Medtronic

Study Title	Safety and Effectiveness Evaluation of the MiniMed™ 780G System Used in Combination with the DS5 CGM
NCT Number	NCT05714059
Document Description	CIP337 Clinical Investigation Plan (Version A)
Document Date	11-JAN-2023

Medtronic **Clinical Investigation Plan**	
Clinical Investigation Plan (CIP)/Study Title	Safety and Effectiveness Evaluation of the MiniMed™ 780G System Used in Combination with the DS5 CGM
CIP Identifier	337
Investigational Device Exemption (IDE) Number	G220306
Product Names & Model Numbers	**Investigational Products** • MiniMed™ 780G Insulin Pump (MMT-1884) - referred to as the study pump throughout this CIP • Disposable Sensor (MMT-5100) – labeled as DS5 and referred to as DS5 throughout this CIP **Non-Investigational/Exempt Products** • Medtronic Extended infusion set (MMT-430, MMT-431, MMT-432, MMT-433, MMT-440, MMT-441, MMT-442, and MMT-443) • Medtronic Extended Reservoir (MMT-342) • Medtronic CareLink™ Personal software (MMT-7333) • Medtronic CareLink system software (MMT-7350) • Roche Accu-Chek™ Guide Link Glucose Meter (08116083022) -referred to as the Accu-Chek Guide Link study meter throughout this CIP • MiniMed Clinical App (MMT-6103 Android™ app; MMT-6104 IOS™ app) • CareLink Clinical App (MMT-6113 Android™ app; MMT-6114 IOS™ app) • Blue Bluetooth® Low Energy Adapter (ACC-1003911)- referred to as the Blue Adapter in this CIP • Abbott™ Precision Xtra™ Blood Glucose & Ketone Monitoring System or other approved ketone meter- to be used for blood ketone measurements only -referred to as the ketone meter throughout this CIP • Accu-Chek Guide test strips (07453736001) • Sponsor-provided smartphone, upon request • Over-the-counter (OTC) tape(s) if needed (e.g., Hypafix™ tape, etc.)
Description of CIP	This study will evaluate the safety and effectiveness of the MiniMed 780G system used in combination with the DS5 CGM in type 1 adult and pediatric subjects in a home setting.
Sponsor	Medtronic MiniMed, Inc. ("Medtronic") 18000 Devonshire St

	Northridge, CA 91325 866.948.6633
Document Version	A (Equivalent to A.4)
Version Date	11-JAN-2023
Document Reference Number	D00459337

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1. Glossary

Abbreviations	
ADE	Adverse Device Effect
AE	Adverse Event
AHCL	Advanced Hybrid Closed Loop
AUC	Area Under Curve
BG	Blood Glucose
BMI	Body Mass Index
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CIP	Clinical Investigation Plan
CRF	Case Report Form
CSII	Continuous Subcutaneous Insulin Infusion
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DD	Device Deficiency
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
DoH	Declaration of Helsinki
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
ER	Emergency Room
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Glycosylated hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ID	Identification
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	Intravenous
MC2	Medtronic Core Clinical Solutions
NGSP	National Glycohemoglobin Standardization Program
PC	Personal Computer
PI	Principal Investigator
QC	Quality Control
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event

Abbreviations	
SAP	Sensor Augmented Pump
SAP	Statistical Analysis Plan
SG	Sensor Glucose
SMBG	Self-Monitoring of Blood Glucose
SOP	Standard Operating Procedure
SR	Significant Risk
TDD	Total Daily Dose
TIR	Time in Range
TLS	Transport Layer Security
TS	Technical Support
TSH	Thyroid-stimulating hormone
UADE	Unanticipated Adverse Device Effect

2. Synopsis

Title	Safety and Effectiveness Evaluation of the MiniMed™ 780G System Used in Combination with the DS5 CGM
Clinical Study Type	Safety and Effectiveness Evaluation
Sponsor	Medtronic MiniMed, Inc. ("Medtronic") 18000 Devonshire St Northridge, CA 91325 866.948.6633
Indication Under Investigation	• Type 1 diabetes • Labeling for the MiniMed 780G system used in combination with the DS5 CGM
Product Names & Model Numbers	**Investigational Products** • MiniMed™ 780G Insulin Pump (MMT-1884) - referred to as the study pump throughout this CIP • Disposable Sensor (MMT-5100) – labeled as DS5 and referred to as DS5 throughout this CIP **Non-Investigational/Exempt Products** • Medtronic Extended infusion set (MMT-430, MMT-431, MMT-432, MMT-433, MMT-440, MMT-441, MMT-442, and MMT-443) • Medtronic Extended Reservoir (MMT-342) • Medtronic CareLink™ Personal software (MMT-7333) • Medtronic CareLink system software (MMT-7350) • Roche Accu-Chek™ Guide Link Glucose Meter (08116083022) - referred to as the Accu-Chek Guide Link study meter throughout this CIP • MiniMed Clinical App (MMT-6103 Android™ app; MMT-6104 IOS™ app) • CareLink Clinical App (MMT-6113 Android™ app; MMT-6114 IOS™ app) • Blue Bluetooth® Low Energy Adapter (ACC-1003911)- referred to as the Blue Adapter in this CIP • Abbott™ Precision Xtra™ Blood Glucose & Ketone Monitoring System or other approved ketone meter- to be used for blood ketone measurements only -referred to as the ketone meter throughout this CIP • Accu-Chek Guide test strips (07453736001) • Sponsor-provided smartphone, upon request • Over-the-counter (OTC) tape(s) if needed (e.g., Hypafix™ tape, etc.)

<table>
<tr><td>Purpose</td><td>The purpose of this study is to confirm the safety and effectiveness of the MiniMed 780G insulin pump used in combination with the DS5 CGM in type 1 diabetes adult and pediatric subjects in a home setting.</td></tr>
<tr><td>Objective(s)</td><td>The objective of this study is to evaluate the safety and effectiveness of the MiniMed 780G insulin pump used in combination with the DS5 CGM.</td></tr>
<tr><td>Study Design</td><td>This study is a multi-center, single arm study in insulin-requiring adult and pediatric subjects with type 1 diabetes on the MiniMed 780G system using DS5 as well as Medtronic Extended infusion set and reservoir. The run-in period and study period will be approximately 120 days long.

The period from Visit 1 (consent and screening) through Visit 6 must be completed in 30 days.

Run-in Period (Visits 2-6):
The run-in period begins at Visit 2 and ends once Visit 7 occurs.

The intent of the run-in period will be to allow subjects to become familiar with new study devices while using their own insulin: Humalog™ (insulin lispro injection), NovoLog® (insulin aspart solution for injection), or Admelog® (insulin lispro injection). During the run-in period, study subjects will be using the study pump with only the Sensor Augmented Pump (SAP) function activated (i.e., SmartGuard™ feature is turned OFF), DS5, Medtronic Extended infusion set and reservoir.

SmartGuard (with Auto Correction OFF) during the run-in period will be permitted for study subjects who are using the Auto Mode feature in a Medtronic pump prior to screening. In the 780G study pump, the term “Auto Mode” has been replaced with “SmartGuard”. All others are to use the system in Manual Mode during the run-in period.

<table>
<tr><th>Therapy at Screening</th><th>Pump Setting During Run-in Period</th></tr>
<tr><td>Continuous Subcutaneous Insulin Infusion (CSII)</td><td>Manual Mode</td></tr>
<tr><td>SAP (no closed loop)</td><td>Manual Mode</td></tr>
<tr><td>SAP (with closed loop) in non-Medtronic pump</td><td>Manual Mode</td></tr>
<tr><td>SAP (with closed loop) in Medtronic pump as Auto Mode</td><td>SmartGuard feature with Auto Correction OFF</td></tr>
</table>

During the run-in period and only for subjects with Auto Mode experience through the use of a Medtronic insulin pump, a 120 mg/dL Auto Basal target should be set. It is recommended that Active Insulin Time is set to 4 hours.</td></tr>
</table>

	Note: The Auto Basal target setting and Active Insulin Time should be set as recommended above, unless there is a documented safety reason that would not permit these settings to be used. Subjects who do not have experience with Medtronic insulin pumps, as specified above, will use the system in Manual Mode. All subjects and their parents/caregivers (if applicable) 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 and how to use glucose and glucagon in case of hypoglycemia. Parents/caregivers (if applicable) will be instructed that they should be with the subject in the same residence or building overnight. If the MiniMed Clinical app and the CareLink Clinical app are being used, parents/caregivers (if applicable) will be instructed that subjects should be connected to CareLink via the appropriate Smartphone app for data uploading and push notifications for low or high blood sugar when they are apart, e.g., at school, other activities. Instructions on the appropriate operation of the apps will be provided. For study purposes, subjects and parents/caregivers (if applicable) will be trained and/or instructed to perform self-monitoring of blood glucose (SMBG) if subjects are experiencing a severe hypoglycemic event, severe hyperglycemic event or diabetic ketoacidosis (DKA). Subjects and their parents/caregivers (if applicable) will also be instructed to check subject blood ketones using a Precision Xtra ketone meter or other approved ketone meter if the Accu-Chek Guide Link study meter reading is greater than 300 mg/dL. As a precaution, subjects and their parents/caregivers (if applicable) will be told that subjects should keep their own insulin pump supplies in a safe place and to have back up supplies on hand (such as insulin and syringe, or insulin pen) 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 and their parents/caregivers (if applicable) will be instructed to insert the DS5 into subjects only in the locations that are specified in the User Guide. Reminders will be given to subjects and their parents/caregivers (if applicable) at each office visit. Information about sensor insertions will be collected at each study visit on an electronic case report form (eCRF) in the study database, e.g., insertion location. Subjects and their parents/caregivers (if applicable) will be trained on all parts of the device system. This will involve live training conducted

by the investigational center staff. A training checklist for both subject and parents/caregivers (if applicable) will be implemented and completed. Parents/caregivers (if applicable) should be available for relevant parts or all of this training, either in person or virtually.

After completion of training on the study devices, subjects and their parents/caregivers (if applicable) may attend additional visits in the days immediately following the start of system use, as needed.

Study Period (Visits 7-15):
All subjects will continue using the study pump with SmartGuard feature enabled (including Auto Correction), Humalog/ NovoLog/ Admelog, DS5, infusion set and reservoir. During the study period, each subject will be encouraged to continue on the same brand of insulin with which they started. All SmartGuard™ features will be activated and should be used for the duration of the study period.

Subjects should use the system with the SmartGuard feature turned on at all times. When prompted by the pump, subjects should take appropriate measures and follow directions on the pump to remain in or return to the SmartGuard feature. During times when subjects are not able to use the SmartGuard feature, they should use the system in Manual Mode (e.g., with Suspend before low or Suspend on low activated).

Therapy at Screening	**Pump Setting During Study Period**
Continuous Subcutaneous Insulin Infusion (CSII)	SmartGuard feature with Auto Correction ON
SAP (no closed loop)	SmartGuard feature with Auto Correction ON
SAP (with closed loop) in non-Medtronic pump	SmartGuard feature with Auto Correction ON
SAP (with closed loop) in Medtronic pump as Auto Mode	SmartGuard feature with Auto Correction ON

During the first 3 weeks (between Visits 7 and 11) of the study period, a 120 mg/dL Auto Basal target should be set. It is recommended that Active Insulin Time is initially set to 4 hours and then titrated towards 2-3 hours or at the investigator's discretion.

During the next 3 weeks (between Visits 11 and 13) of the study period, the Auto Basal target setting should be set to 100 mg/dL. Active Insulin Time is recommended to be set to 2-3 hours or at investigator's discretion.

During the remaining weeks of the study (any time after Visit 13) of the study period, the Auto Basal target as well as Active Insulin Time

<table>
<tr><td></td><td>should be set to what is best for the individual subject, at investigator's discretion.

Note: The Auto Basal target setting and Active Insulin Time should be set as recommended above, unless there is a documented safety reason that would not permit these settings to be used.

After completion of live training on the SmartGuard function, subjects and their parents/caregivers (if applicable) may attend additional visits in the days immediately following the start of SmartGuard use, as needed.

SMBG recommendations for 780G system:
Calibration is not required with the MiniMed 780G system using the DS5. However, a calibration is optional and it will automatically occur any time a blood glucose (BG) is entered. Occasionally, subjects may receive a notification if the pump needs a BG to enter or stay in the SmartGuard feature. Subjects will be instructed to perform SMBG if their symptoms do not match the sensor glucose (SG) value (i.e., they develop symptoms of hypoglycemia or hyperglycemia, but the SG value does not correlate with their symptoms).</td></tr>
<tr><td>Sample Size and Investigational Centers</td><td>A total of up to 250 subjects with insulin-requiring type 1 diabetes age 7-80 will be enrolled at up to 25 investigational centers across the United States in order to have 200 subjects enter the study period. Up to 125 subjects will be enrolled in the pediatric age group (7-17 years of age), up to 125 in the adult age group (18 years or older):

<table>
<tr><th>Subject Age Group</th><th>Sub-groups</th><th>Enrollment Goal (N)</th></tr>
<tr><td rowspan="2">Pediatric
Age 7 – 17 years</td><td>Age 7 - 13 years</td><td>Minimum 20 Subjects</td></tr>
<tr><td>Age 14 - 17 years</td><td>Minimum 20 Subjects</td></tr>
</table>

Investigational centers will be encouraged to enroll a study population that represents a wide variety of backgrounds.</td></tr>
<tr><td>Duration</td><td>The study is anticipated to last approximately 18 months from first investigational center initiation to study completion. Individual subject participation is expected to be approximately 120 days through the study period.</td></tr>
<tr><td>Inclusion Criteria</td><td>1. Age 7 - 80 years at time of screening.
2. Has a clinical diagnosis of type 1 diabetes:
a. 14 – 80 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.
b. 7 – 13 years of age: A clinical diagnosis of type 1 diabetes for 1 year or more as determined via medical record or</td></tr>
</table>

	source documentation by an individual qualified to make a medical diagnosis. 3. Does not require a legally authorized representative to consent on their behalf due to mental or intellectual disability. 4. Subject or parent/caregiver is literate and able to read the language offered in the pump or pump materials. 5. Subject and/or legally authorized representative is willing to provide informed consent for participation. 6. Is willing to perform fingerstick blood glucose measurements as needed. 7. Is willing to wear the system continuously throughout the study. 8. Must have a minimum daily insulin requirement (Total Daily Dose) of greater than or equal to 8 units. 9. 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 National Glycohemoglobin Standardization Program (NGSP) certified Central Laboratory. HbA1c testing must follow NGSP standards. 10. Has thyroid-stimulating hormone (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. Uses pump therapy for greater than 6 months prior to screening (with or without CGM experience). 12. Is willing to upload data from the study pump, must have Internet access, and a computer system, or compatible smartphone that meets the requirements for uploading the study pump. 13. Is willing to take one of the following insulins and can financially support the use of insulin preparations as required by the study: a. Humalog (insulin lispro injection) b. NovoLog (insulin aspart injection) c. Admelog (insulin lispro injection)
Exclusion Criteria	1. Has a history of 2 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. Has been hospitalized or has visited the ER in the 6 months prior to screening resulting in a primary diagnosis of uncontrolled diabetes. 3. Has had DKA in the last 6 months prior to screening visit. 4. Will not tolerate tape adhesive in the area of sensor placement as assessed by a qualified individual. 5. Has any unresolved adverse skin condition in the area of sensor placement (e.g., psoriasis, dermatitis herpetiformis, rash, Staphylococcus infection).

