Medtronic	
Study Title	Safety, Effectiveness and Usability Evaluation of the Hybrid Closed Loop (HCL) System in Type 1 Adult and Adolescent Subjects in Chinese Population
NCT Number	NCT04663295
Document Description	Study Protocol (Version C)
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Medtronic **Clinical Investigation Plan (CIP)**	
CIP/Study Title	Safety, Effectiveness and Usability Evaluation of the Hybrid Closed Loop (HCL) System in Type 1 Adult and Adolescent Subjects in Chinese Population
CIP Identifier	329
Study Product Name	MiniMed™ 670G Insulin Pump
Category of investigational medical device (China Only)	Class III
Class III medical devices requiring clinical trial approval (China Only)	No
Similar product in China	Yes
Sponsor	USA: Medtronic MiniMed, Inc. ("Medtronic") 18000 Devonshire St Northridge, CA 91325 866.948.6633
Local Sponsor (Agent)	Medtronic (Shanghai) Management Co., Ltd. Room 2106A, 2106F, 2106G, 2106H, Floor 21, Donghua Financial Building, No. 28 Maji Road, China (Shanghai) Pilot Free Trade Zone, 200120, Shanghai, P.R.China .
Coordinating Investigator/Lead Study Site	Dr. Yiming Mu / Chinese PLA General Hospital
Document Version	C
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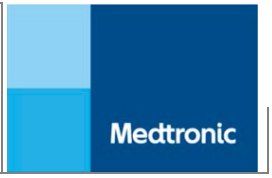

Confidentiality Statement

1. Investigator Statement

Study Product Name	*Investigational Devices:* • MiniMed™ 670G Insulin Pump (MMT-1883)- referred to as the study pump throughout this protocol • Guardian™ Sensor (3) (MMT-7020) • Guardian™ Link (3) Transmitter (MMT-7911) • One-press Serter (MMT-7512) -referred to as the Serter throughout this protocol • Charger (MMT-7715) • Tester (MMT-7736L) • Blue adapter (ACC-1003910) • MiniMed Mobile Application (MMT-6101/6102)- referred to as the Mobile App in this protocol • Roche Accu-Chek™* Guide Link Meter (Model MTR114) -referred to as the Accu-Chek™* Guide Link study meter in this protocol *Non-Investigational Devices:* • Medtronic CareLink™ For Clinical Research software (MMT-7338) -– referred to as CareLink™ software throughout this protocol • Abbott™* FreeStyle Optium Neo Blood Glucose & Ketone Monitoring System to be used for blood ketone measurements only - referred to as the FreeStyle Optium Neo ketone meter throughout this protocol • Subject-owned Smartphone
Sponsor	Medtronic MiniMed
Clinical Investigation Plan Identifier	329

Version Number/Date	C/13-MAY-2020

Investigator's statement

研究者声明

I agree that:

我同意：

1. I will conduct this clinical trial in strict compliance with the Declaration of Helsinki, current laws and regulations of China, and the requirements of the protocol;

1.严格按照赫尔辛基宣言、中国现行法规、以及试验方案的要求进行本次临床试验。

2. And record all required data accurately on the Case Report Form (CRF) and complete the final report of the clinical trial on time;

2.将所要求的全部数据准确记录于病例报告表（CRF）中，按时完成临床试验报告。

3. The investigational medical device will be used only for this clinical trial and the receipt and use of the investigational medical device will be recorded completely and accurately and the records will be retained during the process of the clinical trial;

3.试验用医疗器械仅用于本次临床试验，在临床试验过程中完整准确地记录试验用医疗器械的接收和使用情况，并保存记录。

4. The monitor and verifier authorized or designated by the Sponsor and the regulatory authorities are allowed to conduct monitoring, verification and inspection for the clinical trial;

4.允许申办者授权或派遣的监查员、核查员和监管部门对该项临床试验进行监查、核查和检查。

5. The clinical trial should be conducted in strict compliance with contract/articles of agreement signed by all parties.

5. 严格履行各方签署的临床试验合同/协议条款。

I have already read the clinical study protocol, including the above statement and I fully agree all the above requirements.

