Auto Mode, they should try to mitigate and return to Auto Mode as soon as possible. During times when subjects are not able to use Auto Mode, they should use the remaining SmartGuard™ features (i.e. Suspend before Low).

**Setpoint in the study pump:**

The sponsor will provide guidance on the starting setpoint for subjects based on cohorts listed below:

- A minimum of 50 subjects 14 years of age and older will start the study with an Auto Basal setpoint of 100 mg/dL. They will switch to the 120 mg/dL setpoint after 45 days (± 5 days) of the study period.
- A minimum of 50 subjects 14 years of age and older will start the study with an Auto Basal setpoint of 120 mg/dL. They will switch to the 100 mg/dL setpoint after 45 days (± 5 days) of the study period.

- A minimum of 50 subjects 7-13 years of age will start the study with an Auto Basal setpoint of 100 mg/dL. They will switch to the 120 mg/dL setpoint after 45 days (± 5 days) of the study period.
- A minimum of 50 subjects 7-13 years of age will start the study with an Auto Basal setpoint of 120 mg/dL. They will switch to the 100 mg/dL setpoint after 45 days (± 5 days) of the study period

The investigator has the discretion to start subjects at either the 100 mg/dL or 120 mg/dL setpoints, while the Sponsor will ensure that the required minima for each setpoint are being met. Regardless of which setpoint is being set at the beginning of the study period, subjects should attempt to change the setpoint after 45 days (+/- 5 days) of the study period. For example: A subject who starts at the 100 mg/dL setpoint, should attempt to change the setpoint to 120 mg/dL after 45 days.

**Meal challenges (Run-in and Study period):**

The table below summarizes all meal challenges in the study.

- All meal challenges should only start if the following conditions are met:
  - SMBG at start of meal is $\leq$ 200 mg/dL
  - Sensor glucose is available.

| **Run-in period; Regular sized meal with missed Meal Bolus challenge** | | | | |
|---|---|---|---|---|
| **Timing** | **Type of challenge** | **Day** | **Meal(s)** | **Notes** |
| Run-in | Missed Meal Bolus (regular sized meal) | Day prior to V5 | Regular sized Dinner | If the subject qualified to stay in Auto Mode during the Run-In Period, they must turn off Auto Mode for at least 6 hours prior to the start of the Missed Meal Bolus Challenge. |
| **Study period; Meal challenges** | | | | |
| **Setpoint** | **Type of challenge** | | **Meal(s)** | **Notes** |
| Study Period (100 mg/dL setpoint) | Large sized meals | Day 1 | Large sized Breakfast **and** Large sized Dinner | Meal composition, meal size and time of meal consumption should match meals at **Setpoint of 120 mg/dL.** |

| | | | | |
|---|---|---|---|---|
| Study Period (100 mg/dL setpoint) | Large sized meals | Day 2 | Large sized Breakfast **and** Large sized Dinner | Meal composition, meal size and time of meal consumption should match meals at **Setpoint of 120 mg/dL.** |
| Study Period (100 mg/dL setpoint) | Large sized meal | Day 3 | Large sized Breakfast | Meal composition, meal size and time of meal consumption should match meal at **Setpoint of 120 mg/dL.** |
| | Missed Meal Bolus | | Regular sized dinner meal | Meal composition, meal size and time of meal consumption should match **Run-in period** meal |
| Study Period (100 mg/dL setpoint) | Missed Meal Bolus with Large sized meal | Day 4 | Large sized Dinner | Meal composition, meal size and time of meal consumption should match meal at **Setpoint of 120 mg/dL.** |
| Study Period (120 mg/dL setpoint) | Large sized meals | Day 1 | Large sized Breakfast **and** Large sized Dinner | Meal composition, meal size and time of meal consumption should match meals at **Setpoint of 100 mg/dL.** |
| Study Period (120 mg/dL setpoint) | Large sized meals | Day 2 | Large sized Breakfast **and** Large sized Dinner | Meal composition, meal size and time of meal consumption should match meals at **Setpoint of 100 mg/dL.** |
| Study Period (120 mg/dL setpoint) | Large sized meal | Day 3 | Large sized Breakfast | Meal composition, meal size and time of meal consumption should match meal at **Setpoint of 100 mg/dL.** |
| | Missed Meal Bolus | | Regular sized dinner meal | Meal composition, meal size and time of meal consumption should match **Run-in period** meal |
| Study Period (120 mg/dL setpoint) | Missed Meal Bolus with Large sized meal | Day 4 | Large sized Dinner | Meal composition, meal size and time of meal consumption should match meal at **Setpoint of 100 mg/dL.** |

- **Regular Sized Dinner Challenge with Missed Meal Bolus**

  During the study period, once at each Auto Basal setpoint (i.e. 120 mg/dL and 100 md/dL) on Day 3 of the multi-day meal challenge, subjects will be asked to consume the ***same regular sized dinner that they had during the run-in period***. For example, if the dinner meal was consumed without an insulin bolus for the meal at 5 pm during the run-in period, that same dinner meal should be consumed at approximately the same time on Day 3 at each setpoint during the study period. Subjects will be asked to check BG at the start of

the meal, as well as 2 hours and 4 hours after the start of the meal and provide correction as necessary. Details should be recorded, along with BG values, on the Meal Challenge log.

- **Large sized Meal Challenges:**

  On large sized meal challenge days, all subjects will be instructed to eat at least 1 meal with at least 50% higher caloric intake including 50% more carbohydrates and 50% higher in fat than what the subject reports that he/she usually eats. It is recommended that subjects eat food at restaurants or consume prepared meals (e.g. things like turkey and stuffing), which have not been eaten during the last month. A log will be used to collect information about type of food, name of restaurant (if applicable), confirmation that the meal eaten was different from any meal eaten within the last month and confirmation that meal size was at least 50% more than when subjects usually consume in terms of calories, carbohydrates and fat. The log should also contain the time and date of the meal, as well as confirmation that a BG was taken at the start of the meal, 2 hours after the start of the meal and 4 hours after the start of the meal. The timing of the meal challenges will be at the investigator's discretion. The subject's companion must be physically present in the same building, home or location (if not at home) during the meal challenge (and for 4 hours following the start of the meal), must be able to check SMBG (in case it is needed) and give glucose/administer glucagon as needed. This challenge will include a missed Meal Bolus on Day 4. See Table above.

**Exercise Challenges (Study Period):**

The following exercise challenges are required during the study period:

- 3 consecutive days of exercise challenge at setpoint of 100 mg/dL
- 3 consecutive days of exercise challenge at setpoint of 120 mg/dL

- **Exercise Challenges Details**

  On exercise challenge days, all subjects will be required to engage in 1-2 hours of physical exercise each day. During this time, subjects should use the Auto Basal setpoint target of 100 mg/dL or 120 mg/dL (depending on what is required at that time of the study period), unless a subject prefers to use the 150 mg/dL target before, during and immediately after the exercise challenges. For the remainder of days, the temporary target will be started at the Investigator's discretion. A log will be used to collect information about exercise type, date, time (start and finish of exercise), duration and name of the companion. The log should also contain confirmation that SMBG was done at the beginning of exercise, as well as 2 and 4 hours after the start of the exercise. The timing of the exercise challenge will be at the investigator's discretion. A photograph should be taken on each day of the exercise to indicate that exercise took place. Subjects may also use a Smart Phone application to document their exercise. The subject's companion must be physically present in the same building, home or location (if not at home) during the exercise challenge, must be able to check SMBG (in case it is needed) and give glucose/administer glucagon as needed. Examples of types of exercise include but are not limited to:

  - Running

- Cycling
- Swimming
- Hiking
- Walking
- Games (e.g. Wii interactive video games)
- Indoor/outdoor playground (Pediatric subjects)
- Yoga/stretching
- Any sport activity which involves ongoing physical movement (i.e., tennis, golf, basketball, tee ball or volleyball)
- Dancing
- Zumba
- Aerobics
- Spinning

**Continued Access Period:**

At the end of the study period, subjects will have the opportunity to continue using the AHCL system at home until the Sponsor receives FDA approval to commercialize the products and the system is commercially available. During the continued access period, subjects will be asked to use the system as intended and to upload device data on a weekly basis. See Visit Schedule tables for frequency of device uploading. Office visits will be required at 3 month intervals.

**Continued Access Period expansion:**

During the continued access period, all participating subjects will transition from the 670G system, version 4.0 AHCL, to the 780G system which features Bluetooth® connectivity. The CGM used with 780G will be Guardian™ 4 Transmitter with the Guardian™ Sensor (4).

Subjects will continue to use the 780G system at home until the sponsor notifies sites to end subjects' study participation.

The MiniMed™ Clinical App and the Medtronic CareLink™ Clinical App will be used by subjects when they are available.

**SMBG recommendations for 670G system, version 4.0 AHCL**:
Typically, one SMBG is required every 12 hours for calibration. Routine SMBG is not required. 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 is not low) or high and if they are experiencing a severe hypoglycemic event, a severe hyperglycemic event or DKA.

**SMBG recommendations for 780G system:**
With the 780G system and the Guardian™ 4 transmitter, calibration is not required. However, a calibration is optional and will occur any time a BG is entered. 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 is not low) or high including a severe hypoglycemic event, a severe hyperglycemic event or DKA.

**Companions:**
Subjects will be required to have a companion who resides (or will live) in the same building (or home) during the proposed study at night, and also to be physically present in the same building, home or location (if not at home) during the exercise and meal challenges. A companion should be present during meal challenges and for 4 hours following the start of the meal. Companions should be able to check SMBG (in case it is needed), give glucose or administer glucagon.

### 5.1. Duration

The study is anticipated to last no longer than 36 months from investigational center initiation to completion of all data entry and monitoring procedures. The study will target 6 months to complete subject enrollment. Subjects can expect to participate for approximately 4-5 months between the run-in period and study period. The continued access period may lengthen the overall duration of the study considerably.

### 5.2. Rationale

The design of this study as a single arm trial with safety and effectiveness endpoints represents the next step in the development of a closed loop insulin delivery system. Iterative changes in the control algorithm, which include additional levels of automation, require a study design equivalent to the design that was approved in the study of the predecessor MiniMed™ 670G system.

## 6. Product Description

### 6.1. Intended Population

A diverse population of insulin-requiring subjects will be studied. The study population will have a large range for duration of diabetes and glycemic control, as measured by HbA1c.

## 6.2. General Overview of MiniMed 670G Insulin Pump, version 4.0 AHCL, and 780G Insulin Pump System Components and Consumables

**Table 1. MiniMed™ 670G Insulin Pump, version 4.0 AHCL, and 780G Insulin Pump: System Components and consumable materials**

| Device name | MDT Model number/ part number | Device Status |
|---|---|---|
| MiniMed™ 670G Insulin Pump, version 4.0 AHCL | MMT-1740 | Investigational |
| Guardian™ Sensor (3) | MMT-7020 | Non-Investigational |
| Guardian™ Link (3) Transmitter | MMT-7811 | Non-Investigational |
| Guardian™ Link (3) Transmitter | MMT-7911 | Non-Investigational |
| One-Press Serter | MMT-7512 | Non-Investigational |
| Charger | MMT-7715 | Non-Investigational |
| Tester | MMT-7736L | Non-Investigational |
| Medtronic CareLink™ Personal Software | MMT-7333 | Non-Investigational |
| CareLink™ system software | MMT-7350 | Non-Investigational |
| Precision Xtra™* Ketone Meter | | Non-Investigational |
| CONTOUR® NEXT LINK 2.4 Study Meter | MMT-1352 | Non-Investigational |
| MiniMed™ 780G Insulin Pump | MMT-1884 | Investigational |
| Guardian™ Sensor (4) | MMT-7040 | Investigational |
| Guardian™ 4 Transmitter | MMT-7841 | Investigational |
| MiniMed™ Clinical App | MMT-6103 Android; MMT-6104 IOS | Class II Exempt |
| Medtronic CareLink™ Clinical App | MMT-6113 Android; MMT-6114 IOS | Class II Exempt |
| Roche Accu-Chek™* Guide Link Study Meter | 08116083022M | Non-Investigational |

| Device name | MDT Model number/ part number | Device Status |
|---|---|---|
| Blue Adapter | ACC-1003911 | Non-Investigational |

## 6.3. Investigational Device

### 6.3.1. MiniMed™ 670G Insulin Pump, version 4.0 AHCL

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. These features are similar to the commercially available Medtronic sensor-enabled systems (e.g. MiniMed™ 530G, 670G Systems in the US, MiniMed™ 640G and Veo System outside the US).