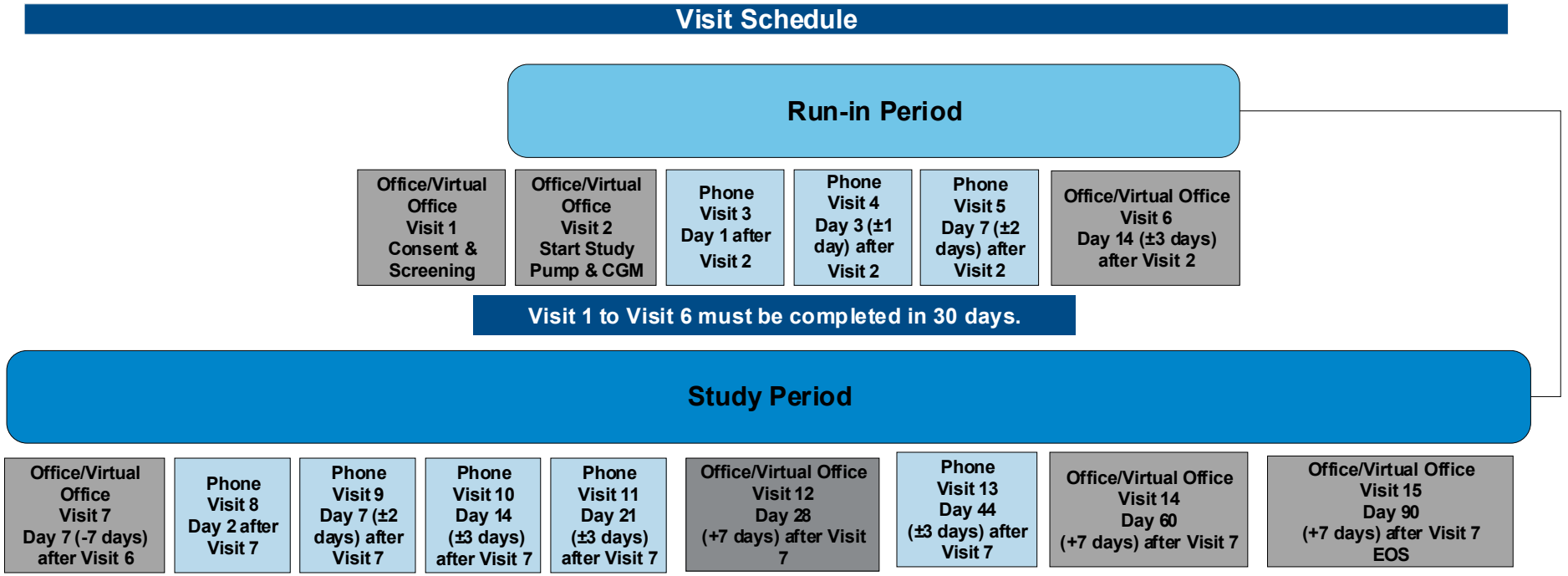
	6. Is female of child-bearing potential and result of pregnancy test is positive at screening. 7. Is sexually active female of child-bearing potential and is not using a form of contraception deemed reliable by the investigator. 8. Is female and plans to become pregnant during the course of the study. 9. Is being treated for hyperthyroidism at time of screening. 10. Has diagnosis of adrenal insufficiency. 11. Has taken any oral, injectable, or intravenous (IV) glucocorticoids within 8 weeks from time of screening visit, or plans to take any oral, injectable, or IV glucocorticoids during the course of the study. 12. Is using hydroxyurea at time of screening or plans to use it during the study. 13. 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. Has used a MiniMed 780G pump prior to screening. 15. Is currently abusing illicit drugs. 16. Is currently abusing marijuana. 17. Is currently abusing prescription drugs. 18. Is currently abusing alcohol. 19. Using pramlintide (Symlin), DPP-4 inhibitor, liraglutide (Victoza or other GLP-1 agonists), metformin, canagliflozin (Invokana or other SGLT2 inhibitors) at time of screening. 20. 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. 21. Has elective surgery planned that requires general anesthesia during the course of the study. 22. Has sickle cell disease, hemoglobinopathy; or has received red blood cell transfusion or erythropoietin within 3 months prior to time of screening. 23. Plans to receive red blood cell transfusion or erythropoietin over the course of study participation. 24. Is diagnosed with current eating disorder such as anorexia or bulimia. 25. Has been diagnosed with chronic kidney disease that results in chronic anemia. 26. Has a hematocrit that is below the normal reference range of lab used. 27. Is on dialysis. 28. Has serum creatinine of >2 mg/dL. 29. Has celiac disease that is not adequately treated as determined by the investigator. 30. 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, or ventricular rhythm disturbances.

	31. Has had history of cardiovascular event 1 year or more from the time of screening without a. a normal EKG and stress test within 6 months prior to screening or during screening or b. clearance from a qualified physician prior to receiving the study devices if there is an abnormal EKG or stress test. 32. Has 3 or more cardiovascular risk factors listed below without a normal EKG within 6 months prior to screening or during screening or clearance from a qualified physician if there is an abnormal EKG: • 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 33. Is a member of the research staff involved with the study. 34. Is a Medtronic Diabetes employee or their immediate family member (excluding adult children and/or adult siblings).
Study Visit Schedule	Subjects may participate in up to 15 planned study visits, as presented below in **Synopsis Figure 1**, for approximately 120 days of device wear. A virtual office visit (audio visual) may be performed for certain office visits where an office visit is not possible. For detailed information, see **Section 9.1.1.** **Visit 1 to Visit 6 must be completed in 30 days.** • Visit 1 (Office/Virtual Office): Consent and screening ○ Collect labs **<u>Run-In</u>:** • Visit 2 (Office/Virtual Office): Start Run-In ○ Eligibility has been confirmed ○ Start study pump and CGM ○ Adjust pump settings as needed ○ Register and upload study pump in CareLink Personal and CareLink system • Visit 3 (Phone): Day 1 after Visit 2 – Required for subjects without CGM or closed loop experience; as needed for all others ○ Ask subjects and their parents/caregivers (if applicable) if they require assistance, e.g., additional training ○ Ask subjects about adverse events and device performance ○ Review CareLink reports

	• Visit 4 (Phone): Day 3 (±1 day) after Visit 2 – Required for subjects without CGM or closed loop experience; as needed for all others
	  ○ Ask subjects and their parents/caregivers (if applicable) if they require assistance, e.g., additional training
	  ○ Ask subjects about adverse events and device performance
	  ○ Review CareLink reports
	• Visit 5 (Phone): Day 7 (±2 days) after Visit 2
	  ○ Ask subjects and their parents/caregivers (if applicable) if they require assistance, e.g., additional training
	  ○ Ask subjects about adverse events and device performance
	  ○ Review CareLink reports
	• Visit 6 (Office/Virtual Office): Day 14 (±3 days) after Visit 2
	  ○ Ask subjects and their parents/caregivers (if applicable) if they require assistance, e.g., additional training
	  ○ Ask subjects about adverse events and device performance
	  ○ Review CareLink reports
	  ○ Visit 6 and 7 may be combined
	
	Study Period:
	• Visit 7 (Office/Virtual Office): Start Study Period, Day 7 (-7 days) after Visit 6
	  ○ Adjust pump settings as needed
	  ○ Ask subjects about adverse events and device performance
	  ○ Review CareLink reports
	  ○ Start Auto Basal target at 120 mg/dL setpoint with Active Insulin Time set to 4 hours, titrate towards 2-3 hours or at investigator's discretion
	  ○ Turn on SmartGuard with Auto Corrections "ON"
	• Visit 8 (Phone): Day 2 after Visit 7 – Required for subjects without CGM or closed loop experience; as needed for all others
	  ○ Adjust pump settings as needed
	  ○ Ask subjects and their parents/caregivers (if applicable) if they require assistance, e.g., additional training
	  ○ Ask subjects about adverse events and device performance
	  ○ Review CareLink reports
	• Visit 9 (Phone): Day 7 (±2 days) after Visit 7
	  ○ Adjust pump settings as needed
	  ○ Ask subjects about adverse events and device performance

	○ Review CareLink reports • Visit 10 (Phone): Day 14 (±3 days) after Visit 7 ○ Adjust pump settings as needed ○ Ask subjects about adverse events and device performance ○ Review CareLink reports • Visit 11 (Phone): Day 21 (±3 days) after Visit 7 ○ Adjust pump settings as needed ○ Ask subjects about adverse events and device performance ○ Review CareLink reports ○ Change Auto Basal target to 100 mg/dL setpoint with Active Insulin Time set to 2-3 hours or at investigator's discretion • Visit 12 (Office/Virtual Office): Day 28 (+7 days) after Visit 7 ○ Adjust pump settings as needed ○ Ask subjects about adverse events and device performance ○ Review CareLink reports • Visit 13 (Phone): Day 44 (±3 days) after Visit 7 ○ Adjust Auto Basal target with Active Insulin Time at investigator's discretion ○ Ask subjects about adverse events and device performance ○ Review CareLink reports • Visit 14 (Office/Virtual Office): Day 60 (+7 days) after Visit 7 ○ Ask subjects about adverse events and device performance ○ Review CareLink reports • Visit 15 (Office/Virtual Office): Day 90 (+7 days) after Visit 7 ○ Collect HbA1C ○ Ask subjects about adverse events and device performance ○ Review CareLink reports ○ Return study devices ○ End of Study (EOS)

Synopsis Figure 1. Visit Schedule



Safety and Monitoring/Risk Analysis	Safety monitoring and risk analysis details are described in **Section 9.4.**
Device Deficiencies	Subject and investigational center reports of device deficiencies (DDs) 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**.
Statistical Analysis for Endpoints and Hypothesis	Safety and effectiveness endpoints will be evaluated independently for ages 18-80 and ages 7-17. **Primary Safety Endpoint** • Age 18-80: The overall mean change in HbA1c from baseline to end of 3-month study period. The goal is to show non-inferiority with a margin of 0.4% comparing to a threshold of -0.5% in reducing HbA1c from baseline to end of 3-month study period. • Age 7-17: The overall mean change in HbA1c from baseline to end of 3-month study period. The goal is to show non-inferiority with a margin of 0.4% comparing to a threshold of -0.38% in reducing HbA1c from baseline to end of 3-month study period. **Primary Effectiveness Endpoint** • Age 18-80: The mean % of time in range (TIR 70-180 mg/dL) will be estimated and compared to a threshold of 73.7% by a non-inferiority test with a margin of 7.5% and a significance level of 0.025 (one-sided). • Age 7-17: The mean % of time in range (TIR 70-180 mg/dL) will be estimated and compared to a threshold of 65.3% by a non-inferiority test with a margin of 7.5% and a significance level of 0.025 (one-sided). **Secondary Effectiveness Endpoints** • Age 18-80: The mean % of time in hypoglycemia (< 54 mg/dL) will be estimated and compared to a threshold of 0.86% by a non-inferiority test with a margin of 2% and a significance level of 0.025 (one-sided). • Age 18-80: The mean % of time in range (TIR 70-180 mg/dL) will be estimated and compared to a threshold of 73.7% by a simple superiority test and a significance level of 0.025 (one-sided). • Age 7-17: The mean % of time in hypoglycemia (< 54 mg/dL) will be estimated and compared to a threshold of 0.71% by a non-inferiority test with a margin of 2% and a significance level of 0.025 (one-sided). • Age 7-17: The mean % of time in range (TIR 70-180 mg/dL) will be estimated and compared to a threshold of 65.3% by a simple superiority test and a significance level of 0.025 (one-sided).

	Descriptive Endpoints
	• Time spent in the SmartGuard feature versus time spent in Manual Mode
	• Change in mean glucose value from baseline to EOS
	• Time in different ranges (% of SG): SG < 70 mg/dL, 70 mg/dL ≤ SG ≤ 140 mg/dL, SG > 140 mg/dL, 180 mg/dL, 250 mg/dL, and 350 mg/dL
	• Number of Events, Area Under Curve (AUC) and Time in the hyperglycemic range: SG > 140 mg/dL, 180 mg/dL, 250 mg/dL, and 350 mg/dL
	• Number of Events, AUC and Time in the hypoglycemic range: SG < 54 mg/dL and 70 mg/dL
	• Change of Total Daily Dose (TDD) of insulin from baseline to EOS
	• Change of weight from baseline to EOS
	• Subgroup analysis will be performed for:
	  ○ Setpoint
	  ▪ 100 mg/dL
	  ▪ 110 mg/dL
	  ▪ 120 mg/dL
	  ▪ 150 mg/dL (Temp Target Usage)
	
	Safety Data Summarized
	• Serious Adverse Events (SAE)
	• Serious Adverse Device Effects (SADE)
	• Unanticipated Adverse Device Effects
	• Incidence of Severe Hypoglycemia
	• Incidence of Severe Hyperglycemia
	• Incidence of DKA
	
	Device Deficiencies
	Descriptive summary will be used to characterize DDs:
	• All reports of device issues.
	
	Subject Feedback
	Descriptive summary will be used to characterize study survey/questionnaire results. Refer to CIP337 Survey/Questionnaire Guide for administration details.
	
	<u>Simulation Data</u>
	Computer simulated data may be compared to study data.

Final Report	The study results 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 (CGM), including sensor-augmented pump therapy, experience improvements in glycemic control. Advanced sensor-augmented insulin pumps are now being used in clinical practice including closed loop systems that automatically adjust the amount of insulin delivered to maintain glucose levels near the target value set by the user. [1]

The MiniMed 780G system is a closed loop insulin system. In addition to automatically adjusting the amount of insulin delivered based on sensor glucose (SG) readings while operating with the SmartGuard feature activated, the MiniMed 780G insulin pump can also automatically deliver correction boluses when the system has been delivering at the maximum allowable basal rate and SG remains elevated. This pump is currently in commercial distribution in Europe and is under review by the United States Food and Drug Administration (FDA). Previous clinical investigations involved the 670G Version 4.0 pump (contains the 780G Advanced Hybrid Closed Loop [AHCL] algorithm) used in combination with the Guardian Sensor (3) glucose sensor, Guardian Link (3) transmitter, Humalog, and Novolog insulin. This investigation is intended to confirm safety and effectiveness of the 780G insulin pump used in combination with the DS5, which combines the glucose sensor and transmitter into one disposable device. Additional details for non-clinical/clinical testing are provided in the report of prior investigations.

3.2 Purpose

The purpose of this study is to confirm the safety and effectiveness of the MiniMed 780G insulin pump used in combination with the DS5 CGM in type 1 diabetes adult and pediatric subjects in a home setting.

4. Objectives and Endpoints

4.1 Objectives

The objective of this study is to evaluate the safety and effectiveness of the MiniMed 780G insulin pump used in combination with the DS5 CGM.

4.2 Endpoints

Safety and effectiveness endpoints will be evaluated independently for ages 18-80 and ages 7-17.

4.2.1 Primary Safety Endpoint

- Age 18-80: The overall mean change in HbA1c from baseline to end of 3-month study period. The goal is to show non-inferiority with a margin of 0.4% comparing to a threshold of -0.5% in reducing HbA1c from baseline to end of 3-month study period.
- Age 7-17: The overall mean change in HbA1c from baseline to end of 3-month study period. The goal is to show non-inferiority with a margin of 0.4% comparing to a threshold of -0.38% in reducing HbA1c from baseline to end of 3-month study period.

4.2.2 Primary Effectiveness Endpoint

- Age 18-80: The mean % of time in range (TIR 70-180 mg/dL) will be estimated and compared to a threshold of 73.7% by a non-inferiority test with a margin of 7.5% and a significance level of 0.025 (one-sided).

- Age 7-17: The mean % of time in range (TIR 70-180 mg/dL) will be estimated and compared to a threshold of 65.3% by a non-inferiority test with a margin of 7.5% and a significance level of 0.025 (one-sided).

4.2.3 Secondary Effectiveness Endpoint

- Age 18-80: The mean % of time in hypoglycemia (< 54 mg/dL) will be estimated and compared to a threshold of 0.86% by a non-inferiority test with a margin of 2% and a significance level of 0.025 (one-sided).

- Age 18-80: The mean % of time in range (TIR 70-180 mg/dL) will be estimated and compared to a threshold of 73.7% by a simple superiority test and a significance level of 0.025 (one-sided).

- Age 7-17: The mean % of time in hypoglycemia (< 54 mg/dL) will be estimated and compared to a threshold of 0.71% by a non-inferiority test with a margin of 2% and a significance level of 0.025 (one-sided).
- Age 7-17: The mean % of time in range (TIR 70-180 mg/dL) will be estimated and compared to a threshold of 65.3% by a simple superiority test and a significance level of 0.025 (one-sided).