我已全部阅读了临床试验方案，包括以上的声明，我同意以上全部内容。

Comments of the sponsor:	Signature (Seal): Date:

Comments of the investigator:	Signature: Date:
Comments of the clinical investigational site:	Signature (Seal): Date:

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2. Glossary

Abbreviation	Definition
AE	Adverse Event
ADE	Adverse Device Effect
ASIC	Application Specific Integrated Circuit
BG	Blood Glucose
CDC	Centers for Disease Control
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CIP	Clinical Investigation Plan
CTA	Clinical Trial Approval
CV	Coefficient of Variation
DD	Device Deficiency
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EIS	Electrochemical Impedance Spectroscopy
EOS	End of Study
ER	Emergency Room
FDA	United States Food and Drug Administration

Abbreviation	Definition
GA	Glycated Albumin
GCP	Good Clinical Practice
HbA1c	Glycosylated hemoglobin
HCL	Hybrid Closed Loop
Hct	Hematocrit
ICF	Informed Consent Form
ID	Identification
IEC	Independent Ethic Committee
IFU	Instructions for Use
ITT	Intention to Treat
IV	Intravenous
MAGE	Mean Amplitude of Glycemic Excursions
NMPA	National Medical Products Administration
OC-RDC	Oracle Clinical Remote Data Capture
PC	Personal Computer
PP	Per Protocol
QC	Quality Control
SAE	Serious Adverse Event
SADE	Serious Adverse Device Events
SAP	Sensor Augmented Pump
SD	Standard Deviation
SG	Sensor Glucose
SMBG	Self-Monitoring of Blood Glucose

Abbreviation	Definition
T1DM	Type 1 Diabetes Mellitus
TDD	Total Daily Dose
TLS	Transport Layer Security
TS	Technical Support
TSH	Thyroid-stimulating Hormone
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

3. Synopsis

Title	Safety, Effectiveness and Usability Evaluation of the Hybrid Closed Loop (HCL) System in Type 1 Adult and Adolescent Subjects in Chinese Population
Clinical Study Type	Prospective Single Arm Multi-center Study
Indication under investigation	Type 1 diabetes
Devices	*Investigational Devices:* • MiniMed™ 670G Insulin Pump (MMT-1883)-referred to as the study pump throughout this protocol • Guardian™ Sensor (3) (MMT-7020) • Guardian™ Link (3) Transmitter (MMT-7911) • One-press Serter (MMT-7512) -referred to as the Serter throughout this protocol • Charger (MMT-7715) • Tester (MMT-7736L) • Blue adapter (ACC-1003910) • MiniMed Mobile Application (MMT-6101/6102)- referred to as the Mobile App in this protocol • Roche Accu-Chek™* Guide Link Meter (Model MTR114) -referred to as the Accu-Chek™* Guide Link study meter in this protocol *Non-Investigational Devices:* • Medtronic CareLink™ For Clinical Research software (MMT-7338) –– referred to as CareLink™ software throughout this protocol • Abbott™* FreeStyle Optium Neo Blood Glucose & Ketone Monitoring System to be used for blood ketone measurements only -referred to as the FreeStyle Optium Neo ketone meter throughout this protocol • Subject-owned Smartphone

Similar product in China	Yes
Purpose	Investigation Purpose: Obtain clinical data in Chinese patients to support product registration of the MiniMed™ 670G system with the National Medical Product Administration (NMPA) in China. The results from the study will be submitted to the NMPA for product registration.
Objective(s)	Primary Objective(s): To evaluate the safety, effectiveness and usability of the Medtronic MiniMed™ 670G system in Chinese patients with type 1 diabetes.
Study Design	This study is a multi-center, single arm study in insulin-requiring subjects with type 1 diabetes who are 14 years of age and older. The run-in period will be approximately up to 35 days long, followed by a study period that will be approximately up to 33 days in duration. The study is anticipated to last no longer than 13 months from investigational center initiation to completion of all data entry and monitoring procedures. The study will target approximately 5 months to complete subject enrollment. Subjects can expect to participate for approximately 2-3 months including the run-in and study periods. A total of up to 75 subjects (aged 14-75) will be enrolled at a minimum 2 investigational centers and up to 6 investigational centers (hospitals) in China to have at least 50 subjects who complete the study. **Overview of the Run-in and Study Periods:** **Run-in Period :** After enrollment and passing Screening requirements, subjects will be trained on pump use as well as the use of Continuous Glucose Monitoring (CGM) with transmitters and sensors. The run-in period will be used to allow subjects to become familiar with new study devices. During the run-in period study subjects will be using the Study Pump (MiniMed™ 670G) and CGM with only the Sensor Augmented Pump (SAP) function activated (i.e. SmartGuard™ features such as Suspend on Low and Suspend before Low will remain turned OFF). All subjects will be trained on the study devices and diabetes management principles, such as the treatment of hyperglycemia and hypoglycemia. A training checklist consisting of review of the MiniMed™ 670G system features will be completed and collected for each subject to ensure competency. In addition, there will be training regarding access to oral glucose, oral carbohydrates or glucagon in case of hypoglycemia.