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 to automatically resume insulin delivery based on specific criteria) and Auto Mode (hybrid closed loop) feature. The Auto Mode and Manual Mode Low Management features will not be active at the same time.

When using the Bolus Wizard feature for meals with the MiniMed™ 670G Insulin Pump, version 4.0 AHCL either in Auto Mode or Manual Mode, there is an option to use sensor glucose values instead of SMBG to calculate insulin amounts for delivery. The pump may also be used as a simple pump without CGM or as a SAP without use of the SmartGuard™ features.

When Auto Mode is enabled on the MiniMed™ 670G Insulin Pump, version 4.0 AHCL, the sensor glucose values (SGVs) received from the Guardian™ Link (3) transmitter by the insulin pump will be used to automatically calculate the insulin dose. It will then deliver insulin to the patient, at five-minute intervals, to achieve glycemic control.

With the AHCL system, subjects must still deliver bolus insulin for meals as calculated by the insulin to carbohydrate ratio. This ratio is determined by the Health Care Professional (HCP)/patient. In addition, the setting for active insulin must be programmed. Basal rates are set for periods of open loop therapy.

When Auto Mode is not active, the user can use the Smart Guard™ Low Management features. Here, basal rate delivery will be suspended either when the SG has reached a programmed low threshold (Suspend on Low) or before the SGV has reached the programmed low threshold (Suspend before Low).

**Figure 1. MiniMed™ 670G Insulin Pump, version 4.0 AHCL**

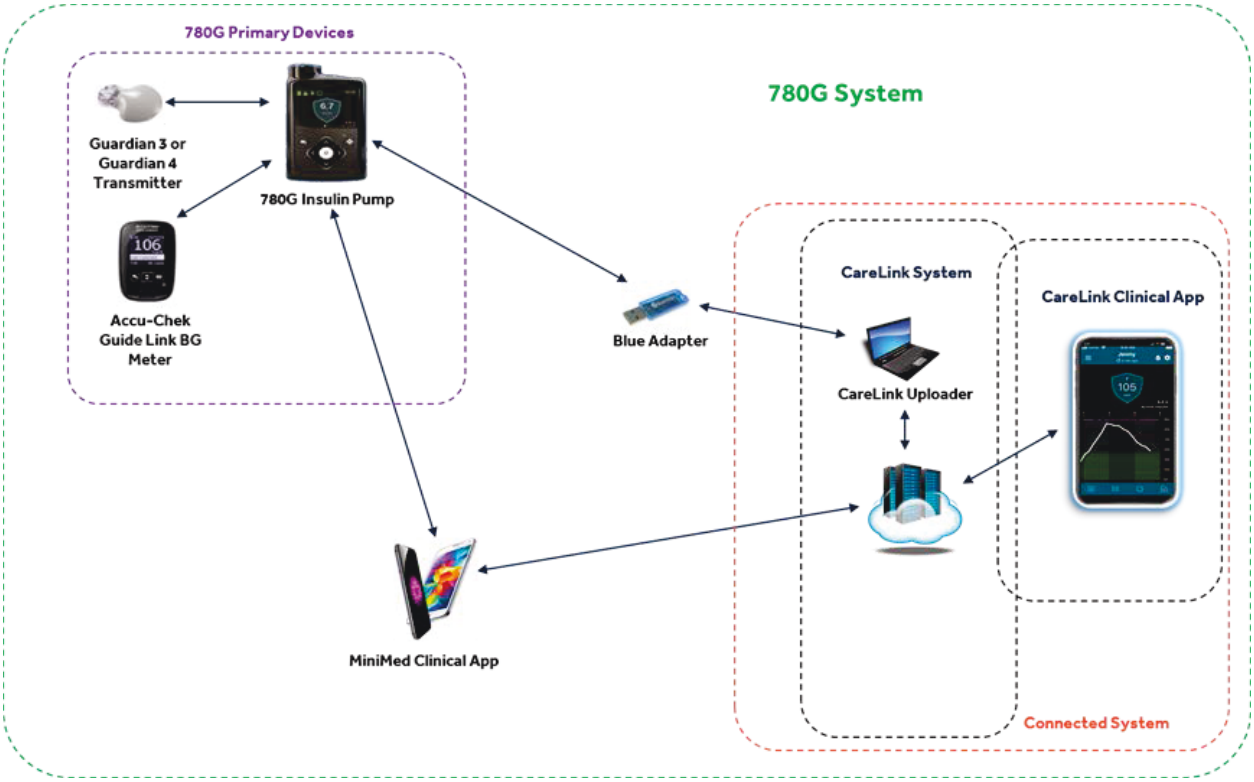

### 6.3.2. MiniMed™ 780G Insulin Pump

The MiniMed™ 780G Insulin Pump houses electronics, a pumping mechanism, a user interface, and a medication reservoir within the same physical device. The pump communicates via Bluetooth® Low Energy wireless communication protocol with compatible devices in the MiniMed™ 780G System: Guardian™ 4 Transmitter (connected to Guardian™ Sensor [4]), Roche's Accu-Chek™* Guide Link Blood Glucose Meter, consumer electronic devices with the MiniMed™ Clinical App, CareLink™ Clinical App with CareLink™ Personal software or Blue Adapter with CareLink™ Personal/CareLink™ system software.

The most notable enhancements to the MiniMed™ 780G System are the incorporation of modifications to the closed loop algorithm that includes the addition of adjustable target setpoints (100 mg/dL, 110 mg/dL and 120 mg/dL), an auto correction bolus without user input or acknowledgement and fine tuning of safeguards in order to reduce auto mode exits and improve the user experience.

The MiniMed™ 780G Pump interacts with the following devices:

- The MiniMed™ 780G Pump receives the sensor glucose values and sensor integrity check from the transmitter.
- The MiniMed™ 780G Pump receives blood glucose values from the Roche's Accu-Chek™* Guide Link blood glucose meter
- In addition, the MiniMed™ 780G Pump transmits data to a compatible consumer electronic device with the MiniMed™ Clinical App, to provide a secondary display for passive monitoring of CGM and pump data for the user.
- The MiniMed™ 780G Pump also transmits data to CareLink™ Personal/CareLink system software through the Blue Adapter/ MiniMed™ Clinical App.




### 6.3.3. Guardian™ Sensor (4)

The Guardian™ Sensor (4), referred to as Guardian™ Sensor (4) 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 represents the next generation in the Enlite™ sensor family with design changes in the engineering reports for improved accuracy. It is intended to penetrate the skin at a 90-degree angle, similar to the Enlite™ sensor. 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.

### 6.3.4. Guardian™ 4 Transmitter

The Guardian™ 4 Transmitter is a portable, electrical current meter intended to process, store, and transmit glucose sensor values to the compatible insulin pump. The transmitter sends sensor glucose (SG) values and sensor integrity (SI) data from the sensor to compatible insulin pumps via a Bluetooth® Low Energy wireless communication protocol.

## 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 represents the next generation in the Enlite™ sensor family with design changes in the engineering reports for improved accuracy. It is intended to penetrate the skin at a 90-degree angle, similar to the Enlite™ sensor. 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.

### 6.4.2. Guardian™ Link (3) Transmitter

The Guardian™ Link (3) transmitter is a device that has the same housing and sensor interface as the MiniLink™ transmitter. However, the internal electronics and firmware of the Guardian™ Link (3) transmitter are new. Like the MiniLink™ transmitter, the Guardian™ Link (3) transmitter reads the electronic signal generated by the sensor. In addition, the transmitter contains a custom Application Specific Integrated Circuit (ASIC), which enables 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) or via the BLE communication protocol. Some elements of the new calibration logic include prompting the user to calibrate when needed, referred to as "Smart Cal," instead of strictly scheduled time-based calibration requirements. The new algorithm is designed to improve and optimize performance when paired with the sensors.

In this study the Guardian™ Link (3) transmitter will be connected to a Guardian™ Sensor 3.

**Figure 2. Guardian Link (3) Transmitter**

### 6.4.3. One-Press Serter

The One-Press Serter, referred to as the Serter (Figure 3) in this protocol, is an insertion device that is used to ensure correct placement of the Guardian™ Sensor (3)/ Guardian™ Sensor (4) 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 3. One-Press Serter**

### 6.4.4. Charger

The Charger is used to recharge the Guardian™ Link (3) Transmitter/ Guardian™ 4 Transmitter as needed. A fully charged battery provides up to 7 days of transmitter use. The system includes a battery charger that will recharge the device according to the user guide.

### 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.

### 6.4.6. CareLink™ Personal Software and CareLink™ System Software

Medtronic CareLink™ Personal software for clinical is an internet-based software system which allows the device data to be uploaded and reviewed by the subject. The CareLink™ Personal allows subjects to upload data from Medtronic MiniMed insulin pumps and a range of system-supported, third-party BG meters.

Medtronic CareLink system software for clinical is an internet-based software system which allows the device data to be uploaded, viewed and easily evaluated by the physician. The CareLink system software allows retrospective review of device data and was developed for use by the investigational center staff.The CareLink™ system software allows the investigational center staff to manage, create, and request for approval to link the subject's account.

The data contained both in CareLink™ Personal software and CareLink™ system software are accessible to users using a standard browser, i.e., Microsoft® Internet Explorer or Google Chrome, on an Internet enabled PC.

The CareLink™ Personal software and CareLink™ system software uses standard Transport Layer Security (TLS) technology. 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, version 4.0 AHCL and can be stored in its memory as a glucose data point. The MiniMed™ 670G Insulin Pump, version 4.0 AHCL 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, can measure both blood glucose (sugar) and blood ß-Ketone. In this study, however, the meter will only be used to measure ß-Ketone levels, which will be collected for reporting and review (see Investigator/Coordinator binder 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 reported.

### 6.4.9. Roche Accu-Chek™* Guide Link Blood Glucose Meter

The Roche's Accu-Chek*™ Guide Link meter is a home blood glucose meter designed to measure and transmit blood glucose (BG) values to the compatible insulin pumps via a Bluetooth® Low Energy wireless communication protocol. The insulin pump then sends the BG values to the transmitter for calibration of the Guardian™ Sensor(3)/ Guardian™ Sensor (4). The transmission of BG values from a compatible meter is an optional feature provided as a convenience to the user; it eliminates the need to manually enter BG values into the pump. The Accu-Chek™* Guide Link blood glucose meter is compatible with Roche's Accu-Chek™* test strips.

### 6.4.10. Accessory Applications – 780G system

The MiniMed Clinical App is an optional accessory which receives pump data via Bluetooth® Low Energy wireless communication from the pump. The MiniMed™ Clinical App provides users with the convenience to wirelessly transfer pump data to CareLink™ and also provides a mirroring display of the pump screen. The MiniMed™ Clinical App is not designed to control or monitor the performance of the insulin pump nor for direct monitoring of pump data. As a mirroring display, the app can provide alerts to the subject via the user interface. All alerts must be addressed on the insulin pump.

The CareLink™ Clinical App is an optional accessory which receives pump data wirelessly from the CareLink™ server. The CareLink™ Clinical App provides a mirroring display of the MiniMed™ Clinical App screen, for remote monitoring by a care partner (i.e. care giver or health care provider). The CareLink™ Clinical App is not designed to monitor the performance of the insulin pump nor for direct monitoring of pump data. As a mirroring display, the app can provide notifications to the care partner via the user interface.