4.2.4 Descriptive Endpoints

- Time spent in the SmartGuard feature versus time spent in Manual Mode
- Change in mean glucose value from baseline to EOS
- Time in different ranges (% of SG): SG < 70 mg/dL, 70 mg/dL ≤ SG ≤ 140 mg/dL, SG > 140 mg/dL, 180 mg/dL, 250 mg/dL, and 350 mg/dL

- Number of Events, Area Under Curve (AUC) and Time in the hyperglycemic range: SG > 140 mg/dL, 180 mg/dL, 250 mg/dL, and 350 mg/dL
- Number of Events, AUC and Time in the hypoglycemic range: SG < 54 mg/dL and 70 mg/dL
- Change of Total Daily Dose (TDD) of insulin from baseline to EOS
- Change of weight from baseline to EOS
- Subgroup analysis will be performed for:
    - Setpoint
        - 100 mg/dL
        - 110 mg/dL
        - 120 mg/dL
        - 150 mg/dL (Temp Target Usage)

4.2.5 Safety Data Summarized

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

- Unanticipated Adverse Device Effects
- Incidence of Severe Hypoglycemia
- Incidence of Severe Hyperglycemia
- Incidence of DKA

4.2.6 Device Deficiencies

Descriptive summary will be used to characterize DDs:

- All reports of device issues.

4.2.7 Subject Feedback

Descriptive summary will be used to characterize study survey/questionnaire results. Refer to CIP337 Survey/Questionnaire Guide for administration details.

4.2.8 Simulation Data

Computer simulated data may be compared to study data.

5. Study Design

This study is a multi-center, single arm study in insulin-requiring adult and pediatric subjects with type 1 diabetes on the MiniMed 780G system using DS5 as well as Medtronic Extended infusion set and reservoir. The run-in period and study period will be approximately 120 days long.

The period from Visit 1 (consent and screening) through Visit 6 must be completed in 30 days.

Run-in Period (Visits 2-6):

The run-in period begins at Visit 2 and ends once Visit 7 occurs.

The intent of the run-in period will be to allow subjects to become familiar with new study devices while using their own insulin: Humalog™ (insulin lispro injection), NovoLog® (insulin aspart solution for injection), or Admelog® (insulin lispro injection). During the run-in period, study subjects will be using the study pump with only the Sensor Augmented Pump (SAP) function activated (i.e., SmartGuard™ feature is turned OFF), DS5, Medtronic Extended infusion set and reservoir.

SmartGuard (with Auto Correction OFF) during the run-in period will be permitted for study subjects who are using the Auto Mode feature in a Medtronic pump prior to screening. In the 780G study pump, the term "Auto Mode" has been replaced with "SmartGuard". All others are to use the system in Manual Mode during the run-in period.

Therapy at Screening	Pump Setting During Run-in Period
Continuous Subcutaneous Insulin Infusion (CSII)	Manual Mode
SAP (no closed loop)	Manual Mode
SAP (with closed loop) in non-Medtronic pump	Manual Mode
SAP (with closed loop) in Medtronic pump as Auto Mode	SmartGuard feature with Auto Correction OFF

During the run-in period and only for subjects with Auto Mode experience through the use of a Medtronic insulin pump, a 120 mg/dL Auto Basal target should be set. It is recommended that Active Insulin Time is set to 4 hours.

Note: The Auto Basal target setting and Active Insulin Time should be set as recommended above, unless there is a documented safety reason that would not permit these settings to be used.

Subjects who do not have experience with Medtronic insulin pumps, as specified above, will use the system in Manual Mode.

All subjects and their parents/caregivers (if applicable) 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 and how to use glucose and glucagon in case of hypoglycemia.

Parents/caregivers (if applicable) will be instructed that they should be with the subject in the same residence or building overnight.

If the MiniMed Clinical app and the CareLink Clinical app are being used, parents/caregivers (if applicable) will be instructed that subjects should be connected to CareLink via the appropriate Smartphone app for data uploading and push notifications for low or high blood sugar when they are apart, e.g., at school, other activities. Instructions on the appropriate operation of the apps will be provided.

For study purposes, subjects and parents/caregivers (if applicable) will be trained and/or instructed to perform self-monitoring of blood glucose (SMBG) if subjects are experiencing a severe hypoglycemic event, severe hyperglycemic event or diabetic ketoacidosis (DKA). Subjects and their parents/caregivers (if applicable) will also be instructed to check subject blood ketones using a Precision Xtra ketone meter

or other approved ketone meter if the Accu-Chek Guide Link study meter reading is greater than 300 mg/dL.

As a precaution, subjects and their parents/caregivers (if applicable) will be told that subjects should keep their own insulin pump supplies in a safe place and to have back up supplies on hand (such as insulin and syringe, or insulin pen) 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 and their parents/caregivers (if applicable) will be instructed to insert the DS5 into subjects only in the locations that are specified in the User Guide. Reminders will be given to subjects and their parents/caregivers (if applicable) at each office visit. Information about sensor insertions will be collected at each study visit on an electronic case report form (eCRF) in the study database, e.g., insertion location.

Subjects and their parents/caregivers (if applicable) will be trained on all parts of the device system. This will involve live training conducted by the investigational center staff. A training checklist for both subject and parents/caregivers (if applicable) will be implemented and completed. Parents/caregivers (if applicable) should be available for relevant parts or all of this training, either in person or virtually.

After completion of training on the study devices, subjects and their parents/caregivers (if applicable) may attend additional visits in the days immediately following the start of system use, as needed.

Study Period (Visits 7-15):
All subjects will continue using the study pump with SmartGuard feature enabled (including Auto Correction), Humalog/ NovoLog/ Admelog, DS5, infusion set and reservoir. During the study period, each subject will be encouraged to continue on the same brand of insulin with which they started. All SmartGuard™ features will be activated and should be used for the duration of the study period.

Subjects should use the system with the SmartGuard feature turned on at all times. When prompted by the pump, subjects should take appropriate measures and follow directions on the pump to remain in or return to the SmartGuard feature. During times when subjects are not able to use the SmartGuard feature, they should use the system in Manual Mode (e.g., with Suspend before low or Suspend on low activated).

Therapy at Screening	Pump Setting During Study Period
Continuous Subcutaneous Insulin Infusion (CSII)	SmartGuard feature with Auto Correction ON
SAP (no closed loop)	SmartGuard feature with Auto Correction ON
SAP (with closed loop) in non-Medtronic pump	SmartGuard feature with Auto Correction ON
SAP (with closed loop) in Medtronic pump as Auto Mode	SmartGuard feature with Auto Correction ON

During the first 3 weeks (between Visits 7 and 11) of the study period, a 120 mg/dL Auto Basal target should be set. It is recommended that Active Insulin Time is initially set to 4 hours and then titrated towards 2-3 hours or at the investigator's discretion.

During the next 3 weeks (between Visits 11 and 13) of the study period, the Auto Basal target setting should be set to 100 mg/dL. Active Insulin Time is recommended to be set to 2-3 hours or at investigator's discretion.

During the remaining weeks of the study (any time after Visit 13) of the study period, the Auto Basal target as well as Active Insulin Time should be set to what is best for the individual subject, at investigator's discretion.

Note: The Auto Basal target setting and Active Insulin Time should be set as recommended above, unless there is a documented safety reason that would not permit these settings to be used.

After completion of live training on the SmartGuard function, subjects and their parents/caregivers (if applicable) may attend additional visits in the days immediately following the start of SmartGuard use, as needed.

SMBG recommendations for 780G system:
Calibration is not required with the MiniMed 780G system using the DS5. However, a calibration is optional and it will automatically occur any time a blood glucose (BG) is entered. Occasionally, subjects may receive a notification if the pump needs a BG to enter or stay in the SmartGuard feature. Subjects will be instructed to perform SMBG if their symptoms do not match the sensor glucose (SG) value (i.e., they develop symptoms of hypoglycemia or hyperglycemia, but the SG value does not correlate with their symptoms).

5.1 Duration

The study is anticipated to last approximately 18 months from first investigational center initiation to study completion. Individual subject participation is expected to be approximately 120 days through the study period.

5.2 Rationale

The accuracy of the DS5 has been evaluated in previous clinical trials and has been confirmed to provide performance that meets the previously established requirements for glucose sensors used with the MiniMed 780G pump. This investigation is required to provide additional confirmation of the safety of the pump used in combination with the DS5.

6. Product Description

6.1 Intended Use

The MiniMed 780G system is intended for use by people seven years and older with type 1 diabetes who require at least 8 units of insulin per day.

6.2 General Overview of MiniMed 780G Insulin Pump System Components and Consumables

Table 1. MiniMed 780G Insulin Pump: System Components and consumable materials

Device name	MDT Model number/ part number	Device Regulatory Status
MiniMed 780G Insulin Pump	MMT-1884	Investigational
DS5	MMT-5100	Investigational
Medtronic Extended infusion set	MMT-430, MMT-431, MMT-432, MMT-433, MMT-440, MMT-441, MMT-442, and MMT-443	Non-Investigational
Medtronic Extended Reservoir	MMT-342	Non-Investigational
Medtronic CareLink Personal software	MMT-7333	Non- Investigational*
Medtronic CareLink system software	MMT-7350	Non-Investigational*
Roche Accu-Chek Guide Link Glucose Meter	08116083022	Non-Investigational
MiniMed Clinical App	MMT-6103 Android; MMT-6104 IOS	Non-Investigational**
CareLink Clinical App	MMT-6113 Android; MMT-6114 IOS	Non-Investigational**
Blue Adapter	ACC-1003911	Non-Investigational
Precision Xtra Ketone Meter or other approved ketone meter	N/A	Non-Investigational

*Class I exempt

**Class II exempt

6.3 Investigational Product

6.3.1 MiniMed 780G Insulin Pump

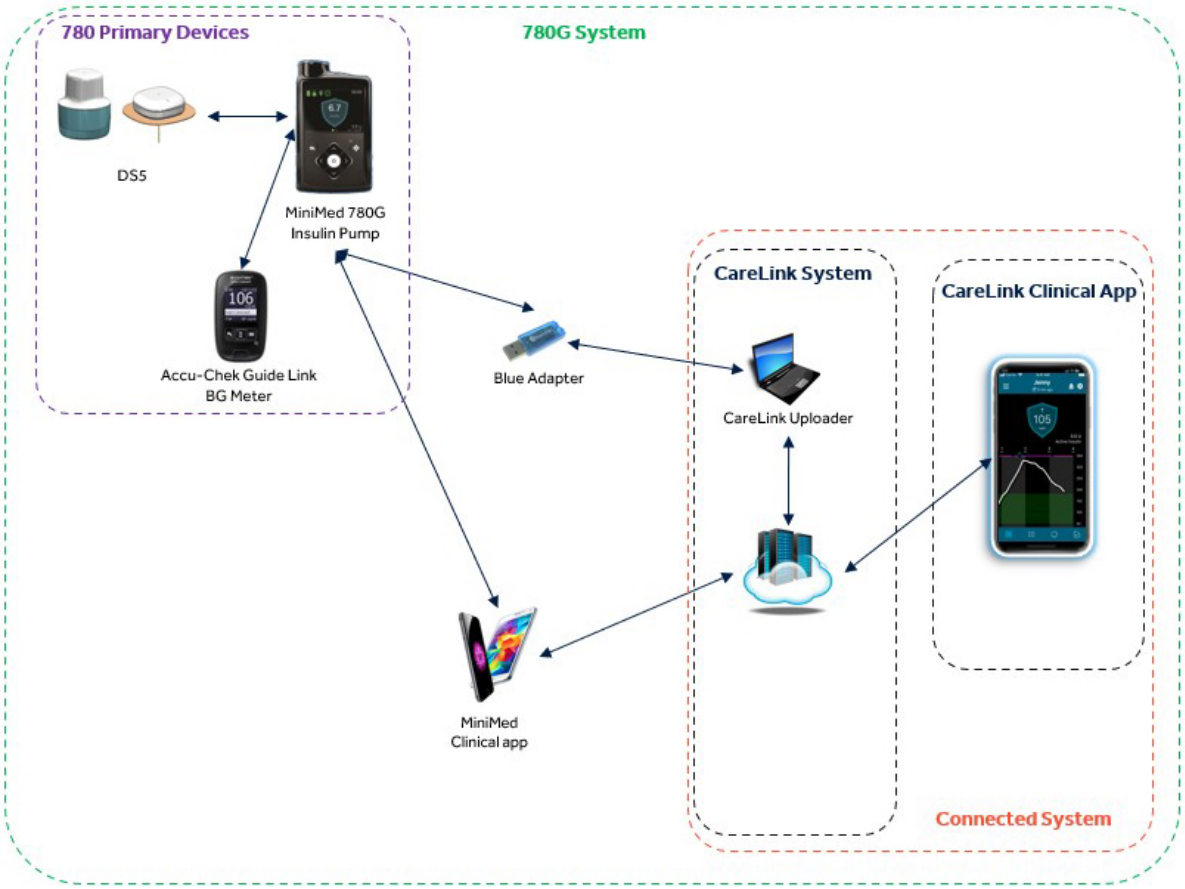
The MiniMed 780G Insulin Pump houses electronics, a pumping mechanism, a user interface, and a medication reservoir within the same physical device. The pump communicates via Bluetooth® Low Energy wireless communication protocol with the compatible devices in the MiniMed 780G System.

In this study, the MiniMed 780G Pump will be used in combination with the following devices (MiniMed 780G System and components presented in **Figure 1**):

- The MiniMed 780G Pump receives the SG values and sensor integrity check from the DS5.
- The MiniMed 780G Pump receives BG values from the Roche's Accu-Chek Guide Link BG meter.
- 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.

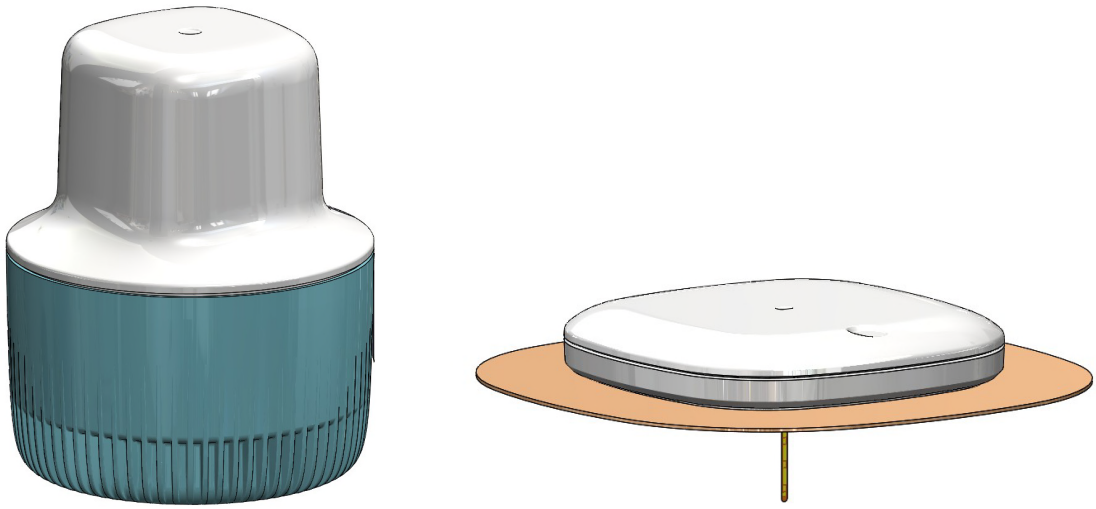
Figure 1. 780G System and Components



6.3.2 Disposable Sensor (DS5)

The Disposable Sensor, referred to as DS5 in this CIP, is a disposable integrated sensor-transmitter platform. The sensor is packaged into a single-use insertion device, called the inserter, resulting in an all-in-one device out of the box. The inserter is designed to simplify the insertion process. The sensor flex is inserted subcutaneously with an introducer needle, which is retracted by the inserter upon removal.

Figure 2. DS5



6.4 Non-Investigational Product(s)

6.4.1 Medtronic Extended Infusion Set

Infusion sets are single-use by patients with diabetes mellitus requiring subcutaneously administered insulin to maintain acceptable BG levels. The Medtronic Extended infusion set is an infusion set with a pre-loaded inserter, inserted into the subcutaneous tissue of a user, and is connected to a Medtronic Extended reservoir (for use with a Medtronic MiniMed insulin pump). There are three basic components of the infusion set:

1. Catheter hub with cannula and adhesive patch
2. Tubing
3. Tubing connector

The cannula, connected to the catheter hub, is introduced into subcutaneous tissue (i.e., infusion site). The tubing connects the catheter hub and the tubing connector to provide the fluid from the medication reservoir housed within the insulin pump.