For study purposes, subjects will be instructed to perform SMBG if they are experiencing a severe hypoglycemic event, severe hyperglycemic event or Diabetic Ketoacidosis (DKA). As a precaution, subjects will be told that they should keep their own insulin pump supplies in a safe place and to have back up supplies on hand (such as insulin and syringe) in the event they are asked to revert back to their own therapy during the study or experience study pump issues (i.e. infusion set occlusion with high glucose).

Subjects will be instructed to insert glucose sensors only in the locations that are specified in the User Guide materials. Reminders will be given to subjects at each office visit. Information about sensor insertions will be collected on an electronic Case Report Form (eCRF) in the study database, i.e. insertion location.

Study Period :

The study period begins at Visit 4 in which subjects will begin using Auto Mode. The subject will have follow up visits after Auto Mode has been turned on to adjust insulin pump settings and then continue wearing the study devices until the end of the study period.

Manual Mode Settings

- High glucose alert limit recommend to be set at 300 mg/dL (16.7 mmol/L)
  - Alert Setting Options may be set per investigator discretion
- Low glucose alert limit recommend to be set at 70 mg/dL (3.9 mmol/L)
  - Subjects will be instructed to follow up with an SMBG confirmatory measurement when receiving a low alert
  - Alert Setting Options may be set per investigator discretion
- Predictive alerts and rate of change alerts are optional
- Consider setting the glucose target in the bolus wizard calculator to the same target as the Auto Mode (HCL algorithm), i.e. 120 mg/dL (6.7 mmol/L) or higher, based on investigator discretion.

Settings for Auto Mode:

- Auto Mode (HCL) basal rate target for the closed loop algorithm is factory set at 120 mg/dL (6.7 mmol/L)
- Auto Mode correction target is factory set at 150 mg/dL (8.3 mmol/L)
- The Temp target setting in the pump may be used when subject exercises. Temp Target Threshold is set to 150 mg/dL (8.3 mmol/L)
- Alarms that are fixed into system:
  - When SG at or below 50 mg/dL (2.8 mmol/L)
  - When SG at or above 300 mg/dL (16.7 mmol/L) for one hour
  - When SG at or above 250 mg/dL (13.9 mmol/L) for 3 hours
- High glucose alert limit (i.e. the setting for a high glucose alert threshold based on sensor reading) is recommended to be set at 300 mg/dL (16.7 mmol/L)
  - Alert setting options may be set per investigator discretion