### 6.4.11. Blue Adapter

The Blue Adapter is an optional accessory with Bluetooth® technology that facilitates the communication between a personal computer and the insulin pump, via a Bluetooth® Low Energy wireless communication protocol. The Blue Adapter is an off-the-shelf non-medical device intended to transfer data to CareLink™ Server. The Blue Adapter does not have any computation, diagnostic, monitoring or therapeutic function/benefit. Medtronic will provide the Blue Adapter as a convenience to subjects as an alternative for subjects without mobile devices.

## 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. Anticipated Devices Change

There are no changes anticipated for any of the devices during the course of the study.

## 6.8. 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, 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 2 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 AHCL (MMT-1740) | **Yes** | **Yes** | **Yes** | **Yes** | **Yes** |

| 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™ 780G Insulin Pump, (MMT-1884) | **Yes** | **Yes** | **Yes** | **Yes** | **Yes** |
| Guardian™ Sensor (3) (MMT-7020) | **Yes** | **Yes** | **Yes (Unused only)** | **Yes** | **Yes (Unused only)** |
| Guardian™ Sensor (4) (MMT-7040) | **Yes** | **Yes** | **Yes (Unused only)** | **Yes** | **Yes (Unused only)** |
| Guardian™ Link (3) Transmitter* (MMT-7811) | **Yes** | **No** | **Yes** | **Yes** | **Yes** |
| Guardian™ Link (3) Transmitter* (MMT-7911) | **Yes** | **Yes** | **Yes** | **Yes** | **Yes** |
| Guardian™ 4 Transmitter* (MMT-7841) | **Yes** | **Yes** | **Yes** | **Yes** | **Yes** |
| One-Press Serter (MMT-7512)* | **No** | **No** | **No** | **No** | **No** |
| Charger (MMT-7715)* | **No** | **No** | **No** | **No** | **No** |
| Tester (MMT-7736L)* | **No** | **No** | **No** | **No** | **No** |
| CONTOUR®NEXT LINK 2.4 Study Meter (MMT-1352) | **Yes** | **Yes** | **Yes** | **Yes** | **Dispose or return unused only** |

| 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 |
|---|---|---|---|---|---|
| Roche Accu-Chek™* Guide Link Study Meter (08116083022M) | **Yes** | **Yes** | **Yes** | **Yes** | **Dispose or return unused only** |
| Precision Xtra™* Ketone Meter | **No** | **No** | **Yes** | **No** | **Dispose or return unused only** |

*Devices may be combined and distributed in kits.

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

### 6.8.1. 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.

### 6.8.2. 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.

### 6.8.3. Disbursement of Study Devices

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

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

### 6.8.4. 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 2 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 2. 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.

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 350 subjects will be enrolled at up to 30 investigational centers across the US in order to have 250 subjects who complete the study period. The number of subjects enrolled in the continued access period depends on the subjects' desire to continue.

## 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 (321XXXXXX). The first three numbers refer to the CIP number (321), 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., 321002001 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 7-75 years at time of Screening
2. Subjects 14-75 years of age: A clinical diagnosis of type 1 diabetes for 2 years or more as determined via medical record or source documentation by an individual qualified to make a medical diagnosis
3. Subjects 7-13 years of age: A clinical diagnosis of type 1 diabetes for 1 year or more as determined via medical record or source documentation by an individual qualified to make a medical diagnosis
4. Individual of legal age is capable of providing consent.

*Study-specific inclusion criteria*

5. Subject is willing to perform $\geqslant$ 4 finger stick blood glucose measurements daily
6. Subject is willing to perform required sensor calibrations
7. Subject is willing to wear the system continuously throughout the study
8. Subject must have a minimum daily insulin requirement (Total Daily Dose) of greater than or equal to 8 units
9. Subject has a Glycosylated hemoglobin (HbA1c) less than 10% (as processed by Central Lab) at time of Screening visit

**Note: All HbA1c blood specimens will be sent to and tested by a NGSP certified Central Laboratory. HbA1c testing must follow National Glycohemoglobin Standardization Program (NGSP) standards.**

10. Subject has TSH in the normal range OR if the TSH is out of normal reference range the Free T3 is below or within the lab's reference range and Free T4 is within the normal reference range.
11. Pump therapy for greater than 6 months prior to screening (with or without CGM experience)
12. 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). A companion or caregiver should also be available during exercise challenges in the same building, home or location (if not at home). This requirement may be verified by subject report at screening visit.
13. Subject willing to upload data from the study pump, must have Internet access and a computer system that meets the requirements for uploading the study pump
14. If subject has celiac disease, it has been adequately treated as determined by the investigator
15. Subject is 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)
    - Humalog™* (insulin lispro injection)
    - NovoLog™* (insulin aspart)
16. Subjects with history of cardiovascular event 1 year or more from the time of screening must have an EKG within 6 months prior to screening or during screening. If subject has an abnormal EKG, participation is allowed if there is clearance from a cardiologist
17. Subjects with the 3 or more cardiovascular risk factors listed below must have an EKG within 6 months prior to screening or during screening. If subject has an abnormal EKG, participation is allowed if there is clearance from a cardiologist
    a. Cardiovascular risk factors include:
        - Age >35 years
        - Type 1 diabetes of >15 years' duration
        - Presence of any additional risk factor for coronary artery disease
        - Presence of microvascular disease (proliferative retinopathy or nephropathy, including microalbuminuria)
        - Presence of peripheral vascular disease
        - Presence of autonomic neuropathy
18. Subjects with history of cardiovascular event 1 year or more from the time of screening must have a stress test within 6 months prior to screening or during run in period. If subject fails stress test, participation is allowed if there is clearance from a cardiologist

## 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 6 months prior to Screening:
    a. Medical assistance (i.e. Paramedics, Emergency Room (ER) or Hospitalization)
    b. Coma
    c. Seizures
2. Subject has been hospitalized or has visited the ER in the 6 months prior to Screening resulting in a **primary diagnosis** of uncontrolled diabetes

3. Subject has had Diabetic Ketoacidosis (DKA) in the 6 months prior to Screening.
4. Subject has Hypoglycemia Unawareness, measured by the Gold questionnaire as ≥4 (Gold, MacLeod et al. 1994) at Screening
5. Subject is unable to tolerate tape adhesive in the area of sensor placement
6. Subject has any unresolved adverse skin condition in the area of sensor placement (e.g., psoriasis, dermatitis herpetiformis, rash, Staphylococcus infection)
7. Women of child-bearing potential who have a positive pregnancy test at Screening or plan to become pregnant during the course of the study
8. 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.
9. Subject has had any of the following cardiovascular events within 1 year of screening: myocardial infarction, unstable angina, coronary artery bypass surgery, coronary artery stenting, transient ischemic attack, cerebrovascular accident, angina, congestive heart failure, ventricular rhythm disturbances or thromboembolic disease
10. Subject is being treated for hyperthyroidism at time of Screening
11. Subject has a diagnosis of adrenal insufficiency
12. Subject has taken any oral, injectable, or intravenous (IV) glucocorticoids within 8 weeks from time of Screening, or plans to take any oral, injectable, or IV glucocorticoids during the course of the study
13. Subject is actively participating in an investigational study (drug or device) wherein he/she has received treatment from an investigational study drug or investigational study device in the last 2 weeks
14. Subject is currently abusing illicit drugs
15. Subject is currently abusing marijuana
16. Subject is currently abusing prescription drugs
17. Subject is currently abusing alcohol
18. 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 Screening
19. 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
20. Subject has elective surgery planned that requires general anesthesia during the course of the study
21. Subject has a sickle cell disease, hemoglobinopathy; or has received red blood cell transfusion or erythropoietin within 3 months prior to time of Screening
22. Subject plans to receive red blood cell transfusion or erythropoietin over the course of study participation
23. Subject diagnosed with current eating disorder such as anorexia or bulimia
24. Subject has been diagnosed with chronic kidney disease that results in chronic anemia
25. Subject has a hematocrit that is below the normal reference range of lab used.
26. Subject is on dialysis
27. Subject has serum creatinine of >2 mg/dL.
28. 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. Overview

### Run-In Period Synopsis (Run-In Visits 1-4)

The purpose of the run-in period is to ensure that study subjects are introduced to study devices. There is a window of 45 days from the end of Visit 1 to the end of Visit 4 during which time subjects should complete run-in. Subjects will be started on the study pump (and CGM if applicable) at Visit 2.

- **Devices Worn:**
  - Study pump
  - Guardian™ Sensor (3)
  - Guardian™ Link (3) transmitter

## Study Period Synopsis (Visits 5-18)

**Overview:**

The study period is approximately 90 days long.

### *Study Period Device Procedures*

- **Devices Worn:**
  - Study pump
  - Guardian™ Sensor (3)
  - Guardian™ Link (3) transmitter
- **Calibration Requirements with Study Meter:**
  - Approximately 30 minutes to 2 hours after the Guardian™ Sensor (3) is initialized, the study pump will alert the user to enter a SMBG to perform initial calibration.
  - After the first calibration, the user must calibrate the Guardian™ Sensor (3) with the study meter within 6 hours of the first calibration. BG values from the study meter, which have been confirmed by subjects, will be used for calibrations.
  - The user must calibrate via SMBG with the study meter when prompted by the study pump. BG values from the study meter, which have been confirmed by subjects, will be used for calibrations.
  - The user must calibrate with the study meter every 12 hours after last calibration.
  - Minimum of one calibration every 12 hours will be required with the study meter
  - Best practices should be followed for each BG measurement (e.g. clean hands, "second drop" technique and accepting the calibration on the pump without delay)
  - Other recommendations:
    - Should always have clean dry fingers when checking blood glucose
    - Only fingertips should be used to obtain blood samples for calibration
- **Auto Mode Settings:**
  - The Auto Mode (Closed Loop) setpoint for the closed loop algorithm:

- The sponsor will provide guidance on the starting setpoint for subjects based on cohorts listed below:

    - A minimum of 50 subjects 14 years of age and older will start the study with an Auto Basal setpoint of 100 mg/dL. They will switch to the 120 mg/dL setpoint after 45 days (± 5 days) of the study period.
    - A minimum of 50 subjects 14 years of age and older will start the study with an Auto Basal setpoint of 120 mg/dL. They will switch to the 100 mg/dL setpoint after 45 days (± 5 days) of the study period.
    - A minimum of 50 subjects 7-13 years of age will start the study with an Auto Basal setpoint of 100 mg/dL. They will switch to the 120 mg/dL setpoint after 45 days (± 5 days) of the study period.
    - A minimum of 50 subjects 7-13 years of age will start the study with an Auto Basal setpoint of 120 mg/dL. They will switch to the 100mg/dL setpoint after 45 days (± 5 days) of the study period

- The investigator has the discretion to start subjects at either the 100 mg/dL or 120 mg/dL setpoints, while the Sponsor will ensure that the required minima for each setpoint are being met. Regardless of which setpoint is being set at the beginning of the study period, subjects should attempt to change the setpoint after 45 days (+/- 5 days) of the study period. For example: A subject who starts at the 100 mg/dL setpoint, should attempt to change the setpoint to 120 mg/dL after 45 days.

- The Temp target setting in the pump may be used any time, e.g., when subject exercises. Temp Target Threshold is set to 150 mg/dL.
    - During this time, subjects may use the temporary target of 150 mg/dL for one of the 3 days at each setpoint.
    - The Temp target may be used during exercise challenges per investigator discretion
- Alerts that are fixed into the system:
    - SG at or below 50 mg/dL
    - When SG at or above 250 mg/dL for more than 3 hours

- High Setup limit (i.e. the setting for a high glucose alert threshold based on sensor reading) is recommended to be set at 300 mg/dL
  - Alert setting options may be set per investigator discretion
- Low Setup limit (i.e. the setting for a low glucose alert threshold based on sensor reading) is recommended to be set at 70 mg/dL
  - Alert setting options may be set per investigator discretion for subjects 14 years and older
  - Low Setup alert for subjects 7-13 years of age should not be set lower than 70 mg/dL
- Insulin carbohydrate ratios may be adjusted throughout the study
- Active insulin time may also be adjusted
- SmartGuard™ features other than Auto Mode (i.e. Suspend on Low and Suspend before Low) should be activated during times when subjects are not in Auto Mode during the study period

- **Manual Mode Settings:**
  - High Setup limit recommended to be set at 300 mg/dL
    - Alert setting options may be set per investigator discretion
  - Low Setup limit recommended to be set at 70 mg/dL
    - Alert setting options may be set per investigator discretion
    - Low Setup alert for subjects 7-13 years of age should not be set lower than 70 mg/dL
  - Predictive alerts and rate of change alerts are optional
  - Alerts that are fixed into the system:
    - SG at or below 50 mg/dL
    - When SG at or above 250 mg/dL for more than 3 hours
  - Consider setting the glucose target in the bolus wizard calculator, i.e. 120 mg/dL or higher, based on investigator discretion.