The device utilizes a new high-performance tubing connector (H-Cap) to replace the current proprietary Paradigm connector (P-Cap), an extended wear tubing to replace the current tubing, and an extended wear adhesive patch. **Figure 2** and **Figure 3** illustrate the device and the tubing connectors.

The Medtronic Extended infusion set enhances patient wear time to 7 days. This is done by maintaining insulin formulation stability (including physical, chemical, and microbiological stability) during infusion through the pump/infusion set system over extended time (up to 7 days).

Figure 3. Medtronic Extended infusion set

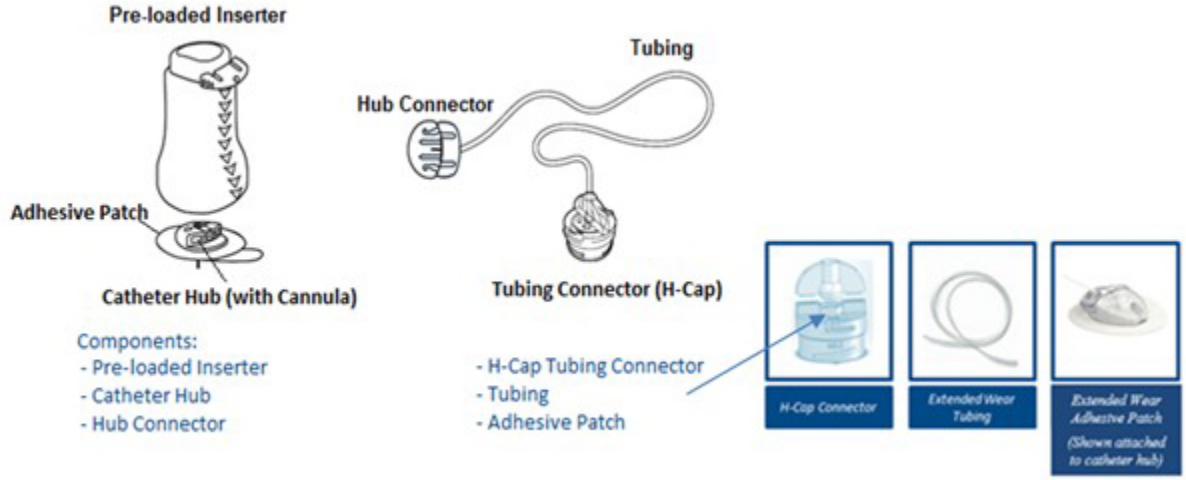
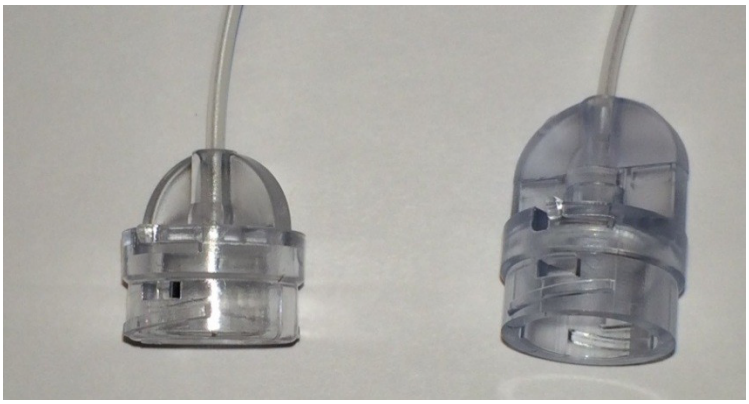


Figure 4. Connector, P-Cap (Left); High-Performance Connector, H-Cap (Right)



6.4.2 Medtronic Extended Reservoir

The Medtronic Extended Reservoir is indicated for the subcutaneous infusion of insulin from compatible Medtronic insulin pumps and Medtronic Extended infusion sets.

6.4.3 CareLink Personal Software

Medtronic CareLink Personal software is an internet-based software system which allows the device data to be uploaded and reviewed by the subject. The CareLink Personal software allows subjects to upload data from Medtronic MiniMed insulin pumps and a range of system-supported, third-party BG meters. The data contained in CareLink Personal software is accessible to users using a standard browser, i.e., Microsoft® Internet Explorer or Google Chrome, on an Internet enabled personal computer (PC).

The CareLink Personal 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.

6.4.4 CareLink System Software

Medtronic CareLink system software 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 in CareLink system software is accessible to users using a standard browser, i.e., Microsoft® Internet Explorer or Google Chrome, on an Internet enabled PC.

The CareLink system software uses standard 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.

6.4.5 Roche Accu-Chek Guide Glucose Meter

The Roche's Accu-Chek Guide Link meter is a home BG meter designed to measure and transmit 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. 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 BG meter is compatible with Roche's Accu-Chek Guide test strips.

6.4.6 Accessory Applications – MiniMed 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 Personal/CareLink system software 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 (e.g., caregiver). 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.

6.4.7 Blue Adapter

The Blue Adapter is an optional accessory with Bluetooth technology that facilitates the communication between a PC 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 when automatic uploads via the MiniMed Clinical app are not possible.

6.4.8 Ketone Meter

The ketone meter can measure both BG (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 CIP. This meter allows quantification of blood ß-Ketone levels and is the preferred patient method of testing over urine testing.

6.5 Smartphone

Sponsor may provide a smartphone, upon request.

6.6 Consumable Devices

Glucose meter accessories (e.g., Accu-Chek Guide test strips), Medtronic infusion sets, Medtronic reservoirs, and other consumable materials will be provided to subjects for use in the study.

6.7 Insulin

Subjects will use their own rapid-acting analogue insulin (Novolog, Humalog, or Admelog) for this study.

6.8 Anticipated Product Changes

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

6.9 Product Accountability

Good Clinical Practice (GCP) requires that investigators and research teams ensure accurate accountability for any investigational devices used in a research trial. It is expected that all investigational devices will be used in the manner intended during the study and that they will be used only by (on) subjects who have consented to participate in the research study and by investigational center staff trained on the study.

Any investigational device being used in clinical research must be strictly accounted for and will not be shipped to any investigational center unless all of the necessary approvals (e.g., regulatory authority and IRB) have been received.

The principal investigator (PI) or an authorized designee shall keep records documenting the receipt, use, return, and disposal of the investigational devices. Additional details regarding device accountability and device disposition requirements are provided in **Table 2**.

Table 2. Device Accountability Requirements

Device	Record on Site Received eCRF	Record Disbursement, Returned or Not Returned from Subject on Subject Device Identification eCRF	Subject Return Device to Investigational Center	Record Returned or Not Returned to Sponsor on Site Returned eCRF	Investigational Center Return Device to Sponsor at Conclusion of Study
MiniMed 780G Insulin Pump (MMT-1884)	Yes	Yes	Yes	Yes	Yes
DS5 (MMT-5100)	Yes	Yes	Yes (Complaint and unused) No* (Non-complaint used)	Yes	Yes (Complaint and unused) No* (Non-complaint used)
Medtronic Extended infusion set (MMT-430, MMT-431, MMT-432, MMT-433, MMT-440, MMT-441, MMT-442, and MMT-443)	Yes	Yes	Yes (Complaint) No* (Non-complaint used and unused)	Yes	Yes (Complaint) No* (Non-complaint used and unused)
Medtronic Extended Reservoir (MMT-342)	Yes	Yes	Yes (Complaint) No* (Non-complaint used and unused)	Yes	Yes (Complaint) No* (Non-complaint used and unused)

Device	Record on Site Received eCRF	Record Disbursement, Returned or Not Returned from Subject on Subject Device Identification eCRF	Subject Return Device to Investigational Center	Record Returned or Not Returned to Sponsor on Site Returned eCRF	Investigational Center Return Device to Sponsor at Conclusion of Study
Roche Accu-Chek Guide Link Study Meter** (08116083022)	Yes	Yes	Yes	Yes	No*
Ketone meter	Yes	Yes	Yes	Yes	No*
Smartphone, as approved for distribution	Yes	Yes	Yes	Yes	Yes

*If subject is unable to dispose, return products to investigational center for disposal.
If investigational center is unable to dispose, return products to sponsor for disposal.
**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.

6.9.1 Receipt and Inventory of Study Devices by Investigational Center

- Upon receipt of the study devices, investigational center staff will 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 or acknowledge the study device information on the appropriate eCRF in the study database, if applicable as described in **Table 2.**

6.9.2 Storage of Study Devices at Investigational Center

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

6.9.3 Dispensing of Study Devices

Each time a study device is dispensed 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:

- Dispensing date
- Subject identification (ID)
- Lot number (where applicable)
- Serial number (where applicable)
- Device type
- Amount dispensed

6.9.4 Return or Disposal of Study Devices

After use by the subject, the investigational center is expected to accept and retain all devices as described in **Table 2** and store them in a secure environment. If containers/units/devices are missing, the reasons should be documented in the applicable eCRF and/or source document. 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 and/or source document.

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 study closure or upon sponsor request.

Other consumable devices (e.g., alcohol wipes, study meter supplies, and tape), and accessories shipped in kits, 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 appropriately by the investigational center staff.

Disposable and consumable devices that have been **used** by a subject will be disposed of appropriately 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 and/or source document must be accounted for as described above before they are returned to the sponsor.

7. Study Site Requirements

7.1 Investigator/Investigational Center Selection

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

The principal investigator must be a physician who has managed patients on both CGM and insulin pump therapy for at least one year and must be familiar with insulin carbohydrate ratios, insulin sensitivity, and treating diabetic emergencies.

7.2 Study Site Activation

During the activation process (prior to subject enrollment), Medtronic will train investigational center staff who may then train other staff at each investigational center. 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, including but not limited to the following:

- IRB approval (and voting list, as required by local law) of the current version of the Clinical Investigation Plan (CIP) and Informed Consent Form (ICF), and report of prior investigations
- Regulatory authority approval or notification (as required per local law)
- Fully executed Clinical Trial Agreement (CTA)
- Financial disclosure (if applicable)
- Curriculum vitae (CV) of investigators
- Documentation of delegated tasks
- Documentation of study training

In addition, all participating investigational center staff must be trained on the current version of the CIP as well as on the applicable study requirements depending on their role and must be delegated by the PI prior to performing delegated study activities.

Medtronic will provide each study investigational center with documentation of study investigational center/investigator subject enrollment readiness; this letter must be received prior to subject enrollment.

8. Selection of Subjects

8.1 Study Population

A total of up to 250 subjects with insulin-requiring type 1 diabetes age 7-80 will be enrolled at up to 25 investigational centers across the United States in order to have 200 subjects enter the study period. Up to 125 subjects will be enrolled in the pediatric age group (7-17 years of age), up to 125 in the adult age group (18 years or older):

Subject Age Group	Sub-groups	Enrollment Goal (N)
Pediatric Age 7 – 17 years	Age 7 - 13 years	Minimum 20 Subjects
	Age 14 - 17 years	Minimum 20 Subjects

Investigational centers will be encouraged to enroll a study population that represents a wide variety of backgrounds.

8.2 Subject Enrollment

Subjects will be considered enrolled in the study upon signing the ICF and assent form (if applicable).

A subject will be assigned a unique study subject ID via the eCRF, which is a 9-digit code (337XXXXXX). The first three digits refer to the CIP number (337), the next three digits refer to the investigational center number, and the last 3 digits refer to the subject number assigned during Visit 1 (e.g., 337002001 is subject 001 from investigational center 002).

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

8.3 Inclusion Criteria

1. Age 7 - 80 years at time of screening.
2. Has a clinical diagnosis of type 1 diabetes:
    a. 14 – 80 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.
    b. 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.
3. Does not require a legally authorized representative to consent on their behalf due to mental or intellectual disability.
4. Subject or parent/caregiver is literate and able to read the language offered in the pump or pump materials.
5. Subject and/or legally authorized representative is willing to provide informed consent for participation.
6. Is willing to perform fingerstick blood glucose measurements as needed.
7. Is willing to wear the system continuously throughout the study.
8. Must have a minimum daily insulin requirement (Total Daily Dose) of greater than or equal to 8 units.
9. 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 National Glycohemoglobin Standardization Program (NGSP) certified Central Laboratory. HbA1c testing must follow NGSP standards.

10. Has thyroid-stimulating hormone (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. Uses pump therapy for greater than 6 months prior to screening (with or without CGM experience).
12. Is willing to upload data from the study pump, must have Internet access, and a computer system, or compatible smartphone that meets the requirements for uploading the study pump.
13. Is willing to take one of the following insulins and can financially support the use of insulin preparations as required by the study:
    a. Humalog (insulin lispro injection)
    b. NovoLog (insulin aspart injection)
    c. Admelog (insulin lispro injection)

8.4 Exclusion Criteria

1. Has a history of 2 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. Has been hospitalized or has visited the ER in the 6 months prior to screening resulting in a primary diagnosis of uncontrolled diabetes.
3. Has had DKA in the last 6 months prior to screening visit.
4. Will not tolerate tape adhesive in the area of sensor placement as assessed by a qualified individual.
5. Has any unresolved adverse skin condition in the area of sensor placement (e.g., psoriasis, dermatitis herpetiformis, rash, Staphylococcus infection).
6. Is female of child-bearing potential and result of pregnancy test is positive at screening.
7. Is sexually active female of child-bearing potential and is not using a form of contraception deemed reliable by the investigator.
8. Is female and plans to become pregnant during the course of the study.
9. Is being treated for hyperthyroidism at time of screening.
10. Has diagnosis of adrenal insufficiency.
11. Has taken any oral, injectable, or intravenous (IV) glucocorticoids within 8 weeks from time of screening visit, or plans to take any oral, injectable, or IV glucocorticoids during the course of the study.
12. Is using hydroxyurea at time of screening or plans to use it during the study.
13. 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. Has used a MiniMed 780G pump prior to screening.
15. Is currently abusing illicit drugs.
16. Is currently abusing marijuana.
17. Is currently abusing prescription drugs.
18. Is currently abusing alcohol.
19. Using pramlintide (Symlin), DPP-4 inhibitor, liraglutide (Victoza or other GLP-1 agonists), metformin, canagliflozin (Invokana or other SGLT2 inhibitors) at time of screening.
20. 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.
21. Has elective surgery planned that requires general anesthesia during the course of the study.
22. Has sickle cell disease, hemoglobinopathy; or has received red blood cell transfusion or erythropoietin within 3 months prior to time of screening.
23. Plans to receive red blood cell transfusion or erythropoietin over the course of study participation.

24. Is diagnosed with current eating disorder such as anorexia or bulimia.
25. Has been diagnosed with chronic kidney disease that results in chronic anemia.
26. Has a hematocrit that is below the normal reference range of lab used.
27. Is on dialysis.
28. Has serum creatinine of >2 mg/dL.
29. Has celiac disease that is not adequately treated as determined by the investigator.
30. 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, or ventricular rhythm disturbances.
31. Has had history of cardiovascular event 1 year or more from the time of screening without
    a. a normal EKG and stress test within 6 months prior to screening or during screening or
    b. clearance from a qualified physician prior to receiving the study devices if there is an abnormal EKG or stress test.
32. Has 3 or more cardiovascular risk factors listed below without a normal EKG within 6 months prior to screening or during screening or clearance from a qualified physician if there is an abnormal EKG:
    - 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
33. Is a member of the research staff involved with the study.
34. Is a Medtronic Diabetes employee or their immediate family member (excluding adult children and/or adult siblings).

9. Study Procedures

9.1 Schedule of Events

Subjects may participate in up to 15 planned study visits, as presented in **Figure 5 (Section 9.1.1)** for approximately 120 days of device wear. A virtual office visit (audio visual) may be performed for certain office visits where an office visit is not possible. The exit visit should occur at the office, unless an emergent situation occurs.

If the subject visits the investigational center outside of the scheduled study visits, a Visit eCRF will be completed to document the reason for the unscheduled visit.

Refer to **Section 9.1.1**, **Table 3** for the Visit Details.

If subject exits the study early (i.e., before their last scheduled visit), HbA1c requirements that apply to the final visit will be completed for subjects who have completed Visit 7. Refer to CIP337 Survey/Questionnaire Guide for collection of early exit survey/questionnaire requirements.

The Exit eCRF and all associated activities should be completed for all subjects who have withdrawn, discontinued, or completed the study.

9.1.1 Study Visit Schedule & Scheduled Follow-Up Visit Windows

Visit 1 to Visit 6 must be completed in 30 days.