	• Low glucose alert limit (i.e. the setting for a low glucose alert threshold based on sensor reading) is recommended to be set at 70 mg/dL (3.9 mmol/L) • Alert setting options may be set per investigator discretion • Subjects will be instructed to follow up with an SMBG confirmatory measurement when receiving a low alert • Insulin carbohydrate ratios may be adjusted throughout study. • Active insulin time may also be adjusted. <u>Blood Glucose Monitoring Method:</u> • Accu-Chek™* Guide Link Study Meter **SMBG recommendations**: Subjects will be instructed to check their blood glucose at least 4-6 times per day and also before driving (as applicable) for diabetes self-management (SMBG), using the supplied Study Meter according to the user guide. Occasionally, subjects may receive a notification if the pump needs a blood glucose (BG) measurement to enter or to stay in Auto Mode.
Sample Size and Investigational Sites	This study will enroll subjects between age of 14 and 75 years old, with a ratio (1:5) between Adolescents (14-17 years) and Adults (≥ 18 years). A total of up to 75 subjects will be enrolled at minimum 2 investigational centers and up to 6 investigational centers (hospitals) in China considering potential drop outs. A maximum of 30 subjects will be enrolled at each investigational center. Sites with less than 6 subjects will be pooled into 'pseudo-sites' of at least 10 subjects per pseudo-site. Pseudo-sites will be pooled by ranking those sites with less than 6 subjects by site number and pooling those sites in order of site number until the number of subjects reaches at least 10.
Duration	The study is anticipated to last no longer than 13 months from investigational center initiation to completion of all data entry and monitoring procedures. The study will target 5 months to complete subject enrollment. Subjects can expect to participate for approximately 2-3 months including the run-in and study periods.
Inclusion Criteria	*General Inclusion Criteria* 1. Subject is age 14- 75 years at time of Screening. 2. Subject has 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. *Study-specific inclusion criteria* 3. Subject is willing to perform ≥ 4 finger stick BG measurements daily. 4. Subject is willing to perform required sensor calibrations. 5. Subject is willing to wear the system continuously throughout the study. 6. Subject must have a minimum daily insulin requirement (Total Daily Dose) of greater than or equal to 8 units.

	7. Subject has a Glycosylated hemoglobin (HbA1c) less than 10% (as processed by the investigational center lab or their contracted Local Lab) at time of Screening visit. 8. Subject 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. Prior labs in the last 6 months are sufficient. 9. Subject has been on pump therapy for greater than 6 months prior to screening (with or without CGM experience). 10. Subject is willing to upload data from the study pump and meter at home. 11. If subject has celiac disease, it has been adequately treated as determined by the investigator. 12. Subject has been taking and is willing to take one of the following insulins throughout the course of the study: ○ Humalog™* (insulin lispro injection) ○ NovoLog™* (insulin aspart) 13. Subject must be able to carbohydrate count or willing to learn how to carbohydrate count for the study.
Exclusion Criteria	1. Subject 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. Subject has been hospitalized or has visited the ER in the 6 months prior to Screening resulting in a **primary diagnosis** of uncontrolled diabetes. 3. Subject has had DKA in the 6 months prior to Screening. 4. Subject is unable to tolerate tape adhesive in the area of sensor placement. 5. Subject has any unresolved adverse skin condition in the area of sensor placement (e.g., psoriasis, dermatitis herpetiformis, rash, Staphylococcus infection). 6. Subject is a female of child-bearing potential who has a positive pregnancy test at Screening or plans to become pregnant during the course of the study. 7. Subject is a female who is sexually active and able to conceive should be excluded if they are not using an effective method of contraception and do not agree to continue using an effective method of contraception for the duration of the study as determined by investigator. 8. Subject has had any of the following cardiovascular events within 1 year of screening: myocardial infarction, unstable angina, coronary artery bypass surgery, coronary artery stenting, transient ischemic attack, cerebrovascular accident, angina, congestive heart failure, ventricular rhythm disturbances or thromboembolic disease. 9. Subject is being treated for hyperthyroidism at time of Screening. 10. Subject has a diagnosis of adrenal insufficiency. 11. Subject has taken any oral, injectable, or intravenous (IV) glucocorticoids within 8 weeks from time of Screening, or plans to take any oral, injectable, or IV glucocorticoids during the course of the study.

	12. Subject is actively participating in an investigational study (drug or device) wherein he/she has received treatment from an investigational study drug or investigational study device in the last 2 weeks. (Please note participation in an observational study is acceptable.) 13. Subject is currently abusing illicit drugs. 14. Subject is currently abusing alcohol. 15. Subject is using pramlintide (Symlin), DPP-4 inhibitor, liraglutide (Victoza or other GLP-1 agonists), metformin, canagliflozin (Invokana or other SGLT2 inhibitors) at time of Screening. 16. Subject has a history of visual impairment which would not allow subject to participate in the study and perform all study procedures safely, as determined by the investigator. 17. Subject has elective surgery planned that requires general anesthesia during the course of the study. 18. Subject has a sickle cell disease, hemoglobinopathy; or has received red blood cell transfusion or erythropoietin within 3 months prior to time of Screening 19. Subject plans to receive red blood cell transfusion or erythropoietin over the course of study participation. 20. Subject diagnosed with current eating disorder such as anorexia or bulimia 21. Subject has been diagnosed with chronic kidney disease that results in chronic anemia. 22. Subject has a hematocrit (Hct) that is below the normal reference range of lab used. Prior labs in the last 6 months are sufficient. 23. Subject is on dialysis. 24. Subject has an estimated glomerular filtration rate (eGFR) of < 30. 25. Subject has a pediatric BMI category of underweight (less than the 5th percentile) as defined by Centers for Disease Control (CDC) (https://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html) 26. Subject is a member the research staff involved with the study.