- **Monitoring Method:**
  - CONTOUR®NEXT LINK 2.4 study meter

## Continued Access 780G System Use Synopsis

**Overview:**

Continued access visits will take place at 90 day (± 14 days) intervals from the last study period visit.

### *Study Period Device Procedures*

- **Devices Worn:**
  - 780G Insulin pump
  - Guardian™ Sensor (4) or Guardian™ Sensor (3)
  - Guardian™ 4 transmitter or Guardian™ Link (3) transmitter
- **Calibration Requirements with Study Meter:**
  - Calibrations are not required
  - Every time a BG is entered, calibration occurs
  - Best practices should be followed for each BG measurement (e.g. clean hands, "second drop" technique and accepting the calibration on the pump without delay)
  - Other recommendations:
    - Should always have clean dry fingers when checking blood glucose
    - Only fingertips should be used to obtain blood samples
- **Auto Mode Settings:**
  - The automatic basal target and active insulin time should be set according to investigator discretion.
- **Manual Mode Settings:**
  - High Setup limit recommended to be set at 300 mg/dL
    - Alert setting options may be set per investigator discretion
  - Low Setup limit recommended to be set at 70 mg/dL
    - Alert setting options may be set per investigator discretion
- **Monitoring Method:**
  - Roche Accu-Chek™* Guide Link study meter

## 9.2. Schedule of Events

Each subject's participation will be comprised of the scheduled visits listed in Section 9.2 over the course of approximately 4-5 months during the run-in period and study period. The continued access period may lengthen the overall duration of the study considerably. Refer to the Appendices (Section 18.4) for the Visit Details Table**.**

With sponsor 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

## 9.3. Study Visit Schedule & Scheduled Follow-Up Visit Windows

**Run-in Period Visits: To be completed in 45 days**

- Screening Visit 1 (Office): Consent and Screening

- Run-in Visit 2 (Office): Day 7 after Visit 1 (+3 days)
  - *Eligibility has been confirmed*
  - Start Study Pump
    - Pump Training
  - Start CGM (if using SAP prior to Screening)
    - If SAP using Suspend on Low/Predictive Suspend before Low prior to Screening, those features may be used from Visit 2
    - CGM Training, if applicable

- Run-in Visit 3 (Office): Day 0 after Visit 2 (+7 days)
  - Start CGM (if not already started at Visit 2)
  - Start 2 weeks of measured sensor wear period
    - System is used in manual Mode by subjects who are not using Auto Mode with 670G at Screening
      - SmartGuard™ features (Suspend on Low, Predictive Suspend before Low) may be activated
    - SAP subjects using Auto Mode with 670G at Screening may use Auto Mode:
      - Auto Correction must be turned off
      - Auto Basal setpoint must be set to 120 mg/dL

- Run-in Visit 4: Office Visit Day 14 after Visit 3 (+7 days)
  - Confirm run-in CGM data:
    - Subject demonstrates sensor compliance (i.e. 3,225 glucose sensor data points equivalent to 11.2 days of sensor wear)
  - Continue using study pump with CGM

    - SmartGuard™ features (Suspend on Low, Predictive Suspend before Low) may be activated
  - SAP subjects using Auto Mode with 670G at Screening may use Auto Mode:
    - Auto Correction must be turned off
    - Auto Basal setpoint must be set to 120 mg/dL

**Study Period Visits:**

- Visit 5: Office Visit 7-14 days after Visit 4
  - Start AHCL (e.g. Auto Mode feature turned ON with auto-correction)
- Visit 6: Telephone Visit (option of office visit) – Day 1 after Visit 5
- Visit 7: Telephone Visit (option of office visit) – Day 2 after Visit 5
- Visit 8: Telephone Visit (option of office visit) – Day 3 after Visit 5
- Visit 9: Telephone Visit (option of office visit) – Day 4 after Visit 5
- Visit 10: Telephone Visit (option of office visit) – Day 5 after Visit 5
- Visit 11: Telephone Visit (option of office visit) – Day 6 after Visit 5
- Visit 12: Telephone Visit (option of office visit) – Day 7 after Visit 5
- Visit 13: Office Visit - Day 14 after Visit 5 (± 3 days)
- Visit 14: Telephone Visit Day 21 after Visit 5 (± 3 days)
- Visit 15: Office Visit - Day 30 after Visit 5 (± 5 days)
- Visit 16: Telephone Visit (option of office visit) – Day 45 after Visit 5 (± 5 days)
  - Change Glucose Target
- Visit 17: Office Visit – Day 60 after Visit 5 (± 7 days)
- Visit 18: Office Visit - Day 90 after Visit 5 (± 7 days)
  - End of Study (EOS) Period

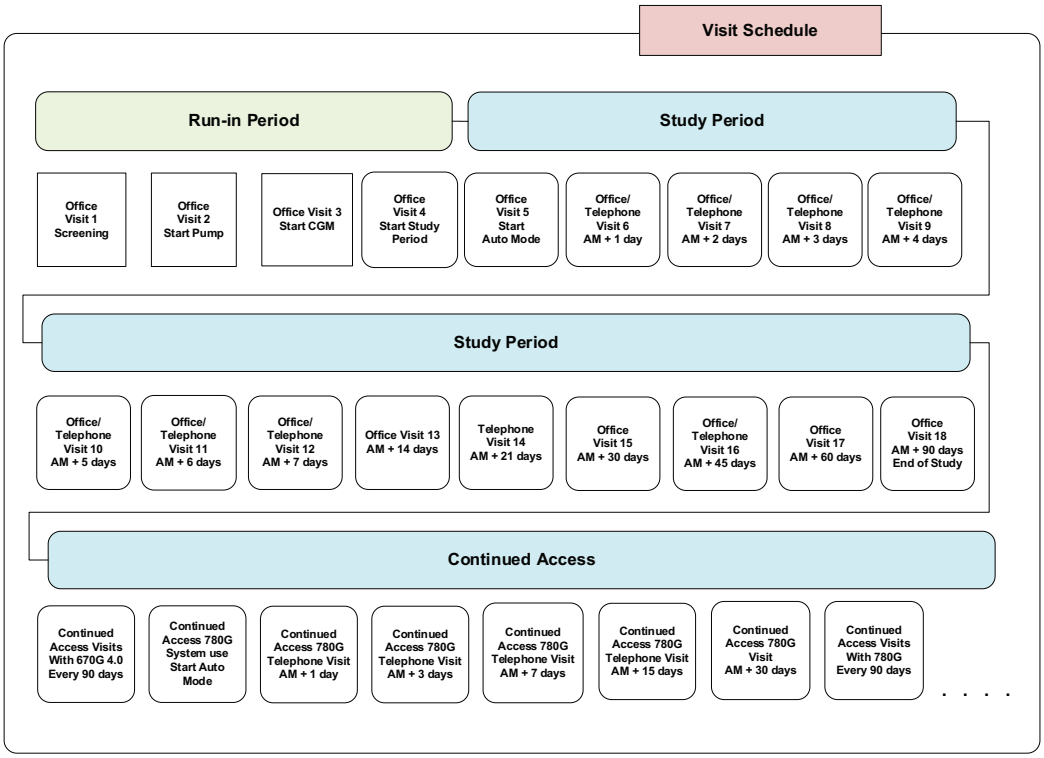
**Continued Access Period Visits:**

- Continued access visits will take place at 90 day (± 14 days) intervals from the last study period visit (Visit 18) – Office or Telemedicine Visit.
  - If the subject is entering continued access directly from the study period, Visit 18 and the first continued access visit may occur on the same day.
  - If the subject has previously completed the study period and exited the study, continued access visits will begin following the signing of the current ICF/Assent.
  - Subjects are instructed to continue uploading study device data weekly
    - It is recommended that an HbA1c sample is drawn and tested at each quarterly visit. If drawn, the test must be run by the Central lab.

- 780G system use Start - Office Visit or Telemedicine Visit
  - Start of 780G system use
  - Dispense 780G system
  - Train subjects on 780G system use
  - Start SmartGuard™ (Auto Mode) with all features turned on
- 780G - Telephone Visit –
  Day 1 after 780G System use Start Visit
  - Check for adverse events
  - Check for device deficiencies
  - Review CareLink data

- 780G - Telephone Visit –
  Day 3 after 780G System use Start Visit
  - Check for adverse events
  - Check for device deficiencies
  - Review CareLink data
- 780G - Telephone Visit –
  Day 7 after 780G System use Start Visit (± 2 days)
  - Check for adverse events
  - Check for device deficiencies
  - Review CareLink data
- 780G - Telephone Visit –
  Day 15 after 780G System use Start Visit (± 3 days)
  - Check for adverse events
  - Check for device deficiencies
- 780G - Office or Telemedicine Visit –
  Day 30 after 780G System use Start Visit (+ 7 days)
  - Check for adverse events
  - Check for device deficiencies
- Subsequent visits following receipt of the 780G system will take place at 90 day intervals (± 14 days) from the initial 780G visit (780G system use start) until Sponsor announces the end of the study. The subject will remain on the 780G system for the remainder of the Continued Access Period. These visits can be Office or Telemedicine Visits.
  - Subjects are instructed to continue uploading study device data weekly
    - It is recommended that an HbA1c sample is drawn and tested at each quarterly visit. If drawn, the test must be run by the Central lab.

**Figure 4. Visit Schedule**




## 9.4. 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 Institutional Review Board (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. Consent by a legal guardian or authorized representative is only allowed for subjects who are younger than legal age according to their state requirements.

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, as well as at the time of initiating the continued access period. 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.
- Use of an ICF/Assent form that has not received approval from the IRB.
- Use of an incorrect version of the ICF/Assent form.

## 9.5. Assessment of Safety

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

## 9.6. Medical Oversight

In order to conduct the study, investigational center staff that have the appropriate medical training is required.

### 9.6.1. Medical Staff

A physician (or designee) who has managed patients on both CGM and insulin pump therapy will be included in the study as the principal investigator.

### 9.6.2. 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.

### 9.6.3. Experience

Investigator (or designee) must also have at least one-year experience in managing patients with insulin carbohydrate ratios and insulin sensitivity ratios in his/her practice

## 9.7. Safety Monitoring/Risk Analysis

### 9.7.1. 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.

### 9.7.2. Hypoglycemic/Hyperglycemic Risk

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

### 9.7.3. 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.

### 9.7.4. Reuse Risk

All study devices will be single patient use.

### 9.7.5. Sterilization Risk

The following devices will be supplied sterilized:

- Infusion sets
- Insulin reservoirs
- Glucose sensors

### 9.7.6. Misuse Risk

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

### 9.7.7. Risk of Blood Sample Collection, Contamination from Sampling Techniques

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

### 9.7.8. HbA1c Risk

A Central laboratory will be used for HbA1c testing. HbA1c is the primary safety endpoint.

## 9.8. Glucose and Glycemia Measurements

During the course of the study, the subjects' BG levels, SG levels, HbA1c, and blood ketones will be assessed using the methods outlined in this section.

### 9.8.1. Daily Blood Glucose

Values will be assessed during the study by all subjects using the CONTOUR®NEXT LINK 2.4 study meter/ Accu-Chek™* Guide Link 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/ Accu-Chek™* Guide Link study meter per the manufacturer's instructions.