- Visit 1 (Office/Virtual Office): Consent and screening
    - Collect labs

Run-In:

- Visit 2 (Office/Virtual Office): Start Run-In
    - Eligibility has been confirmed
    - Start study pump and CGM
    - Adjust pump settings as needed
    - Register and upload study pump in CareLink Personal and CareLink system
- Visit 3 (Phone): Day 1 after Visit 2 – Required for subjects without CGM or closed loop experience; as needed for all others
    - Ask subjects and their parents/caregivers (if applicable) if they require assistance, e.g., additional training
    - Ask subjects about adverse events and device performance
    - Review CareLink reports
- Visit 4 (Phone): Day 3 (±1 day) after Visit 2 – Required for subjects without CGM or closed loop experience; as needed for all others
    - Ask subjects and their parents/caregivers (if applicable) if they require assistance, e.g., additional training
    - Ask subjects about adverse events and device performance
    - Review CareLink reports
- Visit 5 (Phone): Day 7 (±2 days) after Visit 2
    - Ask subjects and their parents/caregivers (if applicable) if they require assistance, e.g., additional training
    - Ask subjects about adverse events and device performance
    - Review CareLink reports
- Visit 6 (Office/Virtual Office): Day 14 (±3 days) after Visit 2
    - Ask subjects and their parents/caregivers (if applicable) if they require assistance, e.g., additional training
    - Ask subjects about adverse events and device performance
    - Review CareLink reports
    - Visit 6 and 7 may be combined

Study Period:

- Visit 7 (Office/Virtual Office): Start Study Period,
  Day 7 (-7 days) after Visit 6

- Adjust pump settings as needed
- Ask subjects about adverse events and device performance
- Review CareLink reports
- Start Auto Basal target at 120 mg/dL setpoint with Active Insulin Time set to 4 hours, titrate towards 2-3 hours or at investigator's discretion
- Turn on SmartGuard with Auto Corrections "ON"

- Visit 8 (Phone): Day 2 after Visit 7 – Required for subjects without CGM or closed loop experience; as needed for all others
  - Adjust pump settings as needed
  - Ask subjects and their parents/caregivers (if applicable) if they require assistance, e.g., additional training
  - Ask subjects about adverse events and device performance
  - Review CareLink reports
- Visit 9 (Phone): Day 7 (±2 days) after Visit 7
  - Adjust pump settings as needed
  - Ask subjects about adverse events and device performance
  - Review CareLink reports
- Visit 10 (Phone): Day 14 (±3 days) after Visit 7
  - Adjust pump settings as needed
  - Ask subjects about adverse events and device performance
  - Review CareLink reports
- Visit 11 (Phone): Day 21 (±3 days) after Visit 7
  - Adjust pump settings as needed
  - Ask subjects about adverse events and device performance
  - Review CareLink reports
  - Change Auto Basal target to 100 mg/dL setpoint with Active Insulin Time set to 2-3 hours or at investigator's discretion
- Visit 12 (Office/Virtual Office): Day 28 (+7 days) after Visit 7
  - Adjust pump settings as needed
  - Ask subjects about adverse events and device performance
  - Review CareLink reports
- Visit 13 (Phone): Day 44 (±3 days) after Visit 7
  - Adjust Auto Basal target with Active Insulin Time at investigator's discretion
  - Ask subjects about adverse events and device performance
  - Review CareLink reports
- Visit 14 (Office/Virtual Office): Day 60 (+7 days) after Visit 7
  - Ask subjects about adverse events and device performance
  - Review CareLink reports
- Visit 15 (Office/Virtual Office): Day 90 (+7 days) after Visit 7
  - Collect HbA1C
  - Ask subjects about adverse events and device performance
  - Review CareLink reports
  - Return study devices
  - End of Study (EOS)

Figure 5. Visit Schedule

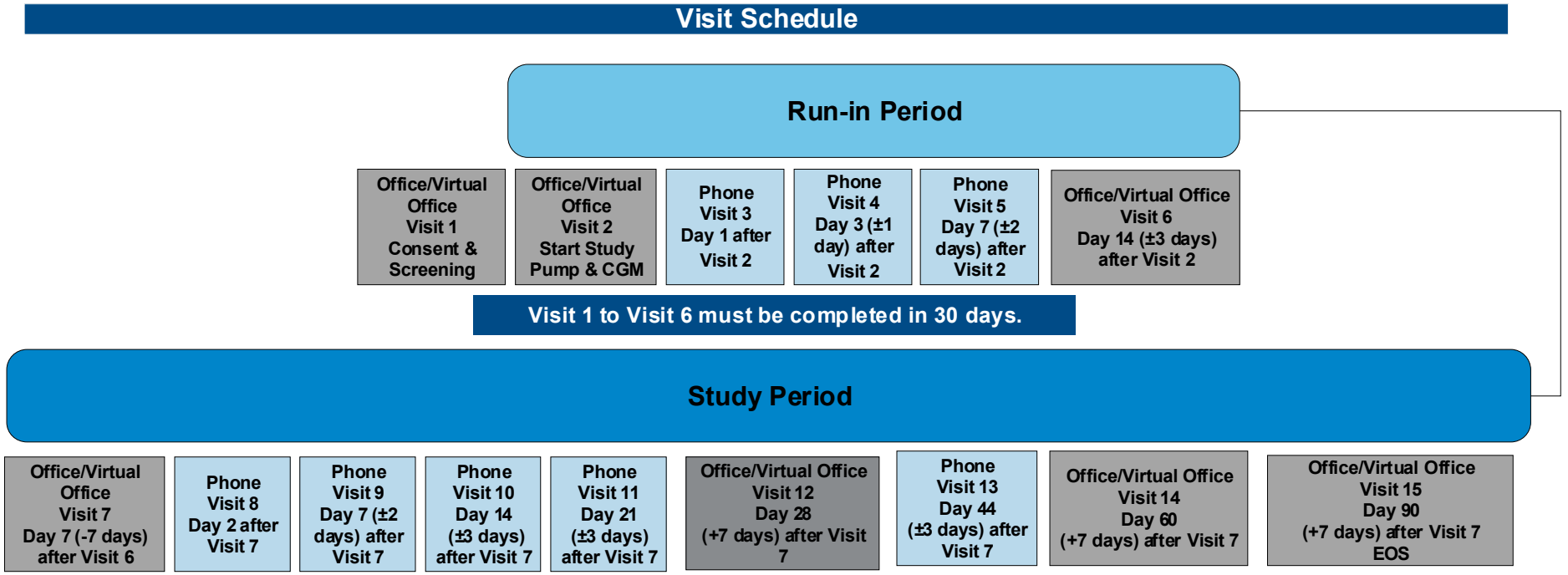


Table 3. Visit Details

	Visit 1 (Office or Virtual Office)	Run-In Period				Study Period						
		Visit 2 (Office or Virtual Office)	Visit 3* and 4* (Phone)	Visit 5 (Phone)	Visit 6 (Office or Virtual Office)	Visit 7 (Office or Virtual Office)	Visit 8* (Phone)	Visit 9, 10 & 11 (Phone)	Visit 12 (Office or Virtual Office)	Visit 13 (Phone)	Visit 14 (Office or Virtual Office)	Visit 15** (Office or Virtual Office)
Visit Window	**Enrollment**		**Day 1 and Day 3 (±1 day) after Visit 2**	**Day 7 (±2 days) after Visit 2**	**Day 14 (±3 days) after Visit 2**	**Day 7 (-7 days) after Visit 6**	**Day 2 after Visit 7**	**Day 7 (±2 days) after Visit 7), Day 14 and Day 21 (±3 days) after Visit 7**	**Day 28 (+7 days) after Visit 7**	**Day 44 (±3 days) after Visit 7**	**Day 60 (+7 days) after Visit 7**	**Day 90 (+7 days) after Visit 7 EOS**
Visit Activities and Data Collection												
Collect consent forms, e.g., ICF, Assent form (if applicable), California Experimental Subject's Bill of Rights (if applicable), HIPAA form and forms required by local regulation	X											
Assess subject eligibility to participate in the study	X											
Measure subject height and weight Note: Body mass index (BMI) will be calculated automatically in the study database, based on height and weight measurements entered.	X											X
Collect demographic and other baseline characteristics according to eCRF questions	X											
Collect urine test for pregnancy from female subjects of child-bearing age or capability (Point of Care or local lab)	X											
Collect blood sample for HbA1c testing. All collected blood specimens will be sent to and tested by a NGSP certified Central Laboratory. HbA1c testing must follow NGSP standards.	X											X
Collect specimens for required lab testing: Hematocrit, Creatinine, TSH (see lab instructions for additional information)	X											
Collect information about medical history	X											
Collect information about concomitant medications	X											
Collect any changes to diabetes medications during the study (including the type of insulin being used). The only insulins permitted for use in the study are Humalog, Novolog, and Admelog. **During the study period, each subject will be encouraged to continue on the same brand of insulin with which they started.**		X (if applicable)	X (if applicable)	X (if applicable)	X (if applicable)	X (if applicable)	X (if applicable)	X (if applicable)	X (if applicable)	X (if applicable)	X (if applicable)	X (if applicable)
Confirm subject eligibility results, including labs, prior to moving forward with any study procedures		X										
Assist with Surveys/Questionnaires - Refer to CIP337 Surveys/Questionnaire Guide for administration details.		X										X
Provide study subjects with the Accu-Chek Guide Link study meter and ketone meter, including needed supplies		X			As needed	As needed			As needed		As needed	
Complete Quality Control (QC) testing of the Accu-Chek Guide Link study meter and ketone meter per respective user guide		X			As needed	As needed	As needed	As needed	As needed	As needed	As needed	
Train subjects and their parents/caregivers (if applicable) on the use of the Accu-Chek Guide Link study meter and ketone meter, refer to user guides		X										

	Visit 1 (Office or Virtual Office)	Run-In Period				Study Period						
		Visit 2 (Office or Virtual Office)	Visit 3* and 4* (Phone)	Visit 5 (Phone)	Visit 6 (Office or Virtual Office)	Visit 7 (Office or Virtual Office)	Visit 8* (Phone)	Visit 9, 10 & 11 (Phone)	Visit 12 (Office or Virtual Office)	Visit 13 (Phone)	Visit 14 (Office or Virtual Office)	Visit 15** (Office or Virtual Office)
Visit Window	**Enrollment**		**Day 1 and Day 3 (±1 day) after Visit 2**	**Day 7 (±2 days) after Visit 2**	**Day 14 (±3 days) after Visit 2**	**Day 7 (-7 days) after Visit 6**	**Day 2 after Visit 7**	**Day 7 (±2 days) after Visit 7), Day 14 and Day 21 (±3 days) after Visit 7**	**Day 28 (+7 days) after Visit 7**	**Day 44 (±3 days) after Visit 7**	**Day 60 (+7 days) after Visit 7**	**Day 90 (+7 days) after Visit 7 EOS**
Train subjects and their parents/caregivers (if applicable) on the use of the 780G pump		X										
Start study subjects on the 780G insulin pump system accordingly: SmartGuard (with Auto Correction OFF) during the run-in period will be permitted for study subjects who are using the Auto Mode feature in a Medtronic pump prior to screening. In the 780G study pump, the term "Auto Mode" has been replaced with "SmartGuard". All others are to use the system in Manual Mode during the run-in period.		X										
Provide study subjects the Medtronic Extended infusion sets, reservoirs, and DS5		X			As needed	As needed	As needed	As needed	As needed	As needed	As needed	
Train subjects and their parents/caregivers (if applicable) on the Medtronic Extended infusion sets, reservoirs, and DS5.		X										
Start study subjects on CGM(DS5) and accessories		X										
Instruct subjects and their parents/caregivers (if applicable) to place the DS5 in a location that is approved for placement per the User guide and study directions and also report the sensor insertion information, as applicable: • Ages 7-17 years: Back of upper arm and upper buttock • Ages 18 years and older: Back of upper arm		X	X	X	X	X	X	X	X	X	X	X
Train study subjects and their parents/caregivers (if applicable) on the 780G SmartGuard features		X				X						
Start study subjects on 780G SmartGuard with Auto Correction ON.						X						
Instruct subjects and their parents/caregivers (if applicable) to switch from pump therapy to manual injections until issue is resolved if: • Hospital admission is needed for any reason • Glucose is persistently elevated (i.e., above 300 mg/dL [16.7 mmol/L]) and not responding to correction boluses and/or infusion set change(s). • There is an occlusion alarm with elevated glucose, where the study subject is not able to address the occlusion by changing the infusion set		X				X						
Create an investigational center account in the CareLink system software (see separate instructions)		X										
Create an account for study subjects in CareLink Personal (see separate instructions)		X										
Link the study subjects account to the investigational center account		X										
Train subjects and their parents/caregivers (if applicable) on the use of CareLink Personal–provide relevant set of written instructions		X										
Set up 780G system apps, if applicable: • MiniMed Clinical app • CareLink Clinical app		X (if applicable)										
If applicable: • Train subjects and their parents/caregivers on the use of the 780G system apps: MiniMed Clinical app and CareLink Clinical app		X (if applicable)										
Adjust pump settings		As needed				As needed	As needed	As needed	As needed			

	Visit 1 (Office or Virtual Office)	Run-In Period				Study Period						
		Visit 2 (Office or Virtual Office)	Visit 3* and 4* (Phone)	Visit 5 (Phone)	Visit 6 (Office or Virtual Office)	Visit 7 (Office or Virtual Office)	Visit 8* (Phone)	Visit 9, 10 & 11 (Phone)	Visit 12 (Office or Virtual Office)	Visit 13 (Phone)	Visit 14 (Office or Virtual Office)	Visit 15** (Office or Virtual Office)
Visit Window	**Enrollment**		**Day 1 and Day 3 (±1 day) after Visit 2**	**Day 7 (±2 days) after Visit 2**	**Day 14 (±3 days) after Visit 2**	**Day 7 (-7 days) after Visit 6**	**Day 2 after Visit 7**	**Day 7 (±2 days) after Visit 7), Day 14 and Day 21 (±3 days) after Visit 7**	**Day 28 (+7 days) after Visit 7**	**Day 44 (±3 days) after Visit 7**	**Day 60 (+7 days) after Visit 7**	**Day 90 (+7 days) after Visit 7 EOS**
During the run-in period and only for subjects with Auto Mode experience through the use of a Medtronic insulin pump, a 120 mg/dL Auto Basal target should be set. It is recommended that Active Insulin Time is set to 4 hours. Note: The Auto Basal target setting and Active Insulin Time should be set as recommended above, unless there is a documented safety reason that would not permit these settings to be used. Subjects who do not have experience with Medtronic insulin pumps, as specified above, will use the system in Manual Mode.		X	X	X	X							
Start Auto Basal target at 120 mg/dL setpoint with Active Insulin Time set to 4 hours, titrate towards 2-3 hours or at investigator's discretion. Turn on SmartGuard with Auto Corrections "ON". Note: The Auto Basal target setting and Active Insulin Time should be set as recommended above, unless there is a documented safety reason that would not permit these settings to be used.						X						
Change Auto Basal target to 100 mg/dL setpoint with Active Insulin Time set to 2-3 hours or at investigator's discretion. Note: The Auto Basal target setting and Active Insulin Time should be set as recommended above, unless there is a documented safety reason that would not permit these settings to be used.								X (Visit 11)				
Adjust the Auto Basal target as well as Active Insulin Time to what is best for the individual subject, at investigator's discretion. Note: The Auto Basal target setting and Active Insulin Time should be set as recommended above, unless there is a documented safety reason that would not permit these settings to be used.										X		
Dispense study materials (e.g., smartphone [upon request and approval], reference guides, subject training materials, etc.)		X										
Dispense other study supplies as needed (e.g., alcohol swabs, adhesive remover, etc.)		X			As needed	As needed			As needed		As needed	
At all visits and/or between visits (if the investigational center is contacted), adjust insulin settings and insulin dose as needed		X	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed	
Confirm the study pump upload data is available in CareLink system software (at office visit or day prior if phone or virtual office visit)		X		X	X	X	X	X	X	X	X	X
Print and review CareLink system reports			X	X	X	X	X	X	X	X	X	X