Study Timeline	**Visit Schedule:**
	
	Run-in Period Visits: To be completed approximately up to 35 days
	
	• Visit 1: Screening (Office):
	  ○ Consent
	  ○ Collect demographic and baseline characteristics:
	  ▪ Age
	  ▪ Gender
	  ▪ Race
	  ▪ Ethnicity
	  ▪ Height and Weight
	  ○ Obtain prior Medical History
	  ○ Collect concomitant medications
	  ○ Labs (pregnancy test [if applicable], HbA1c, TSH, Hct, GA and eGFR)
	  ○ Screening Requirements
	
	• Visit 2: Run-in Period Start - Visit 2 (Office): 2 - 7 days after Visit 1
	  ○ *Eligibility has been confirmed including labs*
	  ○ **All eligible subjects**:
	  ▪ Start study pump; provide pump training
	  ▪ Collect questionnaire(s)
	  ▪ Collect information about food consumed in last 24 hours (food log)
	  ○ Subjects who are using pump **with** CGM at Screening:
	  ▪ Visits 2 and 3 may be combined
	  ▪ Start CGM, provide CGM training
	  ▪ Start CGM run-in (2 weeks)
	  ▪ Install Mobile App to Smartphone (if applicable)
	  ▪ System is set Manual Mode (Sensor Augmented Pump only): **SmartGuard™ features should not be activated**
	
	• Visit 3: Start CGM 0-7 days after Visit 2
	  ○ Subjects who are using pump **without** CGM at Screening:
	  ○ Start CGM, provide CGM Training
	  ▪ Recommend that this visit take place 5-7 days after Visit 2
	  ▪ Start CGM run-in (2 weeks)
	  ▪ Install Mobile App to Smartphone (if applicable)
	  ▪ System is set Manual Mode (Sensor Augmented Pump only): **SmartGuard™ features should not be activated**

	Study Period Visits:
	• Visit 4 (Office): 14 days after Visit 3 (+7 days)
	  ○ Turn on Auto Mode
	• Visit 5 (Office/ Telephone): 1 days after Visit 4 Office or telephone visit
	  ○ Adjust settings as needed
	• Visit 6 (Office/ Telephone): 2 days after Visit 4 Office or telephone visit
	  ○ Adjust settings as needed
	• Visit 7 (Office/ Telephone): 3 days after Visit 4 Office or telephone visit
	  ○ Adjust settings as needed
	• Visit 8 (Office/ Telephone): 4 days after Visit 4 Office or telephone visit
	  ○ Adjust settings as needed
	• Visit 9 (Office/ Telephone): 5 days after Visit 4 Office or telephone visit
	  ○ Adjust Settings as needed
	  ○ Provide training as needed
	• Visit 10 (Office) – 14 days after Visit 4 (±3 days)
	• Visit 11 (Office) – 20 days after Visit 4 (±3 days)
	• Visit 12 (Office) – 30 days after Visit 4 (±3 days)
	  ○ Remove Mobile App from Smartphone (if applicable)
	  ○ Collect questionnaire(s)
	  ○ Collect lab test for GA
	  ○ End of Study

Safety Monitoring/ Risk Analysis	Safety monitoring/risk analysis details are outlined in Section 9.6.
Device Deficiencies	Subject and investigational center reports of device deficiencies will be collected on electronic Case Report Forms (eCRF) and by subjects and/or investigational centers calling the 24-Hour Technical Support (TS) for device troubleshooting and device complaints from time of enrollment to end of study. For additional information, see Section 13.