### 9.8.2. Blood Ketone Values

Blood ketones will be measured by all subjects using the Precision Xtra™* ketone meter when certain conditions are met. The control solution test will be performed following the manufacturer's user guide. The investigational center staff will be trained on the use of the Precision Xtra™* ketone meter per the manufacturer's instructions. All ketone measurements will be reported by study subjects.

**Note:** In the event the blood ketone meter is not used by subjects to collect ketone values, urine ketones should be measured and reported

### 9.8.3. Sensor Glucose Values

SG data will be collected by subject's study pump and calibrated by each subject's CONTOUR®NEXT LINK 2.4 study meter/ Accu-Chek™* Guide Link study meter.

### 9.8.4. HbA1c

Collected at baseline, the first HbA1c value, will be used as demographic information. HbA1c is also collected at the end of subjects' participation during study period, during continued access period (see Visit Details table for schedule) and at the end of subject's participation during continued access period.

## 9.9. 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 software and CareLink™ system 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. Electronic device data could also be collected by the Clinical App and the CareLink™ Clinical App.

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.

## 9.10. 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 subject is not compliant with his/her SMBG and pump uploads, a study deviation will be given.
- If subjects do not follow the fingerstick recommendations or upload devices perfectly, no study deviation will be given unless the site staff did not train the subject on SMBG study procedures or upload procedures.

### 9.10.1. Documenting Requirements for Study Deviations

#### 9.10.1.1. 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 deviations 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;
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.

#### 9.10.1.2. 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.

### 9.10.2. 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
- 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 5, for specific deviation reporting requirements and timeframes for reporting to Medtronic, IRB, and regulatory agency (if applicable).

### 9.10.3. 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.

## 9.11. 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 both in source documents and on the Exit eCRF. All study devices and supplies must be returned (as applicable) and documented both in source documents and on an eCRF.

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 study, subject begins using hydroxyurea.
- During the course of the study, subject begins participation in another investigational study (drug or device).
- During the study it becomes known that subjects are using own SMBG or system that replaces SMBG
- During the course of the study, subject begins abusing illicit drugs or marijuana.
- During the course of the study, subject begins abusing prescription 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, subject receives red blood cell transfusion or erythropoietin.
- 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 study, a subject repeatedly activates SmartGuard™ when instructed otherwise, e.g. Auto Mode is turned on (as applicable)
- 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 file.

## 9.12. Stopping Rules

### 9.12.1. Subject Stopping Rules

Any event of DKA or severe hypoglycemia will result in withdrawal of subject from study, if it is related to the use of AHCL Auto Mode.

### 9.12.2. Stopping Rules for Entire Study

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

- Unanticipated Adverse Device Effects (UADE)
- Device related Diabetic Ketoacidosis (DKA)
- Device 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 7 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.

# 10. Risks and Benefits

## 10.1. Potential Risks

**Table 3. Risks, Prevention and Mitigation**

| Risks with Infusion Sets | Prevention and Mitigation |
|---|---|
| Risks with infusion sets may include:<br>• Localized infection<br>• Skin irritation/redness<br>• Bruising<br>• Discomfort/pain<br>• Bleeding<br>• Irritation<br>• Rash<br>• Hyperglycemia secondary to infusion set occlusion or infusion site failure including DKA<br>• Hyperglycemia secondary to site falling off including DKA<br>• Anxiety associated with insertion | Prevention and mitigation include:<br>• Follow the provided user guides for insertions and care of infusion sets.<br>• If an infusion site becomes irritated or inflamed, the infusion set will be removed and another placed in a new location.<br>• 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.<br>• Follow the provided user guides for insulin pump management.<br>• 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:<br>• Hypoglycemia<br>• Hyperglycemia<br>• Diabetic ketoacidosis<br>• Severe hypoglycemia with or without associated seizure, coma or death<br>• Kinked cannula leading to hyperglycemia<br>• Infusion set disconnection from pump leading to hyperglycemia<br>• Subject removes the reservoir from the pump but forgets to disconnect the infusion | Prevention and mitigation include:<br>• Follow the provided user guides & instructions for insulin pump management which includes information on infusion set change.<br>• Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems.<br>• Instruct to check their meter glucose if their high or low symptoms do not match their sensor alerts or sensor glucose readings in order to make diabetes treatment decisions.<br>• Instruct to check their meter glucose if there are any concerns that the sensor glucose value is not accurate.<br>• Instruct to have glucose on hand for hypoglycemia<br>• Instruct to change infusion set if suspected catheter occlusion or administer insulin with syringe for persistent hyperglycemia especially if ketones develop. |

| | |
|---|---|
| set from the body which results in hypoglycemia or severe hypoglycemia<br>• Dislodged cannula leading to hyperglycemia<br>• A pump error may lead to under delivery or over-delivery of insulin<br>• Battery failure – no insulin delivered<br>• Insulin deterioration leading to hyperglycemia<br>• Incomplete priming; fails to prime tubing and/or cannula, leading to hyperglycemia<br>• Remove a reservoir, without suspending and reconnecting after a while resulting in a Hypoglycemia<br>• Patient not filling pump reservoir when needed leading to hyperglycemia<br>• Magnetic Resonance Imaging resulting in pump/transmitter malfunction<br>• Inaccurate insulin delivery due to sudden altitude changes.<br>• Hypoglycemia or hyperglycemia from manual bolus<br>• Hypoglycemia or Hyperglycemia from the use of the AHCL Auto Mode feature where sensor glucose values may be used to calculate insulin bolus amounts<br>• Hypoglycemia or hyperglycemia from computer hacking | • 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. |
| Risks with hyperglycemia may include<br>• Diabetic ketoacidosis<br>• Symptomatic ketosis<br>• Cardiovascular event<br>• Dehydration<br>• Potassium and sodium imbalance<br>• Shock<br>• Altered mental status<br>• Coma<br>• Acidosis | Prevention and mitigation include:<br>• Follow the provided user guides for insulin pump management.<br>• 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.<br>• Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems.<br>• Instruct to check their meter glucose if their high symptoms do not match their sensor alerts or sensor glucose readings in order to make diabetes treatment decisions.<br>• Instruct to check their meter glucose if there are any concerns that the sensor glucose value is not accurate.<br>• Alternative method of managing glucose levels will be available (insulin and syringe for example) |

| | |
|---|---|
| Risks with hypoglycemia may include:<br>• Seizure<br>• Coma<br>• Altered mental status<br>• Loss of consciousness<br>• Cardiovascular event<br>• Death<br>• Risk of rebound hyperglycemia with ketosis | Prevention and mitigation include:<br>• Follow the provided user guides for insulin pump management.<br>• 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 with problems.<br>• Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems.<br>• Instruct to check their meter glucose if their low symptoms do not match their sensor alerts or sensor glucose readings in order to make diabetes treatment decisions.<br>• Instruct to check their meter glucose if there are any concerns that the sensor glucose value is not accurate.<br>• Instruct to have glucose on hand for hypoglycemia |
| **Risk with Sensors** | **Prevention and Mitigation** |
| Risks with Sensors may include:<br>• Skin irritation or reaction to adhesives<br>• Bruising<br>• Discomfort<br>• Redness<br>• Bleeding<br>• Excessive bleeding due to anticoagulants<br>• Pain<br>• Rash<br>• Infection<br>• Irritation from tapes used with glucose-sensing products<br>• Raised bump<br>• Appearance of a small "freckle-like" dot where needle was inserted<br>• Allergic reaction<br>• Syncopal episode secondary to needle insertion<br>• Soreness or tenderness<br>• Swelling at insertion site<br>• Sensor fracture, breakage or damage<br>• Minimal blood splatter associated with sensor needle removal<br>• Residual redness associated with adhesive and or tapes<br>• Scarring<br>• Scab<br>• Blister<br>• Itchiness<br>• Inflammation<br>• Anxiety | Prevention and mitigation include:<br>• Follow the provided user guides for insertions and care of sensors.<br>• If a sensor site becomes infected or inflamed, the sensor will be removed and another placed in a new location<br>• Instruct to check their meter glucose if their high or low symptoms do not match their sensor alerts or sensor glucose readings in order to make diabetes treatment decisions.<br>• Instruct to check their meter glucose if there are any concerns that the sensor glucose value is not accurate.<br>• Instruct if there are no sensor values, no treatment decisions will be made until a BG is confirmed. |

| | |
|---|---|
| • Incorrect sensor glucose reading results in incorrect diabetes management<br>• Subject over-treating secondary to alarms which can result in hyperglycemia or hypoglycemia<br>• Anxiety associated with insertion | |
| **Risks with Transmitter** | **Prevention and Mitigation** |
| Risks with Transmitter may include:<br>• Skin irritation or reaction to adhesives<br>• Bruising<br>• Discomfort<br>• Redness<br>• Pain<br>• Rash<br>• Infection<br>• Irritation from tapes used with glucose-sensing products<br>• Raised bump<br>• Allergic reaction<br>• Soreness or tenderness<br>• Residual redness associated with adhesive and/ or tapes<br>• Scarring<br>• Scab<br>• Blister<br>• Itchiness<br>• Inflammation | Prevention and mitigation include:<br>• Follow the provided user guides.<br>• Train on the proper use of the transmitters. |
| **Risks with Serter** | **Prevention and Mitigation** |
| Risks with serters may include:<br>• Improper insertion may lead to device performance issue or hyperglycemia | Prevention and mitigation include:<br>• Follow the provided user guides for insertions and care of device.<br>• 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:<br>• Potential risks associated with frequent meter testing of blood glucose and blood ketones include discomfort and ecchymosis at tips of fingers<br>• Potential risks associated with finger stick testing include discomfort and bruising | Prevention and mitigation include:<br>• Follow the provided user guides for use of the study meter(s) with fingerstick testing.<br>• Train on the proper use of the study meter(s) and fingerstick testing. |

| Risk with Closed Loop Therapy | Prevention and Mitigation |
|---|---|
| Risks with Closed Loop may include:<br>• Hypoglycemia<br>• Severe hypoglycemia<br>• Hyperglycemia<br>• Diabetic ketoacidosis<br>• User Entry Error<br>  ○ Patient administering boluses by entering false carb doses leading to hypoglycemia or hyperglycemia<br>  ○ Patient entering false glucose values for any reason leading to hypoglycemia and hyperglycemia<br>  ○ Patient entering false BG values for calibration leading to hypoglycemia or hyperglycemia<br>• Sensor failure resulting from patient failure to calibrate leading to hypoglycemia or hyperglycemia<br>• Sensor over-reading resulting in hypoglycemia<br>• Sensor under-reading resulting in hyperglycemia<br>• Sensor missed transmission, or any other fault resulting in no SG value, leading to hyperglycemia or hypoglycemia<br>• 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<br>• Hypoglycemia related to patient taking insulin via injection while in Closed Loop (Auto Mode)<br>• Hypoglycemia or hyperglycemia related to entering or exiting Closed Loop(Auto Mode)<br>• Insulin over-delivery due to potential interference from acetaminophen<br>• Cyber security hacking into pump | Prevention and mitigation include:<br>• Follow the provided user guides for insulin pump management.<br>• Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems.<br>• Instructed to check their meter glucose if their high or low symptoms do not match their sensor alerts or sensor glucose readings in order to make diabetes treatment decisions.<br>• Instructed to check their meter glucose if there are any concerns that the sensor glucose value is not accurate.<br>• Instructed if there are no sensor values, no treatments decision will be made until a BG is confirmed.<br>• Instruct to have glucose on hand for hypoglycemia<br>• Instruct to avoid the use of products containing acetaminophen<br>• 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.<br>• If acetaminophen is taken, while the SmartGuard™ feature is active, subjects will be instructed to use the temp target feature (when used, Auto Correction is not available)<br>• Instruct subjects that in case of prolonged use of acetaminophen, the temp target feature can be used repeatedly and in succession<br>• Pump has cybersecurity encryptions to prevent hacking |