	Visit 1 (Office or Virtual Office)	Run-In Period				Study Period						
		Visit 2 (Office or Virtual Office)	Visit 3* and 4* (Phone)	Visit 5 (Phone)	Visit 6 (Office or Virtual Office)	Visit 7 (Office or Virtual Office)	Visit 8* (Phone)	Visit 9, 10 & 11 (Phone)	Visit 12 (Office or Virtual Office)	Visit 13 (Phone)	Visit 14 (Office or Virtual Office)	Visit 15** (Office or Virtual Office)
Visit Window	**Enrollment**		**Day 1 and Day 3 (±1 day) after Visit 2**	**Day 7 (±2 days) after Visit 2**	**Day 14 (±3 days) after Visit 2**	**Day 7 (-7 days) after Visit 6**	**Day 2 after Visit 7**	**Day 7 (±2 days) after Visit 7), Day 14 and Day 21 (±3 days) after Visit 7**	**Day 28 (+7 days) after Visit 7**	**Day 44 (±3 days) after Visit 7**	**Day 60 (+7 days) after Visit 7**	**Day 90 (+7 days) after Visit 7 EOS**
Review surveillance report in Medtronic's secure upload application and review with subjects as necessary			As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed	As needed
Enter data into eCRFs as required	X	X	X	X	X	X	X	X	X	X	X	X
Schedule next visit day and time	X	X	X	X	X	X	X	X	X	X	X	
Collect study devices at study end (see device disposition **Table 2** for details) Note: If the visit must be conducted via Virtual Office, the blood tests may be collected via mobile phlebotomy service. Subjects should send devices back to the investigational center.												X
Questions To Ask at Study Visits												
Ask if subjects and their parents/caregivers (if applicable) have general study-related questions and concerns	X	X	X	X	X	X	X	X	X	X	X	X
Ask subjects about the occurrence of adverse events. • Record the event on the appropriate eCRF, if a study subject reports a change in health status that results in a new medical condition or in a deterioration of an existing medical condition, such as illness or glycemic problems • Instruct subject to call the investigational center to report any changes to their health status (see adverse event definition).		X	X	X	X	X	X	X	X	X	X	XWe
Ask subjects about device performance issues and if they called the Medtronic 24 -Hour Technical Support (TS) line to report them. Instruct/Remind subjects to contact the Medtronic 24-Hour TS in the event they experience problems with their study devices.		X	X	X	X	X	X	X	X	X	X	X
Ask subjects and their parents/caregivers(if applicable) if they require assistance, e.g., additional training			X	X	X		X					
Study Subject General Training and Instructions												
Remind subjects and their parents/caregivers (if applicable) that the use and wear of study devices throughout the study is a requirement		X	X	X	X	X	X	X	X	X	X	
Instruct/Remind subjects regarding the content of the Home Reference Guide		X										
Instruct subjects on carbohydrate (CHO) counting as needed (Investigator discretion)		X	X	X	X	X	X	X	X	X	X	
Instruct subjects and their parents/caregivers (if applicable) on diabetes self-management principles, including response to glycemic events, e.g., use of oral glucose and glucagon in case of hypoglycemia or checking ketones in case of severe hyperglycemia.		X										
Instruct subjects and their parents/caregivers (if applicable) that subject blood ketone testing is required every time BG is greater than 300 mg/dL (16.7 mmol/L), as measured by the Accu-Chek Guide Link study meter.		X	X	X	X	X	X	X	X	X	X	
Instruct subjects and their parents/caregivers (if applicable) to consider avoiding the use of products containing acetaminophen If medications containing acetaminophen are taken: • Wait until use of the medication is stopped before using SG to make treatment decisions • Use additional BG meter readings to verify glucose levels		X	X	X	X	X	X	X	X	X	X	

	Visit 1 (Office or Virtual Office)	Run-In Period				Study Period						
		Visit 2 (Office or Virtual Office)	Visit 3* and 4* (Phone)	Visit 5 (Phone)	Visit 6 (Office or Virtual Office)	Visit 7 (Office or Virtual Office)	Visit 8* (Phone)	Visit 9, 10 & 11 (Phone)	Visit 12 (Office or Virtual Office)	Visit 13 (Phone)	Visit 14 (Office or Virtual Office)	Visit 15** (Office or Virtual Office)
Visit Window	**Enrollment**		**Day 1 and Day 3 (±1 day) after Visit 2**	**Day 7 (±2 days) after Visit 2**	**Day 14 (±3 days) after Visit 2**	**Day 7 (-7 days) after Visit 6**	**Day 2 after Visit 7**	**Day 7 (±2 days) after Visit 7), Day 14 and Day 21 (±3 days) after Visit 7**	**Day 28 (+7 days) after Visit 7**	**Day 44 (±3 days) after Visit 7**	**Day 60 (+7 days) after Visit 7**	**Day 90 (+7 days) after Visit 7 EOS**
• While the SmartGuard feature is active, instruct subjects to use the temp target feature (when used, Auto Correction is not available) • Instruct subjects that in case of prolonged use of acetaminophen, the temp target feature can be used repeatedly and in succession												
Remind subject and their parents/caregivers (if applicable) to bring in both Accu-Chek Guide Link study meter and ketone meter at each required office visit.		X		X	X			X	X	X	X	
Remind subject and their parents/caregivers (if applicable) to keep their devices charged, as applicable		X	X	X	X	X	X	X	X	X	X	
Instruct subjects and their parents/caregivers (if applicable) regarding the use of the Accu-Chek Guide Link study meter to make treatment decisions: • When a BG required alert is received: ○ Clear the alert and enter a BG meter reading before using the SG to make treatment decisions • When symptoms are present: ○ If SG readings are not aligned with symptoms (e.g., if a study subject is feeling low while the SG reading is not low), use the meter to confirm BG. ○ If SG readings continue to be different from symptoms, call the study doctor		X	X	X	X	X	X	X	X	X	X	
Instruct subjects their parents/caregivers (if applicable) to refer primary healthcare providers to the investigational center staff if they have any questions about study devices and their functions		X	X	X	X	X	X	X	X	X	X	X
Instruct subjects and their parents/caregivers (if applicable) that they should not assume that SmartGuard is able to prevent all hypoglycemia or all hyperglycemia, including diabetic ketoacidosis		X				X						
Instruct study subjects and their parents/caregivers (if applicable) that regular weekly uploads of the study pump is required. With Bluetooth connection and the MiniMed Clinical app, scheduled uploads are not required for subjects with compatible smartphones, as they are designed to occur continuously. Subjects that do not have compatible smartphones will be required to use the Blue Adapter to facilitate uploads to their computers.		X	X	X	X	X	X	X	X	X	X	
Instruct/Remind subjects and their parents/caregivers (if applicable) to give subjects meal bolus of insulin 15-20 minutes before meals during the study		X	X	X	X	X	X	X	X	X	X	

**Required for subjects without CGM or closed loop experience; as needed for all others.*
***When subjects exit the study early, all requirements that are listed for the final visit apply.*

9.2 Data Collection

All data collection and study procedure requirements are described at the subject visits in **Section 9.1**.

9.3 Subject Consent

Informed Consent and assent (if applicable) 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's Bill of Rights (if applicable), the Institutional Review Board (IRB) and Medtronic approved ICF form and assent form (if applicable) 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 and their parent, guardian, or legally authorized representative (as applicable) will be given ample time and offered the opportunity to review these documents away from the investigational center.

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

Neither the investigator, nor the investigational center staff shall coerce or unduly influence a subject or their parent, guardian, or legally authorized representative 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. The assent, if required, should be administered according to the investigational center's Standard Operating Procedures (SOPs) and the IRB instructions, as applicable.

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 documents. The subject and their parent, guardian, or legally authorized representative 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. When the subject decides to participate in the study, the ICF must be signed and personally dated by the subject and investigator or authorized designee, as required by the ICF. A patient contact card will be provided to the subject.

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 and their parent, guardian, or legally authorized representative in a timely manner.

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

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

- Whether or not active subjects and their parent, guardian, or legally authorized representative 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 be re-consented.

Subjects and their parent, guardian, or legally authorized representative will be informed that qualified personnel from the investigational center, the sponsor (Medtronic), regulatory authorities 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 and their parent, guardian, or legally authorized representative.
- 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.

9.4 Safety Monitoring/Risk Analysis

9.4.1 Glucose Monitoring Risk

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

9.4.2 Hypoglycemic/Hyperglycemic Risk

Intervention and treatment for hypoglycemia and hyperglycemia is addressed in **Section 10.1**.

9.4.3 Calibration of CGM Risk

When an erroneous blood glucose value is used to calibrate a CGM, this can result in inaccurate SG values. Subjects will be trained on appropriate calibration.

9.4.4 Reuse Risk

All study devices will be single patient use.

9.4.5 Sterilization Risk

The following devices will be supplied sterilized:

- Infusion sets
- Insulin reservoirs
- DS5

9.4.6 Misuse Risk

Comprehensive training will take place at the initiation visit for investigational center staff regarding the operation of the MiniMed 780G system, to include all of its functional components and all other study devices to be used during the study at the investigational center.

9.4.7 Risk of Blood Sample Collection, Contamination from Sampling Techniques

Detailed mitigations to blood sampling risk are provided in **Section 10.1**.

9.4.8 HbA1c Risk

A Central laboratory will be used for HbA1c testing.

9.5 Glucose and Glycemia Measurements

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

9.5.1 Daily Blood Glucose

Values will be assessed during the study by all subjects using the 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 Accu-Chek Guide Link study meter per the manufacturer's instructions.

9.5.2 Blood Ketone Values

Subject's blood ketones will be measured by all subjects and parents/caregivers (if applicable) using the ketone meter when certain conditions are met:

- When a subject is symptomatic for high blood glucose
- When sensor glucose displays a glucose value >300mg/dL, BG should be checked by fingerstick and, if BG is >300mg/dL, blood ketones should be checked.

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 ketone meter per the manufacturer's instructions. All ketone measurements will be reported by study subjects.

9.5.3 Sensor Glucose Values

SG data will be collected by subject's study pump and calibrated by each subject's Accu-Chek Guide Link study meter.

9.5.4 HbA1c

HbA1c is collected at baseline and the end of subjects' participation; if subjects have completed Visit 7 and exit early, a HbA1c will be collected.

9.6 Recording Data

Data, except questionnaires, entered by the investigational center staff will be captured on eCRFs using the Electronic Data Capture (EDC) system. Original eCRFs will not be considered as source data and supporting documentation will be required. In addition, the subject will complete the questionnaires online via direct entry. In case the online link is unavailable, subjects will complete the questionnaire using a paper format (this will be source data) and subsequently the investigator or designated investigational center staff will enter the responses online. If paper format is used, the investigator or designated investigational center staff should maintain the original paper source in the subject's source file.

Electronic device data will be collected from the study pump using CareLink Personal/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 MiniMed 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 EDC system; otherwise, irresolvable data-related issues will be routed to the sponsor for review and final disposition. An audit trail is maintained in the EDC system to capture any corrections or changes of the eCRFs. System backups for data stored in the EDC system will be consistent with Medtronic SOPs.

Medtronic will only consider eCRFs to be complete when all discrepancies between source data and eCRF have been resolved. eCRF content will be reviewed by a study monitor, as described in the Monitoring Plan. 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.

9.7 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 regulatory authority (if applicable) or IRB, except where necessary to eliminate an immediate hazard(s) to subjects. The use of waivers from the CIP are prohibited in this study.

If there is a documented safety reason that would not permit the use of CIP defined Auto Basal target setting and Active Insulin Time settings, then use of the alternative settings will not be considered a deviation.

9.7.1 Documenting Requirements for Study Deviations

9.7.1.1 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).

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, the reason for deviation, and the corrective action. Refer to **Table 6** for reporting timelines for emergency deviations.

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 authority (reported by sponsor).

9.7.2 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, description, and reason for each deviation will be documented (21 CFR 812.140 Records).

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 consenting
- 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/or
- regulatory authority requirements

They must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation. Refer to Investigator Reports, **Table 6**, for specific deviation reporting requirements and timeframes for reporting to Medtronic, IRB, and regulatory authority (if applicable).

9.7.3 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.

9.8 Subject Exit, Withdrawal or Discontinuation

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

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

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 (e.g., infection at skin site, severe skin reaction to adhesive).
- In the opinion of the investigator, it is in the subject's best interest to discontinue participation in the study.
- During the course of the study, subject begins using hydroxyurea.
- During the course of the study, subject uses insulin that is not allowed to be used in the study. The only permitted insulins are Humalog, Novolog, and Admelog.
- During the course of the study, subject begins participation in another investigational study (drug or device).
- At the discretion of the investigator: during the study it becomes known that subjects are repeatedly using a non-linked BG meter for SMBG or a system that replaces SMBG.
- During the course of the study, subject begins abusing illicit drugs.
- During the course of the study, subject begins abusing 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 run-in period, a subject repeatedly activates SmartGuard feature when instructed otherwise, e.g., SmartGuard feature is turned on (as applicable at the discretion of the investigator).
- 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, if it is related to the use of MiniMed 780G system SmartGuard feature.
- During the study, the subject experiences one episode of DKA, if it is related to the use of MiniMed 780G system SmartGuard feature.
- During the study, subject has a cardiovascular event or any vascular event such as stroke.

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

9.8.1 End of Subject Participation in Study/ Completion of Study

After the study has been completed or in case of early termination, subjects will be exited from the study. Subjects will continue to work with their physician after study exit per normal standard of care. The clinical investigation is considered completed once the last subject has exited the study.

9.8.2 Lost to Follow-Up

If a subject does not return to the investigational center for required follow-up visit(s) and cannot be reached, the investigational center staff should make 3 documented attempts to contact the subject by phone to verify if the subject should be considered "lost-to follow up". In the event the subject is not able to perform follow-up visits at the investigational center, subject will be considered "lost to follow up" and this needs to be documented in the Study Exit eCRF. All efforts will be made by investigational center staff to collect all study devices and supplies back from subject, if applicable.

9.9 Study Stopping Rules

The study may be stopped if the Data Monitoring Committee (DMC) determines that there are significant safety issues, including the occurrence of certain types of individual adverse events (i.e., UADE, device related DKA, and device related severe hypoglycemia) that have undergone expedited adjudication by the Clinical Events Committee (CEC). See CEC **Section 12.1** and DMC **Section 12.2** for more details regarding the expedited review responsibilities of both committees.

10. Risks and Benefits

10.1 Potential Risks

The potential residual risks and mitigations associated with the devices used during this study are listed in **Table 4**. Risks associated with the commercially available devices used in the study are listed in the associated device labeling/user guides/instructions for use or report of prior investigations.

The clinical investigation has been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible for the subjects, and both the risk threshold and the degree of distress are specifically defined in the CIP and constantly monitored.

Table 4. Risks, Prevention and Mitigation

Risks with Infusion Sets	Prevention and Mitigation
Risks with infusion sets may include: • Localized infection • Skin irritation/redness • Bruising • Discomfort/pain • Bleeding • Irritation • Rash • Hyperglycemia secondary to infusion set occlusion or infusion site failure including DKA • Hyperglycemia secondary to site falling off including DKA • Anxiety associated with insertion	Prevention and mitigation include: • Follow the provided user guides for insertions and care of infusion sets. • If an infusion site becomes irritated or inflamed, the infusion set will be removed and another set placed in a new location. • In case of hyperglycemia secondary to infusion set occlusion, remove current infusion set and replace with new infusion set and give correction insulin if needed with syringe. • Follow the provided user guides for insulin pump management. • Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems.
Risks with Insulin Administration and Pumps	**Prevention and Mitigation**
Risks with the use of an insulin infusion pump may include the risk of malfunction of the components of the system (pump, software, infusion set and reservoir) as well as the risk of use error during use of the system. DDs or use errors can result in administration of too much or too little insulin which can lead to the following clinical consequences: • Hypoglycemia • Hyperglycemia • Diabetic ketoacidosis • Severe hypoglycemia with or without associated seizure, coma or death • Kinked cannula leading to hyperglycemia • Infusion set disconnection from pump leading to hyperglycemia • Subject removes the reservoir from the pump but forgets to disconnect the infusion set from the body which results in hypoglycemia or severe hypoglycemia • Dislodged cannula leading to hyperglycemia • A pump error may lead to under delivery or over-delivery of insulin • Battery failure – no insulin delivered	Prevention and mitigation include: • Follow the provided user guides & instructions for insulin and insulin pump management which includes information on infusion set change. • Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems. • Instruct to check their meter glucose if their high or low symptoms do not match their sensor alerts or SG readings in order to make diabetes treatment decisions. • Instruct to check their meter glucose if there are any concerns that the SG value is not accurate. • Instruct to have glucose and glucagon on hand for hypoglycemia. • Instruct to change infusion set if suspected catheter occlusion or administer insulin with syringe for persistent hyperglycemia especially if ketones develop. • Parent(s)/guardian(s), if applicable, should be present at night with subjects and will be trained on study device and diabetes management principles and instructed to call investigator with problems.