| | |
|---|---|
| Risks with hyperglycemia may include<br>• Diabetic ketoacidosis<br>• Symptomatic ketosis<br>• Cardiovascular event<br>• Dehydration<br>• Potassium and sodium imbalance<br>• Shock<br>• Altered mental status<br>• Coma<br>• Acidosis | Prevention and mitigation include:<br>• Follow the provided user guides for insulin pump management.<br>• Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems.<br>• Instruct to check their meter glucose if their high symptoms do not match their sensor alerts or sensor glucose readings in order to make diabetes treatment decisions.<br>• Instruct to check their meter glucose if there are any concerns that the sensor glucose value is not accurate.<br>• Instruct if there are no sensor values, no treatments decision will be made until a BG is confirmed. |
| Risks with hypoglycemia may include:<br>• Seizure<br>• Coma<br>• Altered mental status<br>• Loss of consciousness<br>• Cardiovascular event<br>• Death<br>• Risk of rebound hyperglycemia with ketosis | Prevention and mitigation include:<br>• Follow the provided user guides for insulin pump management.<br>• Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems.<br>• Instruct to check their meter glucose if their low symptoms do not match their sensor alerts or sensor glucose readings in order to make diabetes treatment decisions.<br>• Instruct to check their meter glucose if there are any concerns that the sensor glucose value is not accurate.<br>• Instruct if there are no sensor values, no treatment decisions will be made until a BG is confirmed.<br>• Instruct to have glucose on hand for hypoglycemia |
| **Risk with Acetaminophen Use** | **Prevention and Mitigation** |
| Potential risks with acetaminophen may include:<br>• False elevation of sensor glucose readings potentially resulting in an over-delivery of insulin which may cause hypoglycemia. The level of inaccuracy depends on the amount of acetaminophen active in subject's body and may be different for each subject<br>• Liver damage, liver failure and/or rare but fatal liver failure can occur<br>• Skin rash and/or serious and potentially fatal skin reactions have been reported<br>• Allergic reactions including those which are serious and potentially fatal can occur<br>• Kidney disease<br>• Lowered blood counts (red cells, and white | Prevention and mitigation include:<br>• Follow the user guide<br>• Instruct to avoid the use of products containing acetaminophen<br>• 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<br>• If acetaminophen is taken, while the SmartGuard™ feature is active, subjects will be instructed to use the temp target feature (when used, Auto Correction is not available)<br>• Instruct subjects that in case of prolonged use of acetaminophen, the temp target feature can be used repeatedly and in succession |

| | |
|---|---|
| cells) | |

## 10.2. Risk Minimization

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

## 10.3. Potential Benefits

Subjects are not expected to benefit from participation in this study; however, 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 may experience improved glucose control. The risk, as with all automated 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 revised device algorithm.

## 10.5. Risk Determination

In the opinion of the sponsor, this study is considered to be a significant risk (SR) study. Results of an evaluation of the requirements per 21 CFR Part 812.3, led to the SR determination as follows:

- The devices could present a potential for serious risk to subject health, safety or welfare.
- The devices are for a use of substantial importance in treating disease, and presents potential for serious risk to subject health, safety or welfare.

Therefore, submission of an Investigational Device Exemption (IDE) application to the United States Food and Drug Administration is required.

# 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***: 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.

| Causality Categories for Investigational Center | Causality Categories for CEC: |
|---|---|
| • Not Related<br>• Unlikely<br>• Possible<br>• Probable<br>• Causal relationship | • Not Related<br>• Possible<br>• 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.

Refer to Section 9.12.2 for Stopping Rules for Entire Study and 7 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 software and CareLink™ system software report (when applicable)
- Review of pump data from CareLink™ Personal software and CareLink™ system 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 software and CareLink™ system software upload and review of 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 progress and safety. The Board will convene approximately every 90 days. The Board will also meet when ad hoc review is required.

**The DMC will perform 3 main functions:**

**First:** DMC will track and trend the overall Safety of the study.

Event rate, defined as number of events per 100 patient years will be reviewed by the DMC with respect to the following:

- Event rate of all SAEs.
- Event rate of severe hypoglycemia
- Event rate of severe hyperglycemia
- Event rate of DKA
- Event rate of device related AEs.

**Second:** Based on their meetings, DMC will recommend a decision to the sponsor regarding the following:

- Whether or not enrollment should be halted.
- Whether or not the entire study will need to be stopped including for those subjects who have received study devices already.

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

- The DMC will provide a recommendation to proceed with enrollment of subjects 7-13 years of age after 15 subjects 14-75 years of age have completed 30 days of the study period.

**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.

In their recommendation to the sponsor, the DMC may take into account the thresholds listed below for the number of subjects experiencing hypoglycemia requiring assistance from another person or DKA to identify when the number of subjects experiencing these events exceeds the number that would be anticipated for the study population over the duration of this study. These thresholds should be interpreted with caution due to potential differences in study populations and study design.

a. Rates taken from Type 1 exchange (Cengiz et. Al, and Weinstock et. Al), are higher than the clinical studies STAR 3, 530G adult in-home study (CEP266) and 530G Pediatric in-home study (CEP287).
b. Reasons for lower rates of severe hypoglycemia and DKA in the clinical studies mentioned could be related to several factors including but not limited to the exclusion of those with DKA or severe hypoglycemia, additional attention secondary to mandatory study visits, selection bias of motivated patients willing to perform study procedures and access to free study devices during the course of the study.
c. The DMC should consider stopping study if rates of severe hypoglycemia and DKA are significantly worse (e.g. higher) in AHCL than rates provided by clinical trials mentioned in Table 4.
d. Age consideration may also be factored in by the DMC. For example, severe hypoglycemia rates in those >25 years may be higher than those 25 years and below.
e. Should DKA and/or severe hypoglycemia occur early in the study, the DMC should consider that the higher event rate may not necessarily represent a significant safety concern.

**Table 4. Hypoglycemia / Hyperglycemia / DKA Threshold**

| Adverse Event | Reference | Reference Rate > 25 years old | Reference Rate 15-25 years old | Reference Rate <15 years old |
|---|---|---|---|---|
| Severe Hyperglycemia events per 100 patient years | CER 302 | NA | NA | 71.64 |
| DKA events per 100 patient years | STAR 3<br>Bergenstal et. al | SAP arm: 0.68<br>Control arm: 0 | SAP arm: 2.7<br>Control arm: 3.6 | SAP arm: 2.2<br>Control arm: 0 |
| | 530G Adult in-home study CEP 266<br>(MDT on file) | 1.27 | 3.4 | N/A |
| | Pediatric in-home study CEP 287<br>(MDT on file) | N/A | N/A | 0 |
| | Type 1 exchange Weinstock et. al | 4.8 | N/A | N/A |
| | Type 1 exchange Cengiz et. al | N/A | 9.9 | 9.9 |
| | | | | |
| Severe hypoglycemia per 100 patient years | STAR 3<br>Bergenstal et. al | SAP arm: 16.5<br>Control arm: 20.9 | SAP arm: 5.4<br>Control arm: 3.9 | SAP arm: 10.2<br>Control arm: 3.6 |
| | 530G Adult in-home study CEP 266<br>(MDT on file) | 0.85 | 0 | N/A |
| | 530G Pediatric in-home study CEP 287<br>(MDT on file) | N/A | N/A | 1.42 |
| | Type 1 exchange Weinstock et. al | 11.8 | N/A | N/A |
| | Type 1 exchange Cengiz et. al | N/A | 6.2 | 6.2 |

Descriptive summary (i.e. not statistically powered) for severe hypoglycemia and DKA events rates will be performed between the HCL and control arms for each age group (< 15 years, 15-25 years, and > 25 years), as well as the overall event rates.

**Severe hypoglycemia and DKA event rates were taken from the following:**

1. Richard Bergenstal et.al: Effectiveness of Sensor-Augmented Insulin-Pump Therapy in Type 1Diabetes.New England Journal of Medicine, 2010; 363:311-20

2. Weinstock et. al: Severe hypoglycemia and diabetic ketoacidosis in adults with type 1 diabetes: results from the T1D Exchange clinic registry. J Clin Endocrinol Metab. 2013 Aug;98(8):3411-9.

3. Cengiz et. al: Severe hypoglycemia and diabetic ketoacidosis among youth with type 1 diabetes in the T1D Exchange clinic registry. Pediatr Diabetes. 2013 Sep;14(6):447-54.
4. MDT on file: Statistical Analysis Plan (SAP) for CEP304, 056-F286

## 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 discontinuing prior to study completion will be summarized.

## 14.3. Subject Demographics and Baseline Characteristics

Subject characteristics, including age, gender, race, ethnicity, medical diagnosis, height, weight, BMI, and baseline HbA1c 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 – During Study Period

- The mean change in HbA1c will be presented from baseline to EOS Period
- Change of Total Daily Dose (TDD) of insulin from baseline to EOS Period
- Change of weight from baseline to EOS Period
- Time spent in Auto Mode versus time spent in Manual Mode
- Time in different range (% of SG): SG < 50, 54, 60, 70 mg/dL, SG > 140, 180, 250 mg/dL, 350 mg/dL
- Number of Events, Area Under Curve (AUC) and Time in the hyperglycemic range: sensor glucose (SG) > 140, 180, 250, 350 mg/dL
- Number of Events, AUC and Time in the hypoglycemic range: SG < 50, 54, 60, and 70 mg/dL
    - Change in BG values during meal challenge (BG prior and BG 2 hours after meal)
    - Change in % of time in euglycemia (70-180 mg/dL) during meal challenge, prior and 2 hours after meal
    - Difference in AUC during meal challenge prior and 2 hours after meal
- Subgroup analysis will be performed for:
    - Age
        - 7-13

        - 14-75
    - Setpoint
        - 100 mg/dL
        - 120 mg/dL
    - Temp Target usage
        - Yes
        - No

### 14.4.2. Descriptive Endpoints – During Continued Access Period

**Descriptive Endpoints for Continued Access**

- Time in Target Range (TIR, 70 – 180 mg/dL)
- Time Below Range (TBR, SG < 70 mg/dL)
- Time Above Range (TAR, SG > 180 mg/dL)
- Time in different range (% of SG): SG < 54, 60 mg/dL, SG > 140, 250 mg/dL, 350 mg/dL
- Number of Events, Area Under Curve (AUC) and Time in the hyperglycemic range: sensor glucose (SG) > 140, 180, 250, 350 mg/dL
- Number of Events, AUC and Time in the hypoglycemic range: SG < 54, 60, and 70 mg/dL
- Time spent in Auto Mode versus time spent in Manual Mode
- The mean change in HbA1c , if applicable
- Change of Total Daily Dose (TDD) of insulin

### 14.4.3. Safety Endpoints – During Study Period and Continued Access

The safety of the study will be evaluated and summarized per arm, including but not limited to the following:

- Serious Adverse Events (SAE)
- Serious Adverse Device Effects (SADE)
- Unanticipated Adverse Device Effects (UADE)
- Incidence of Severe Hypoglycemia
- Incidence of DKA

### 14.4.4. Device Deficiencies – During Study Period and Continued Access

Device Deficiencies summary will be used to characterize device deficiencies:

- All reports of device issues.

### 14.4.5. Subject Feedback

Descriptive summary will be used to characterize study questionnaire results. Refer to CIP321 AHCL Questionnaire Guide for administration details.

## 14.5. Sample Size Considerations

A total of up to 350 subjects (aged 7-75) will be enrolled at up to 30 investigational centers in the US in order to reach 250 subjects who will complete the study (125 for 14-75 years old and 125 for 7-13 years old).

## 14.6. Exploratory Analysis for Study Period

### 14.6.1. Analysis of Primary Safety Endpoint

The overall mean difference of the change in HbA1c from baseline to end of 3-month study period. The goal is to show simple superiority in reducing HbA1c from baseline to end of 3-month study period.

### 14.6.2. Analysis of Primary Effectiveness Endpoint

The primary effectiveness endpoint is change in % of time in euglycemia (70 – 180 mg/dL).

The overall mean change in % of time in euglycemia (70-180 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

### 14.6.3. Analysis of Secondary Effectiveness Endpoint

The secondary effectiveness endpoints are hierarchically ordered and will be evaluated in the fixed sequence from endpoint 1 to 3 during the study period.