• Insulin deterioration leading to hyperglycemia • Incomplete priming; fails to prime tubing and/or cannula, leading to hyperglycemia • Remove a reservoir, without suspending and reconnecting after a while resulting in a hypoglycemia • Patient not filling pump reservoir when needed leading to hyperglycemia • Magnetic resonance imaging resulting in pump transmitter malfunction • Inaccurate insulin delivery due to sudden altitude changes. • Hypoglycemia or hyperglycemia from manual bolus • Hypoglycemia or hyperglycemia from the use of the SmartGuard feature where SG values may be used to calculate insulin bolus amounts • Hypoglycemia or hyperglycemia from computer hacking	
Risks with hyperglycemia may include • Diabetic ketoacidosis • Symptomatic ketosis • Cardiovascular event • Dehydration • Potassium and sodium imbalance • Shock • Altered mental status • Coma • Acidosis	Prevention and mitigation include: • Follow the provided user guides for insulin pump management. • Parent(s)/guardian(s), if applicable, should be present at night with subjects and will be trained on study device and diabetes management principles and instructed to call investigator with problems. • Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems. • Instruct to check their meter glucose if their high symptoms do not match their sensor alerts or SG readings in order to make diabetes treatment decisions. • Instruct to check their meter glucose if there are any concerns that the SG value is not accurate. • Alternative method of managing glucose levels will be available (insulin and syringe for example).

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

• Subject over-treating secondary to alarms which can result in hyperglycemia or hypoglycemia	
Risks with Inserter	**Prevention and Mitigation**
Risks with inserters may include: • Improper insertion may lead to device performance issue	Prevention and mitigation include: • Follow the provided user guides for insertions and care of device. • Train on the proper use of the inserter and skin preparation prior to insertion.
Risks with Fingersticks and Blood Draws	**Prevention and Mitigation**
Risks with frequent fingerstick testing and blood draws may include: • Potential risks associated with frequent meter testing of BG and blood ketones include discomfort and ecchymosis at tips of fingers • Potential risks associated with fingerstick testing include discomfort and bruising • Potential risks associated with drawing blood include discomfort, bruising and hematoma	Prevention and mitigation include: • Follow the provided user guides for use of the study meter with fingerstick testing. • Train on the proper use of the study meter and fingerstick testing. • Blood draws will be performed by a trained healthcare professional.
Risk with Closed Loop Therapy	**Prevention and Mitigation**

Risks with Closed Loop may include:
• Hypoglycemia
• Severe hypoglycemia
• Hyperglycemia
• Diabetic ketoacidosis
• User entry error
  ○ Patient administering boluses by entering false carb doses leading to hypoglycemia or hyperglycemia
  ○ Patient entering false glucose values for any reason leading to hypoglycemia and hyperglycemia
  ○ Patient entering false BG values for calibration leading to hypoglycemia or hyperglycemia
• Sensor failure resulting from patient failure to calibrate leading to hypoglycemia or hyperglycemia
• Sensor over-reading resulting in hypoglycemia
• Sensor under-reading resulting in hyperglycemia
• Sensor missed transmission, or any other fault resulting in no SG value, leading to hyperglycemia or hypoglycemia
• Voluntary insulin delivery (with the pump or with a syringe) immediately prior to entering SmartGuard may result in severe hypoglycemia despite shutting down insulin delivery by the algorithm
• Hypoglycemia related to patient taking insulin via injection while in Closed Loop (SmartGuard)
• Hypoglycemia or hyperglycemia related to entering or exiting Closed Loop (SmartGuard)
• Insulin over-delivery due to potential interference from acetaminophen
• Cyber security hacking into pump
	Prevention and mitigation include:
	• Follow the provided user guides for insulin pump management.
	• Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems.
	• Instruct to check their meter glucose if their high or low symptoms do not match their sensor alerts or SG readings in order to make diabetes treatment decisions.
	• Instruct to check their meter glucose if there are any concerns that the SG value is not accurate.
	• Instruct if there are no sensor values, no treatments decision will be made until a BG is confirmed.
	• Instruct to have glucose and glucagon on hand for hypoglycemia.
	• Instruct to avoid the use of products containing acetaminophen.
	• If acetaminophen is taken, subjects will be instructed to use additional BG meter readings to verify their glucose levels.
	• 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).
	• Instruct subjects that in case of prolonged use of acetaminophen, the

	temp target feature can be used repeatedly and in succession. • Pump has cybersecurity encryptions to prevent hacking.
Risks with hyperglycemia may include • Diabetic ketoacidosis • Symptomatic ketosis • Cardiovascular event • Dehydration • Potassium and sodium imbalance • Shock • Altered mental status • Coma • Acidosis	Prevention and mitigation include: • Follow the provided user guides for insulin pump management. • Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems. • Instruct to check their meter glucose if their high symptoms do not match their sensor alerts or SG readings in order to make diabetes treatment decisions. • Instruct to check their meter glucose if there are any concerns that the SG value is not accurate. • Instruct if there are no sensor values, no treatments decision will be made until a BG is confirmed.
Risks with hypoglycemia may include: • Seizure • Coma • Altered mental status • Loss of consciousness • Cardiovascular event • Death • Risk of rebound hyperglycemia with ketosis	Prevention and mitigation include: • Follow the provided user guides for insulin pump management. • Train prior to study device use on appropriate device use and diabetes management principles and instruct to call investigator with problems. • Instruct to check their meter glucose if their low symptoms do not match their sensor alerts or SG readings in order to make diabetes treatment decisions. • Instruct to check their meter glucose if there are any concerns that the SG value is not accurate. • Instruct if there are no sensor values, no treatment decisions will be made until a BG is confirmed. • Instruct to have glucose and glucagon on hand for hypoglycemia.
Risk with Acetaminophen Use	**Prevention and Mitigation**
Potential risks with acetaminophen may include: • False elevation of SG 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	Prevention and mitigation include: • Follow the user guide. • Instruct to avoid the use of products containing acetaminophen. • If acetaminophen is taken, subjects will be instructed to use additional BG meter readings to verify their glucose levels.

• Liver damage, liver failure and/or rare but fatal liver failure can occur • Skin rash and/or serious and potentially fatal skin reactions have been reported • Allergic reactions including those which are serious and potentially fatal can occur • Kidney disease • Lowered blood counts (red cells, and white cells)	• 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). • Instruct subjects that in case of prolonged use of acetaminophen, the temp target feature can be used repeatedly and in succession.

10.2 Risk Minimization

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

10.3 Potential Benefits

The main benefit of this study is that subjects may experience improved glucose control. 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 subjects may experience improved glucose control. With all closed loop insulin pumps, there is a risk that the pump will deliver too much or not enough insulin, resulting in hypoglycemia or hyperglycemia. These risks have been minimized through previous characterization of the performance of the DS5 and a variety of safety checks that are an integral part of the MiniMed 780G closed loop 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 present 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 FDA is required.

11. Adverse Events

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, assessment of seriousness, 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. [2]

Severe Hyperglycemia is defined as hyperglycemia (BG greater than [>] 300 mg/dL or 16.7 mmol/L) with BG ketones greater than (>) 1.5 mmol/L, and/or accompanied by symptoms of nausea, vomiting or abdominal pain.
The meter and ketone test strips are supplied for the evaluation of ketone monitoring. Only blood ketones will be recognized (not urine ketones) for assisting in diagnosis of severe hyperglycemia. The monitors/test strips are quality controlled prior to dispensing to subjects. Blood ketones provide contemporaneous understanding of ketone levels associated with elevations in glucose.

Diabetic Ketoacidosis/DKA diagnostic criteria: BG 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. [3]

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)

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.

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 Recording 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., needle (blood draw) 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 needle (blood draw) 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 CIP 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 EOS 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 AEs to Medtronic in a timely manner. All severe hypoglycemia, DKA, SAE, SADE, and UADE 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 and 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 de-identified 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 upon request to the sponsor via Medtronic's secure upload application. 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)). See **Section 12.2** for expedited reporting requirements for UADE.

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 four possible causality categories listed below:

- **Not related:** relationship to the device, comparator, or procedures can be excluded when:
  - the event has no temporal relationship with the use of the investigational device or the procedures related to the application of the investigational device;
  - 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 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;

  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 event.

- **Possible:** the relationship with the use of the investigational device, comparator, or the relationship with procedures, is weak but cannot be ruled out completely. 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, or no information has been obtained should also be classified as possible.

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

- **Causal relationship:** the event is associated with the investigational device, comparator, 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 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 CIP, which include reports of:

- Serious adverse event
- Serious adverse device effect
- Unanticipated adverse device effect
- Severe hypoglycemia
- Diabetic ketoacidosis
- Severe hyperglycemia

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

- Unanticipated adverse device effects (UADE)
- Device related DKA
- Device related severe hypoglycemia

CEC is to review and adjudicate the event within 10 business days from the time that the sponsor is notified. Adjudication will occur once all applicable documentation has been received and reviewed by the CEC.

The CEC will assess events to determine agreement or disagreement with the investigator classification of an event.

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 IRBs and regulatory authorities, if required.

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/CareLink system software report (when applicable)
- Review of pump data from CareLink Personal/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 investigational center
- Device return and failure analysis
- CareLink Personal/CareLink system software upload and review of software reports
- Subject clarification to investigational center 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 780G 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.

Note: If it is decided to withdraw subjects from participation in the study or if the study is stopped, subjects will be followed-up in accordance with standard practice by their own providers.

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

- Unanticipated adverse device effects (UADE)
- Device related DKA
- Device related severe hypoglycemia

1. Investigational center staff will notify the sponsor within approximately 24 hours of investigator or study coordinator awareness of events described above.
2. Sponsor will notify the FDA within approximately 3 business days of awareness of the event and provide updates to the agency as information becomes available.

3. DMC is to meet within 10 business days from CEC adjudication of the event. The investigator should be available to answer questions from DMC, as needed.
4. Based on their review, DMC will recommend that the sponsor make a decision regarding the following:

   a) Whether or not subject enrollment may continue.
   b) Whether or not new subject enrollment should be suspended, with enrolled subjects continuing in the study.
   c) Whether or not the entire study should be stopped, including those subjects who have already received study devices.

5. DMC and/or IRB will recommend whether or not the study should be stopped based on the number of events that have occurred during the study, weighed against the potential benefits of continuing the study.

Note: If it is decided to withdraw subjects from participation in the study or if the study is stopped, subjects will be followed-up in accordance with standard practice by their own providers.

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 5**.
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 5. 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 Bergenstal et. al	SAP arm: 0.68 Control arm: 0	SAP arm: 2.7 Control arm: 3.6	SAP arm: 2.2 Control arm: 0
	530G Adult in-home study CEP 266 (MDT on file)	1.27	3.4	N/A
	Pediatric in-home study CEP 287 (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 Bergenstal et. al	SAP arm: 16.5 Control arm: 20.9	SAP arm: 5.4 Control arm: 3.9	SAP arm: 10.2 Control arm: 3.6
	530G Adult in-home study CEP 266 (MDT on file)	0.85	0	N/A
	530G Pediatric in-home study CEP 287 (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

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 1 Diabetes. 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 DDs 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 DDs 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 DD the investigational center may have should be reported to the TS.

Device Deficiency (ISO 14155:2020)
A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance.

Note 1 to entry: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling.

Note 2 to entry: This definition includes device deficiencies related to the investigational medical device or the comparator.

To return a study device as part of a DD, 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 DDs.

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 on eCRFs, subject surveys/questionnaires, and electronically by uploading 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, completed, and early terminated 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

Safety and effectiveness endpoints will be evaluated independently for ages 18-80 and ages 7-17.

14.4.1 Primary Safety Endpoint

Age 18-80:

- The overall mean change in HbA1c, $\Delta\mu_{780G}$, from baseline to end of 3-month study period will be estimated and compared by a non-inferiority test to the threshold of -0.50% with a margin of 0.4%. A significance level of 0.025 (one-sided) will be used.

  The hypothesis of non-inferiority is mathematically expressed as:

  H_0: $\Delta\mu_{780G} \geq -0.50\% + 0.4\%$

  H_a: $\Delta\mu_{780G} < -0.50\% + 0.4\%$

Age 7-17:

- The overall mean change in HbA1c, $\Delta\mu_{780G}$, from baseline to end of 3-month study period will be estimated and compared by a non-inferiority test to the threshold of -0.38% with a margin of 0.4%. A significance level of 0.025 (one-sided) will be used.

  The hypothesis of non-inferiority is mathematically expressed as:

  H_0: $\Delta\mu_{780G} \geq -0.38\% + 0.4\%$

  H_a: $\Delta\mu_{780G} < -0.38\% + 0.4\%$

14.4.2 Analysis of Effectiveness Endpoint

14.4.2.1 Primary Effectiveness Endpoint

Age 18-80:

- The mean % of time, μ_{780G}, in range (TIR 70-180 mg/dL) will be estimated and compared by a non-inferiority test to the threshold of 73.7% with a margin of 7.5%. A significance level of 0.025 (one-sided) will be used.

  The hypothesis of non-inferiority is mathematically expressed as:
  H_0: $\mu_{780G} \leq 73.7\% - 7.5\%$
  H_a: $\mu_{780G} > 73.7\% - 7.5\%$

Age 7-17:

- The mean % of time, μ_{780G}, in range (TIR 70-180 mg/dL) will be estimated and compared by a non-inferiority test to the threshold of 65.3% with a margin of 7.5%. A significance level of 0.025 (one-sided) will be used.

  The hypothesis of non-inferiority is mathematically expressed as:
  H_0: $\mu_{780G} \leq 65.3\% - 7.5\%$
  H_a: $\mu_{780G} > 65.3\% - 7.5\%$

14.4.2.2 Analysis of Secondary Effectiveness Endpoints

Age 18-80:

- Secondary Effectiveness Endpoint: The mean % time, μ_{780G}, in hypoglycemia (< 54 mg/dL) will be estimated and compared by a non-inferiority test to the threshold of 0.86% with a margin of 2%. A significance level of 0.025 (one-sided) will be used.
  The hypothesis of non-inferiority is mathematically expressed as:
  H_0: $\mu_{780G} \geq 0.86\% + 2\%$

  H_a: $\mu_{780G} < 0.86\% + 2\%$

- Secondary Effectiveness Endpoint: The mean % of time, μ_{780G}, in range (TIR 70-180 mg/dL) will be estimated and compared by a simple superiority test with a significance level of 0.025 (one-sided).
  The hypothesis of superiority is mathematically expressed as:
  H_0: $\mu_{780G} \leq 73.7\%$

  H_a: $\mu_{780G} > 73.7\%$

Age 7-17:

- Secondary Effectiveness Endpoint: The mean % time, μ_{780G}, in hypoglycemia (< 54 mg/dL) will be estimated and compared by a non-inferiority test to the threshold of 0.71% with a margin of 2%. A significance level of 0.025 (one-sided) will be used.
  The hypothesis of non-inferiority is mathematically expressed as:
  H_0: $\mu_{780G} \geq 0.71\% + 2\%$

  H_a: $\mu_{780G} < 0.71\% + 2\%$

- Secondary Effectiveness Endpoint: The mean % of time, μ_{780G}, in range (TIR 70-180 mg/dL) will be estimated and compared by a simple superiority test with a significance level of 0.025 (one-sided).
  The hypothesis of superiority is mathematically expressed as:
  H_0: $\mu_{780G} \leq 65.3\%$

  H_a: $\mu_{780G} > 65.3\%$

14.4.3 Descriptive Endpoints

- Time spent in the SmartGuard feature versus time spent in Manual Mode
- Change in mean glucose value from baseline to EOS
- Time in different ranges (% of SG): SG < 70 mg/dL, 70 mg/dL ≤ SG ≤ 140 mg/dL, SG > 140 mg/dL, 180 mg/dL, 250 mg/dL, and 350 mg/dL

- Number of Events, Area Under Curve (AUC) and Time in the hyperglycemic range: SG > 140 mg/dL, 180 mg/dL, 250 mg/dL, and 350 mg/dL
- Number of Events, AUC and Time in the hypoglycemic range: SG < 54 mg/dL and 70 mg/dL
- Change of Total Daily Dose (TDD) of insulin from baseline to EOS
- Change of weight from baseline to EOS
- Subgroup analysis will be performed for:
    - Setpoint
        - 100 mg/dL
        - 110 mg/dL
        - 120 mg/dL
        - 150 mg/dL (Temp Target Usage)

14.4.4 Safety Data Summarized

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

14.4.5 Device Deficiencies

Descriptive summary will be used to characterize DDs:

- All reports of device issues.