- Secondary Endpoint: % of Time in Hyperglycemia (> 180 mg/dL)

The overall mean change in % of time in hyperglycemia (> 180 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

- Secondary Endpoint: % of Time in Hyperglycemia (> 140 mg/dL)

The overall mean change in % of time in hyperglycemia (> 140 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

- Secondary Endpoint: % of Time in Hypoglycemia (< 70 mg/dL)

The overall mean change in % time in hypoglycemia (< 70 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

### 14.6.4. Sample Size Justification

### 14.6.5. Sample Size for Primary Safety Endpoint

The overall mean change in HbA1c from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

The hypothesis is mathematically expressed as:

Ho: $\mu \geq 0\%$

Ha: $\mu < 0\%$

Where μ is the mean of % of change in HbA1c (3-month - baseline). The null hypothesis will be rejected if the one-sided 97.5% upper confidence limit of the mean change in HbA1c is less than 0%.

Assuming the mean difference of change in HbA1c from baseline to the 3-month visit is 0.4%, the standard deviation of change in HbA1c is 1.1%, SAS power and sample size calculator shows that a total of 125 subjects will provide greater than 90% power with one-sided type I error of 0.025.

A total of up to 150 subjects will be enrolled to account for subject attrition

### 14.6.6. Sample Size for Primary Effectiveness Endpoint: % of Time in Euglycemia (70- 180 mg/dL)

The overall mean change in % of time in euglycemia (70- 180 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

The hypothesis is mathematically expressed as:

Ho: $\mu \leq 0\%$

Ha: $\mu > 0\%$

Where μ is the mean of change in % of time in time in euglycemia (3-month - baseline). The null hypothesis will be rejected if the one-sided 97.5% lower confidence limit of the mean change in % of time in Time in Range is greater than 0%.

Assuming the mean of change in time in time in euglycemia (%) from baseline to the 3-month visit is 4.0%, the standard deviation of change in percentage time in Time in Range is 11.0%, SAS power and sample

size calculator shows that a total of 125 subjects will provide greater than 90% power with one-sided type I error of 0.025.

A total of up to 150 subjects will be enrolled to account for subject attrition.

### 14.6.7. Sample Size for Secondary Effectiveness Endpoint

### 14.6.8. Sample Size for Secondary Effectiveness Endpoint: % of Time in >180 mg/dL

The overall mean change in % of time in hyperglycemia (> 180 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

The hypothesis is mathematically expressed as:

Ho: $\mu \geq 0\%$

Ha: $\mu < 0\%$

Where μ is the mean of change in % of time in hyperglycemia (3-month - baseline). The null hypothesis will be rejected if the one-sided 97.5% upper confidence limit of the mean change in % of time in hyperglycemia is less than 0%.

Assuming the mean of change in time in hyperglycemia from baseline to the 3-month visit is 3.0%, the standard deviation of change in percentage time in hyperglycemia is 8.0%, SAS power and sample size calculator shows that a total of 125 subjects will provide greater than 90% power with one-sided type I error of 0.025.

A total of up to 150 subjects will be enrolled to account for subject attrition.

### 14.6.9. Sample Size for Secondary Effectiveness Endpoint: % of Time in >140 mg/dL

The overall mean change in % of time in hyperglycemia (> 140 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

The hypothesis is mathematically expressed as:

Ho: $\mu \geq 0\%$

Ha: $\mu < 0\%$

Where μ is the mean of change in % of time in hyperglycemia (3-month - baseline). The null hypothesis will be rejected if the one-sided 97.5% upper confidence limit of the mean change in % of time in hyperglycemia is less than 0%.

Assuming the mean of change in time in hyperglycemia from baseline to the 3-month visit is 4.0%, the standard deviation of change in percentage time in hyperglycemia is 10.0%, SAS power and sample size calculator shows that a total of 125 subjects will provide greater than 90% power with one-sided type I error of 0.025.

A total of up to 150 subjects will be enrolled to account for subject attrition.

### 14.6.10. Sample Size for Secondary Effectiveness Endpoint: % of Time in <70 mg/dL

The overall mean change in % time in hypoglycemia (< 70 mg/dL) from baseline to the end of study will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

The hypothesis is mathematically expressed as:

Ho: $\mu \geq 0\%$

Ha: $\mu < 0\%$

Where μ is the mean of change in % of time in hypoglycemia (3-month - baseline). The null hypothesis will be rejected if the one-sided 97.5% upper confidence limit of the mean change in % of time in hypoglycemia is less than 0%.

Assuming the mean of change in time in hypoglycemia from baseline to the 3-month visit is 3.5%, the standard deviation of change in percentage time in hypoglycemia is 10.0%, SAS power and sample size calculator shows that a total of 125 subjects will provide greater than 90% power with one-sided type I error of 0.025.

A total of up to 150 subjects will be enrolled to account for subject attrition.

## 14.7. Final Reports

### 14.7.1. Study Phase Final Report for Subjects 14-75 Years Old

A study phase final report will be generated once the 14-75 years old cohort have completed the study period. Descriptive and exploratory endpoints and safety data for 14-75 years old subjects will be summarized and presented in the final report. This report will be sent to FDA as part of the Pre-Market Application before the report for pediatric subjects 7-13 years of age will be submitted.

### 14.7.2. Study Phase Final Report for Subjects 7-13 Years Old

A separate study phase final report will be generated once the 7-13 years old cohort have completed the study period. Descriptive and exploratory endpoints and safety data for 7-13 years old subjects will be summarized and presented in the final report. This report will be sent to FDA as part of the Pre-Market Application after the report for subjects 14-75 years has been submitted.

### 14.7.3. Continued Access Phase Final Report for Subjects 14-75 Years Old

An addendum continuation phase final report will be generated once the 14-75 year old cohort have completed the continuation phase visits. Descriptive endpoints, subject feedback, and safety data for the continuation phase will be summarized and presented in the final report.

### 14.7.4. Continued Access Phase Final Report for Subjects 7-13 Years Old

An addendum continuation phase final report will be generated once the 7-13 year old cohort have completed the continuation phase visits. Descriptive endpoints, subject feedback, and safety data for the continuation phase will be summarized and presented in the final report.

# 15. Ethics

## 15.1. Statement(s) of Compliance

IRB

This CIP, any subsequent amendments to this CIP, the ICF/Assent form, subject material, 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 the CIP, Clinical Investigation Agreement; US 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 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, CIP applicable regulations set forth in 21 CFR Part 812 and all other applicable and other applicable FDA 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.
- Protecting the rights, safety, and welfare of subjects under the investigator's care
    - Providing reasonable medical care for study subjects for medical problems that arise during participation in the trial that are, or could be, related to the study intervention
    - Providing reasonable access to needed medical care, either by the investigator or by another identified, qualified individual (e.g., when the investigator is unavailable, when specialized care is needed)
    - Adhering to the CIP so that study subjects are not exposed to unreasonable risks
- Controlling devices under investigation (21 CFR 812.100)
- Investigator is responsible for providing adequate supervision of those to whom tasks have been delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of a clinical study.
- 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.
- 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, an IRB, the sponsor, a monitor, or FDA, including required reports.
    - records of receipt, use or disposition of study devices
    - 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, FDA and 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 FDA and 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 FDA and 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 on 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. At minimum, it will be verified whether signed and dated ICF/Assent form 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 Software and CareLink™ System Software

During the course of the study, subject's BG values may be assessed from the CONTOUR®NEXT LINK 2.4 study meter/Accu-Chek™* Guide Link study meter. The SG values may be assessed from the study pump. The study pump will be uploaded in CareLink™ Personal software/ CareLink™ system 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 software data, CareLink™ system software and source worksheets 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, if applicable, for the purposes of monitoring, audit, or inspection. If applicable, where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigational center team with a statement that it is a true and complete reproduction of the original source document.

### 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's and/or user guides
- 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 ICF/Assent form
- Source document requirements
- 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 5. Investigator Reporting Requirements**

| Report | Submit to | Description/Constraints |
|---|---|---|
| AEs | Sponsor, IRB, and 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. |
| 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. |
| Failure to obtain informed consent/assent 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 of study completion or termination 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

Gold AE, Macleod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. Diabetes Care. 1994;17(7):697–703.

# 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<br>800 SW 39th St, Ste 110<br>Renton, WA 98057 | Advarra | 6100 Merriweather Drive, Suite 600<br>Columbia, Maryland 21044 | Active |
| 002 | Bruce Bode | Atlanta Diabetes Associates<br>1800 Howell Mill Road, Suite 450,<br>Atlanta, GA 30318 | Advarra | 6100 Merriweather Drive, Suite 600<br>Columbia, Maryland 21044 | Active |
| 003 | Satish Garg | Barbara Davis Center for Diabetes<br>1775 Aurora Court, A1321, Aurora, CO 80045 | Western Institutional Review Board | Bonnie Love (Chairperson)<br>Susan Abramson, MD (Vice Chairperson)<br>1019 39th Avenue SE Suite 120<br>Puyallup, WA 98374-2115 | Inactive |
| 004 | Kevin Kaiserman | SoCal Diabetes<br>3400 Lomita Boulevard, Suite 209, Torrance, CA 91316 | Advarra | 6100 Merriweather Drive, Suite 600<br>Columbia, Maryland 21044 | Active |
| 005 | John Reed | Endocrine Research Solutions<br>1475 Holcomb Bridge Rd., Suite129<br>Roswell, GA 30076, USA | Advarra | 6100 Merriweather Drive, Suite 600<br>Columbia, Maryland 21044 | Active |
| 006 | Rodica Pop-Busui | University of Michigan<br>Frank Lloyd Wright Dr. Lobby G, Suite 1500<br>Ann Arbor, MI 48109, USA | Advarra | 6100 Merriweather Drive, Suite 600<br>Columbia, Maryland 21044 | Active |

| Site No. | Principal Investigator Name | Investigational Center's Name & Address | IRB Name | IRB Chairperson* and Address | Investigational Center Status |
|---|---|---|---|---|---|
| 007 | Mark Christiansen | Diablo Clinical Research 2255 Ygnacio Valley Road, Suite M Walnut Creek, CA 94598, USA | Advarra | 6100 Merriweather Drive, Suite 600 Columbia, Maryland 21044 | Inactive |
| 008 | David Liljenquist | Rocky Mountain Diabetes and Osteoporosis Center 3910 Washington Pkwy Idaho Falls, ID 83404, USA | Western Institutional Review Board | Bonnie Love (Chairperson) Susan Abramson, MD (Vice Chairperson) 1019 39th Avenue SE Suite 120 Puyallup, WA 98374-2115 | Active |
| 010 | Dorothy Shulman | University of South Florida Diabetes Center Faculty Offices 13220 USF Laurel Dr., suite 1100 Tampa, FL 33612, USA | Advarra | 6100 Merriweather Drive, Suite 600 Columbia, Maryland 21044 | Active |
| 011 | Robert Slover | Barbara Davis Center for Diabetes 1775 Aurora Court, A140, Aurora, CO 80045 | Western Institutional Review Board | Bonnie Love (Chairperson) Susan Abramson, MD (Vice Chairperson) 1019 39th Avenue SE Suite 120 Puyallup, WA 98374-2115 | Active |
| 012 | Athena Philis-Tsimikas | Scripps Whittier Diabetes Institute 9898 Genesee Ave., 6th Floor La Jolla, CA 92037, USA | Advarra | 6100 Merriweather Drive, Suite 600 Columbia, Maryland 21044 | Active |
| 013 | Kamalpreet Singh | Texas Diabetes and Endocrinology 110 Deer Ridge Drive, Round Rock, TX 78681 | Advarra | 6100 Merriweather Drive, Suite 600 Columbia, Maryland 21044 | Active |

| Site No. | Principal Investigator Name | Investigational Center's Name & Address | IRB Name | IRB Chairperson* and Address | Investigational Center Status |
|---|---|---|---|---|---|
| 014 | 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 |
| 015 | Jennifer Sherr | Yale School of Medicine One Long Wharf Drive Suite 503 New Haven, CT 06519, USA | Advarra | 6100 Merriweather Drive, Suite 600 Columbia, Maryland 21044 | Active |
| 016 | Mark Kipnes | Diabetes and Glandular Disease Clinic 5107 Medical Drive, San Antonio, TX 78229 | Western Institutional Review Board | Bonnie Love (Chairperson) Susan Abramson, MD (Vice Chairperson) 1019 39th Avenue SE Suite 120 Puyallup, WA 98374-2115 | Active |
| 017 | Catherine Pihoker | Seattle Children's Hospital 4800 Sand Point Way NE Seattle, WA 98105, USA | Western Institutional Review Board | Bonnie Love (Chairperson) Susan Abramson, MD (Vice Chairperson) 1019 39th Avenue SE Suite 120 Puyallup, WA 98374-2115 | Active |
| 018 | James Thrasher | Medical Investigations Inc. 11400 Huron Lane Little Rock AR 72211 | Western Institutional Review Board | Bonnie Love (Chairperson) Susan Abramson, MD (Vice Chairperson) 1019 39th Avenue SE Suite 120 Puyallup, WA 98374-2115 | Active |

| Site No. | Principal Investigator Name | Investigational Center's Name & Address | IRB Name | IRB Chairperson* and Address | Investigational Center Status |
|---|---|---|---|---|---|
| 019 | Bruce Buckingham | Stanford University<br>780 Welch Road<br>CJHuang Bldg.<br>Suite CJ320<br>Palo Alto, CA<br>94304, USA | Western Institutional Review Board | Bonnie Love (Chairperson)<br>Susan Abramson, MD (Vice Chairperson)<br>1019 39th Avenue SE<br>Suite 120<br>Puyallup, WA 98374-2115 | Active |
| 020 | Kashif Latif | AM Diabetes and Endocrinology Center<br>Insulin Pump Center<br>3025 Kate Bond Rd<br>Bartlett, TN<br>38133, USA | Advarra | 6100 Merriweather Drive, Suite 600<br>Columbia, Maryland 21044 | Active |

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

### 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

## 18.2. Labeling and IFUs of Devices

The current labeling and IFU for the study devices 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. CIP321 Visit Details Table

Refer to excel sheet labeled as "CIP321_ Visit Details Table".

# 19. Version History

| Version | Summary of Changes | Author(s)/Title |
|---|---|---|
| A.1 | • Initial release | [redacted] Principal Medical Writer |

| | | |
|---|---|---|
| A.2 | • Update Study Title and purpose to include pediatric and removed "effectiveness"<br>• Updated Study Design:<br>  ○ Increased study period duration to 90 days<br>  ○ Number of subjects to complete the study is added for each age subgroup: 14-75 and 7-13<br>  ○ Added staged enrollment<br>  ○ Correction target in study pump updated for all age groups<br>• Increased sample size and investigational centers<br>• Updated Inclusion criteria #1 and #2<br>• Added additional criteria #3<br>• Updated DMC section regarding staged enrollment<br>• Added HbA1c as part of primary safety endpoint | [redacted] Principal Medical Writer |
| A.3 | • Harmonized 90 days study period throughout CIP<br>• Updated staged enrollment instructions<br>• Clarified temporary target<br>• Provided examples for exercise<br>• Added inclusion criteria #11<br>• Updated setpoint in the study pump<br>• Updated exercise and meal challenge instructions<br>• Updated exclusion criteria #1<br>• Added exclusion criteria #5: | [redacted] Principal Medical Writer |

| | | |
|---|---|---|
| | • Updated subject stopping rules<br>• Updated Descriptive Endpoints<br>• Updated Primary Safety Endpoints<br>• Updated Risks with Insulin Administration and Pumps<br>• Updated Risks with Closed Loop Therapy:<br>• Updated Visit Details Table associated with CIP amendment | |
| A.4 | • Updated Study Design (includes setpoint in study pump, instructions on exercise and meal challenges, and companions instructions)<br>• Updated Study Periods Synopsis for Auto Mode Settings<br>• Updated prevention and mitigation with Insulin Administration and Pumps<br>• Updated prevention and mitigation with Closed Loop Therapy<br>• Updated prevention and mitigation with Acetaminophen Use<br>• Updated Ethics<br>• Updated Visit Details Table associated with CIP amendment | [redacted] Principal Medical Writer |
| A.5 | • Updated meal challenges with and without Meal Bolus<br>• Removed exclusion criteria on subjects who has used any closed loop therapy<br>• Updated study timeline<br>• Updated Rationale section<br>• Updated Auto Mode settings | [redacted] Principal Medical Writer |
| B (Equivalent to FDA Version B.1) | • Updated Study Design:<br>○ added continued access period and updated the study diagram figure | [redacted] Principal Medical Writer |

| | | |
|---|---|---|
| | ○ Added notes for meal challenges during the run-in period<br>• Updated exclusion criteria #4 (Subject has Hypoglycemia Unawareness, measured by the Gold questionnaire as ≥4)<br>• Updated Visit Schedule, Visit Figure and Visit Details Table<br>○ Removed combining V4 and 5 if all sensor wear criteria are met under Run-in period.<br>○ Added continued access visits<br>• Updated exercise challenge details during study period and on temp target<br>• Updated header title for clarity on the analysis of the endpoints (if for study period, continued access, or both)<br>• Added the continued access phase final report for the completed continuation phase visits.<br>• Updated 670G insulin pump description<br>• Updated Temp target setting instructions under Study Procedures Overview Box<br>• Corrected 670G pump model under DA Table<br>• Updated DA Table<br>• Updated Subject Consent section to add revised ICF/Assent may be available also prior to entering the continued access period<br>• Updated Notification of Adverse Events<br>• Updated name of IRB and Chairperson contact | |

| | | |
|---|---|---|
| | • Corrected abbreviation of MC2 under Monitors Contact Information and added to Glossary<br>• Removed the names and address of the monitor(s)<br>• Unit typo error: mg/L corrected to mg/dL | |
| C (Equivalent to FDA Version C.1) | • Added clarification around HbA1c test collection recommendation during the continued access period<br>• Updated CIP321 Visit Details Table reflecting above change | [redacted] Principal Medical Writer |
| D.1 | • Updated Glossary section- Added IB, TAR, TBR and TIR<br>• Updated the following sections to reflect the use of the 780G system in continued access period:<br>○ Investigational and non-investigational/exempt devices<br>○ Study Design<br>○ Purpose<br>○ Objective(s)<br>○ Study Visit Schedule<br>○ Overview of Study Procedures<br>○ Sample Size and Investigational Sites<br>○ Duration<br>○ Schedule of Events<br>○ Descriptive Endpoints for Continued Access with two periods<br>○ Background<br>○ Product Accountability<br>○ Final Report Report after 30-day 780G study period during Continued Access Phase | [redacted] Principal Medical Writer |

| | | |
|---|---|---|
| | • Updated device classification for devices which are Class I/Class II exempt<br>• Updated excel sheet labeled as "CIP321_ Visit Details Table"<br>• Added new inclusion criteria to include capable individuals of legal age.<br>• Updated Subject Consent section for a legal guardian or authorized representative only allowed for subjects who are younger than legal age according to their state requirements.<br>• Potential Risks section:<br>  ○ Added a title and number for table listed under this section<br>  ○ Added new risks with blood glucose meter (investigational meter)<br>  ○ Updated section to align with Medtronic<br>• Adverse Events Assessments section updated to align with safety template. The update includes all ISO definitions to align with ISO 14155:2020.<br>• Updated following sections to align with safety template:<br>  ○ Risk Minimization<br>  ○ Clinical Event Committees<br>  ○ Device Deficiencies and Troubleshooting<br>• Updated the following subsections under Deviation Handling:<br>  ○ Reporting Requirements for Study Deviations<br>  ○ Unplanned CIP Deviations<br>• Updated Ethics section | |

| | | |
|---|---|---|
| | • Updated Accessibility of Investigational Center Staff and Study Materials section<br>• Updated Investigational Center Disqualification section<br>• Updated CIP Amendments section<br>• Updated Suspension or Early Termination section<br>• Updated Early Investigational Center Suspension or Termination section<br>• Updated Investigational Centers and IRBs section<br>• Trademark updated- added Accu-Chek® and Bluetooth® and updated year to current<br>• Transferred protocol to the revised Enterprise Clinical QMS CIP template (056-F275, Version B)<br>• Updated the following clinical document names:<br>  ○ Delegation of Authority Log/ Delegated Task List<br>  ○ Investigator Statement<br>  ○ Investigator Site File<br>• Updated References section | |
| D.2 | • Updated year to 2021 in copyright statement<br>• Added new non-investigational device: Guardian™ (3) Link Transmitter (MMT-7911)<br>• Updated the following sections to remove the 780G Study period in continued access period:<br>  ○ Study Design<br>  ○ Purpose<br>  ○ Study Visit Schedule and figure | [redacted] Principal Medical Writer |

| | | |
|---|---|---|
| | ○ Overview of Study Procedures<br>○ CIP321 Visit Details Table<br>• Updated new names for the CareLink™ softwares and apps<br>• Updated Purpose and Objective section<br>• Updated Study Design section for continued access period expansion and SMBG recommendations for 780G system<br>• Added the word “high” under SMBG recommendations for 670G system, version 4.0 AHCL and 780G system<br>• Updated Subject Feedback - removed names of questionnaires and replaced with a reference to CIP321 AHCL Questionnaire Guide<br>• Updated other compatible CGM device options to be used with the 780G system throughout the CIP, as applicable<br>• Removed the analysis for Period 1 and Period 2 for continued access period<br>• Corrected data that will be summarized in the final report for the continued access phase<br>• Removed Final Report after 30-day 780G study period during Continued Access Phase<br>• Updated Background section<br>• Generalized the statement for reporting of urine ketones<br>• Updated “CIP321_ Visit Details Table” to align with CIP amendment<br>• Updated DA Requirements table<br>• Updated HbA1c collection under the CAS period (refer to Visit Details table for schedule) | |

| | | |
|---|---|---|
| | • Updated Subject Exit, Withdrawal or Discontinuation section (hydroxyurea withdrawal criteria)<br>• Updated Prevention and Mitigation with Closed Loop<br>• Updated Risks, Prevention and Mitigation with Acetaminophen use<br>• Removed risks related to investigational blood glucose meter use<br>• Added other regulatory authorities to access study records under Investigator's Responsibilities section<br>• Updated definition for Serious Adverse Event to align with ISO 14155:2020<br>• Updated Investigational Centers table, including Advarra's new address. | |
| D.3 | • Corrected model number for Guardian™ Sensor (4)<br>• Clarified that the Guardian™ Sensor (3) and Guardian™ Sensor (4) may be connected interchangeably with the Guardian™ 4 Transmitter. The following sections were updated to reflect this:<br>○ Study Design under the CA Period<br>○ Guardian™ Transmitter description<br>○ 780G Insulin Pump description<br>• Updated Device Accountability Requirements table for both Guardian™ Sensor (3) and Guardian™ Sensor (4)<br>• Updated "CIP321_ Visit Details Table" to align with CIP amendment | [redacted] Principal Medical Writer |

| | | |
|---|---|---|
| D(Equivalent to FDA Version D.4) | • See "Attachment 1: CIP321 Description of Protocol Changes Version C to D" for details on changes<br>• Corrected product number for Blue Adapter<br>• Updated Study Design for Continued Access Period expansion and SMBG recommendations for 780G system<br>• Updated CA Period Visits and figure (added 3 more visits under the CA Period)<br>• Updated MiniMed™ 780G Insulin Pump description<br>• Updated Guardian™ Sensor (4) description<br>• Updated Guardian™ 4 Transmitter description<br>• Updated Guardian™ Sensor (3) description<br>• Updated Prevention and Mitigation with Closed Loop and acetaminophen use<br>• Updated "CIP321_ Visit Details Table" to align with CIP amendments | [redacted] Principal Medical Writer |