14.4.6 Subject Feedback

Descriptive summary will be used to characterize study survey/questionnaire results. Refer to CIP337 Survey/Questionnaire Guide for administration details.

14.4.7 Simulation Data

Computer simulated data may be compared to study data.

14.5 Sample Size Considerations/Sample Size Justification

14.5.1 Age 18-80

- Sample size for the primary safety endpoint: the overall mean change in HbA1c from baseline to end of 3-month study period, non-inferiority test

  The overall mean change in HbA1c from baseline to end of 3-month study period from 670G (CEP294 HCL age 18 to 75, N = 101) study was -0.50%. Assuming the mean change in HbA1c from baseline to end of 3-month study period from 780G is the same as 670G, with a standard deviation of 0.7%, SAS power and sample size calculator with one sample T test shows that a total of 80 subjects will provide > 80% power to detect the non-inferiority (with a margin of 0.4%) with a significance level of 0.025 (one-sided).

- Sample size for the primary effectiveness endpoint: the mean % of time in range (TIR 70-180 mg/dL), non-inferiority test

  The mean % of time in target from 670G (CEP294 HCL age 18 to 75, N = 104) study was 73.7%. Assuming the mean time in target (%) from 780G is the same as 670G, with a standard deviation of 8.8%, SAS power and sample size calculator with one sample T test shows that a total of 80 subjects will provide > 80% power to detect the non-inferiority (with a margin of 7.5%) with a significance level of 0.025 (one-sided).

- Sample size for the secondary effectiveness endpoint: the mean % of time below range (< 54 mg/dL), non-inferiority test

  The mean % of time below range (< 54 mg/dL) from 670G (CEP294 HCL age 18 to 75, N = 104) study was 0.86%. Assuming the mean time below target (%) from 780G is the same as 670G, with a standard deviation of 0.79%, SAS power and sample size calculator with one sample T test shows that a total of 80 subjects will provide > 80% power to detect the non-inferiority (with a margin of 2%) with a significance level of 0.025 (one-sided).

- Sample size for the secondary effectiveness endpoint: the mean % of time in range (TIR 70-180 mg/dL), simple superiority test

  The mean % of time in target from 670G (CEP294 HCL age 18 to 75, N = 104) study was 73.7%. Assuming the mean time in target (%) from 780G is 76%, with a standard deviation of

7.2%, SAS power and sample size calculator with one sample T test shows that a total of 80 subjects will provide > 80% power to detect the simple superiority with a significance level of 0.025 (one-sided).

14.5.2 Age 7-17

- Sample size for the primary safety endpoint: the overall mean change in HbA1c from baseline to end of 3-month study period, non-inferiority test

  The overall mean change in HbA1c from baseline to end of 3-month study period from 670G (CEP294 and CEP302 HCL age 7 to 17, N = 125) study was -0.38%. Assuming the mean change in HbA1c from baseline to end of 3-month study period from 780G is the same as 670G, with a standard deviation of 0.7%, SAS power and sample size calculator with one sample T test shows that a total of 80 subjects will provide > 80% power to detect the non-inferiority (with a margin of 0.4%) with a significance level of 0.025 (one-sided).

- Sample size for the primary effectiveness endpoint: the mean % of time in range (TIR 70-180 mg/dL), non-inferiority test

  The mean % of time in target from 670G (CEP294 and CEP302 HCL age 7 to 17, N = 125) study was 65.3%. Assuming the mean time in target (%) from 780G is the same as 670G, with a standard deviation of 8%, SAS power and sample size calculator with one sample T test shows that a total of 80 subjects will provide > 80% power to detect the non-inferiority (with a margin of 7.5%) with a significance level of 0.025 (one-sided).

- Sample size for the secondary effectiveness endpoint: the mean % of time below range (< 54 mg/dL), non-inferiority test

  The mean % of time below range (< 54 mg/dL) from 670G (CEP294 and CEP302 HCL age 7 to 17, N = 125) study was 0.71%. Assuming the mean time below target (%) from 780G is the same as 670G, with a standard deviation of 0.60%, SAS power and sample size calculator with one sample T test shows that a total of 80 subjects will provide > 80% power to detect the non-inferiority (with a margin of 2%) with a significance level of 0.025 (one-sided).

- Sample size for the secondary effectiveness endpoint: the mean % of time in range (TIR 70-180 mg/dL), simple superiority test

  The mean % of time in target from 670G (CEP294 and CEP302 HCL age 7 to 17, N = 125) study was 65.3%. Assuming the mean time in target (%) from 780G is 67.6% , with a standard

deviation of 7%, SAS power and sample size calculator with one sample T test shows that a total of 80 subjects will provide > 80% power to detect the simple superiority with a significance level of 0.025 (one-sided).

14.5.3 Expected Drop-out Rates

Incorporating the expected drop-out rates, a total of up to 250 subjects will be enrolled, in order to have 200 subjects enter the study period .

14.6 Final Report

The study results will be summarized and presented in the final report.

15. Ethics

15.1 Statement(s) of 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 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 (DoH) have been implemented in this clinical study by means of the informed consent/assent process, IRB approval, study training, clinical trial registration, pre-clinical testing, risk-benefit assessment, publication policy, etc.

15.2 IRB Approval

This CIP, any subsequent amendments to this CIP, the ICF/assent form, subject materials, and any form

of subject recruitment information (e.g., advertisements) relating to this study will be approved by the responsible IRB in accordance with 21 CFR Part 56.

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

15.3 Role of the Sponsor's Representatives

Sponsor representatives may provide support as required for the study, such as 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.

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.

15.4 Investigator's Responsibilities

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." Each investigational center shall designate a primary investigator who will have overall responsibility for the conduct of the investigation at the investigational center.

The principal investigators (and co-investigators if applicable) are responsible for conducting the study in accordance with this CIP, CTA, and 21 CFR Part 812 that apply to significant risk (SR) device studies. The investigator's responsibilities include, but are not limited to:

- 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)
- 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:
  - attribution, legibility, and timeliness of source data
  - 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, including information reported in the eCRFs and in all other required reports
- 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 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.

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. 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. 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** 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, monitor, regulatory authority personnel, and the Clinical Study Manager. This accessibility is of particular importance for reviewing data in the eCRF. Access to subject's medical files for source data verification will need to be granted 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 authorities 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 authorities 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 CIP 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 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 included in the Investigator Site File. The EDC system maintains an audit trail on entries, changes, and corrections in the 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 centers 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 subject's enrollment.

16.3.2 CareLink Personal/CareLink System Software

During the course of the study, subject's BG values may be assessed from the 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/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 subject's ID.

16.3.3 Subject Surveys/Questionnaires

Subjects will be provided a link to complete the questionnaires that will be kept online. Refer to CIP337 Questionnaire Guide. If the online link cannot be accessed due to technical issues, subjects will complete the questionnaire using a paper format. The investigator, or designated investigational center staff, will then enter the subject's responses from the paper questionnaires to online once it becomes available. If paper format is used, the investigator or designated investigational center staff should maintain the original paper source in the subject's source file.

16.3.4 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 AEs (see **Section 11**). After data entry, eCRFs should be submitted (i.e., saved) so that monitors can proceed with data verification without delay.

16.3.5 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/CareLink system software data, laboratory reports, surveys/questionnaires and source documents are handled as source data.

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

16.5 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 investigational center 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 and Subject Compensation

Subjects will be paid for participation. Refer to the ICF for 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, or for other reasons, and will submit any significant amendment to the CIP, including a justification for this amendment, to the appropriate regulatory authority (if applicable) for their approval and to the investigators to obtain approval from their IRB. The investigator will only implement the amendment after the sponsor has obtained regulatory authority (if applicable) approval and the amendment has been approved by the IRB. Administrative amendments to the CIP will be submitted to the IRB for notification.

16.8 Records and Reports

16.8.1 Investigator Records

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

- All essential study documents and correspondence that pertains to the clinical study
- CIP and, if applicable, any amendments
- Report of prior investigations and/or user guide
- Medtronic and IRB-approved Subject ICF/assent form
- IRB and regulatory authority approval or notification
- Fully signed clinical study agreements (i.e., including Investigator Statement and Signature Page, Clinical Trial Agreement and Confidential Disclosure Agreement)
- Completed Delegation of Authority Log
- Training documentation of all investigational center staff
- Subject Screening log and/or subject ID log
- Signed, dated and fully executed Subject ICF/assent form
- Source documentation
- Fully executed eCRFs and corrections
- Report of AEs and DDs
- 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 CV of PI (and key study team members if required per local requirements)
- Study reports

16.8.2 Investigator Reporting Responsibilities

Table 6. Investigator Reporting Requirements

Report	Submit to	Description/Constraints
AEs and DDs	Sponsor, IRB, and regulatory authority, where applicable	Refer to **Section 11** 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 authority, 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 authorities. 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 and regulatory authority 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 and regulatory authority (if applicable). 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. Following suspension or early termination, subjects will receive standard medical care from their own providers.

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

Publications from the study will be handled according to Medtronic Global Standard Operating Procedures and as indicated in the Clinical Trial Agreement.

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 study will be publicly registered on http://www.clinicaltrials.gov prior to subject enrollment. Study results, when available, will be posted in this database.

17. References

1. Beato-Víbora PI, Gallego-Gamero F, Lázaro-Martín L, Romero-Pérez MDM, Arroyo-Díez FJ. Prospective Analysis of the Impact of Commercialized Hybrid Closed-Loop System on Glycemic Control, Glycemic Variability, and Patient-Related Outcomes in Children and Adults: A Focus on Superiority over Predictive Low-Glucose Suspend Technology. *Diabetes Technology and Therapeutics.* 2020;22(12):912-919.
2. Cryer PE. Defining and reporting hypoglycemia in diabetes: A report from the American diabetes association workgroup on hypoglycemia. *Diabetes Care.* 2005;28(5):1245-1249.
3. Hyperglycemic Crises in Diabetes. *Diabetes Care.* 2004;27(SUPPL. 1):S94-S102.

18. Appendices

18.1 Names and addresses

18.1.1 Investigational Centers and IRB

At the time this CIP was finalized, the investigational centers at which the study will be conducted had not been identified nor had any IRBs reviewed the investigational plan. The names and addresses of investigators, and participating investigational centers will be kept under separate cover.

18.1.2 Monitor(s) 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

The names and addresses of monitors will be kept under separate cover.

18.2 Labeling of Devices

The current labels and user guides for the investigational 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.

19. Version History

Version	Summary of changes	Author(s)/Title
A.1	Not Applicable, New Document	[redacted]
A.2	• See "Attachment 1: CIP337 Description of CIP Changes Version A.1 to A.2" for details on changes • Added Admelog to list of trademarks • Updated attribution statement and year in copyright statement • Transferred CIP to the revised Enterprise Clinical QMS CIP template (056-F275, Version E) • Updated Glossary section • Replaced the term "IFU" with "user guide" throughout CIP • Harmonized the header name for products under the title page and synopsis table • Updated word "protocol" to "CIP" to maintain consistent term used throughout the document • Updated Title page, Synopsis (Clinical Study Type), Purpose, Objective, and Background section: Harmonized term "efficacy" to "effectiveness" • Updated Medtronic Extended infusion set model numbers and harmonized throughout CIP, as applicable in title page, synopsis, device system Table 1, and DA Requirements Table • Updated Medtronic Extended Reservoir device regulatory status	[redacted]

	to non-investigational. Harmonized throughout CIP, as applicable in title page, synopsis, device system Table 1, product description moved from "Investigational Product" section to "Non-Investigational Product" section, and DA Requirements Table
	• Clarified the use of SmartGuard during Run-in Period and Study Period for both subjects with Auto Mode and without Auto Mode experience. The changes are reflected under the following sections:
	  ○ Study Design
	  ○ Visit Details Table
	• Updated Study Design & Visit Details section:
	  ○ Updated Auto Basal target settings and Active Insulin Time settings during run-in period and study period
	  ○ Changed setting requirements for more flexibility per investigator's discretion
	  ○ Added language during the study period to encourage subjects to continue on the same brand of insulin with which they started
	• Added new visit 13 under Study Period –Day 44 (±3 days) after Visit 7. The changes are reflected under the following sections:
	  ○ Study Design
	  ○ Schedule of Events
	  ○ Study Visit Schedule
	  ○ Visit Schedule figure
	  ○ Visit Details Table
	• Added "Adjust pump settings" in Study Visit Schedule and Visit Details Table
	• Updated Visit Details Table:
	  ○ Added "Instruct/Remind subjects regarding the content of the Home Reference Guide"	

	○ Updated to "(including the type of insulin being used). The only insulins permitted for use in the study are Humalog, Novolog, and Admelog." ○ Added instructions for subjects and their parents/caregivers (if applicable) to report the Medtronic Extended infusion set and reservoir changes and reason for the changes, as applicable. ○ Added insertion locations and instructions for subjects and their parents/caregivers(if applicable) to report the sensor insertion information as specified for the applicable age group according to the User guide • Updated the following Study Visit Schedule – Visit 1, Visit 4 windows, and Visit 15 • Updated number of investigational centers • Added use of Admelog. The changes are reflected under the following sections: ○ Study Design ○ Inclusion Criteria (#13) ○ Insulin ○ Visit Details Table ○ Subject Exit, Withdrawal or Discontinuation • Updated Exclusion Criteria #11 • Added Exclusion Criteria for 780G users • Updated Consumable Devices section • Updated Product Accountability section: Table 2. DA Requirements • Updated Return or Disposal of Study Devices section • Updated Deviation Handling section • Updated End of Subject	

	Participation in Study/ Completion of Study section • Updated Subject Exit, Withdrawal or Discontinuation section • Updated Study Stopping Rules section • Updated Section 11.3: updated section title from "Reporting of Adverse Events" to "Recording of Adverse Events" • Updated Notification of Adverse Events section • Updated Expedited Safety Reporting Requirements section • Updated prevention and mitigation for the following (added "and glucagon"): Risks with Insulin Administration and Pumps and Risk with Closed Loop Therapy • Updated Clinical Events Committee section • Updated Data Monitoring Committee section • Updated Monitor(s) Contact Information section • Updated Labeling of Devices section	

A.3 (FDA Approved)	• See "Attachment 1: CIP337 Description of CIP Changes Version A.2 to A.3" for details on changes
	• Added Exclusion Criteria for Medtronic Diabetes employee or their immediate family member (excluding adult children and/or adult siblings)
	• Updated Study Visit Schedule Fig.
	• Updated Visit Details Table:
	  ○ Harmonized start of 780G pump during run-in period and study period with study design
	  ○ Removed instructions for subjects and their parents/caregivers (if applicable) to report the Medtronic Extended infusion set and reservoir changes and reason for the changes, as applicable
		[redacted]

A (Equivalent to A.4)	• See "Attachment 1: CIP337 Description of CIP Changes Version A.3 to A.4 " for details on changes
	• Updated IDE number
	• Updated year in copyright statement
	• Updated Schedule of Events Section- removed Telemedicine since we are allowing virtual office visits where office visit occurs (this includes blood draws and device related assistance)
	• Added option for Virtual Office under Visit 1 and Visit 2 for the following:
	  ○ Study Visit Schedule section
	  ○ Visit Schedule Figure
	  ○ Visit Details Table
	• Harmonized start of Auto Basal target at 120 mg/dL, 100 mg/dL, and investigator's discretion as specified under Study Design for the following:
	  ○ Study Visit Schedule section
	  ○ Visit Details Table
	• Updated Table 1: For Precision Xtra Ketone Meter or other approved ketone meter, added "N/A" under "MDT Model number/ part number" column
	• Updated Publication and Use of Information section
		[redacted]