Study Stopping Rules for Entire Study	During the study period, the following steps will be taken for:
	• Unanticipated Adverse Device Effects (UADE)
	• Device related Diabetic Ketoacidosis (DKA)
	• Device related Severe hypoglycemia
	
	1. Site will notify the sponsor within approximately 24 hours of receiving knowledge of the event.
	2. CEC is to review and adjudicate the event.
	3. CEC will provide recommendation to the sponsor on the following:
	  a) If enrollment and the study may continue
	  b) If enrollment should be stopped, while already enrolled subjects are allowed to continue in study
	  c) If the entire study must be stopped, including subjects who have already received study devices.

Subject Stopping Rules	Any event of DKA or severe hypoglycemia will result in withdrawal of subject from study.
Statistical Analysis for Endpoints and Hypothesis	**Study endpoints** **Primary endpoint:** Time in target range (% of SG): 70 mg/dL (3.9 mmol/L) ≤ SG ≤ 180 mg/dL (10 mmol/L) The overall mean change in % of time in target range from run-in period to study period will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided). **Secondary endpoints:** • Time in hypoglycemic range (% of SG): SG < 70 mg/dL (3.9 mmol/L), 60 mg/dL (3.3 mmol/L) and 54 mg/dL (3.0 mmol/L) • Time in hyperglycemic range: SG > 180 mg/dL (10 mmol/L), 250 mg/dL (13.9 mmol/L) and 350 mg/dL (19.4 mmol/L) • Glucose variation: the standard deviation (SD) of SG and the glucose coefficient of variation (CV) • Change of Total Daily Dose (TDD) of insulin and weight from baseline to EOS • Time spent in Auto Mode (HCL) versus time spent in Manual Mode (open loop) • Stratified by HbA1c Ranges (< 7%, 7 – 7.5%, 7.5 – 8%, > 8%) ○ Time in target range (% of SG): 70 mg/dL (3.9 mmol/L) ≤ SG ≤ 180 mg/dL (10 mmol/L) ○ Time in hypoglycemic range (% of SG): SG < 70 mg/dL (3.9 mmol/L), 60 mg/dL (3.3 mmol/L) and 54 mg/dL (3.0 mmol/L) ○ Time in hyperglycemic range: SG > 180 mg/dL (10 mmol/L), 250 mg/dL (13.9 mmol/L) and 350 mg/dL (19.4 mmol/L) **Safety Data Summarized:** All adverse events will be collected from enrollment (i.e., time of consent) to study end including but not limited to: ○ Serious Adverse Events (SAE) ○ Serious Adverse Device Events (SADE)

	○ Unanticipated Adverse Device Effects (UADE) ○ Incidence of Severe Hypoglycemia ○ Incidence of Severe Hyperglycemia ○ Incidence of DKA **Device Deficiencies** Descriptive summary will be used to characterize device deficiencies, which will be collected from enrollment (i.e., time of consent) to study end. **Subject Feedbacks** Descriptive summary will be used to characterize study questionnaire(s) results.

4. Introduction

4.1. Background

4.1.1. Introduction to the MiniMed™ 670G System

The MiniMed™ 670G system combines insulin infusion pump and continuous glucose monitoring (Guardian™ Sensor [3]) system to achieve automatic adjustment of basal insulin delivery. The MiniMed™ 670G system is currently in commercial distribution in the United States, Canada and Europe. The Hybrid Close Loop (HCL) algorithm and Sensor Glucose Technology are the two most essential core technologies of the MiniMed™670G system. The HCL algorithm calculates an insulin dose at 5-minute intervals based on Continuous Glucose Monitoring (CGM) data from the Guardian™ Sensor (3) and past basal insulin delivery history to achieve glycemic control throughout the day. In addition to the HCL algorithm, the MiniMed™ 670G system also includes other SmartGuard™ features in Manual Mode: 1) one feature which enables insulin delivery to be suspended before sensor glucose reaches a user selected low limit (Suspend Before Low) and thus can help patients avoid hypoglycemia 2) the other suspends insulin delivery when preset limit has been reached (Suspend on Low). Pre-market clinical study (CEP294) and post-market data review in CareLink™ have demonstrated that the MiniMed™ 670G system offers substantial clinical benefits to individuals with T1DM.

4.1.2. Current Evidence of Clinical Benefits

Previous studies have shown that the MiniMed™ 670G system can increase time in target glucose range, reduce time spent in the hyperglycemic range without increasing the risk of hypoglycemia, and improve overall glycemic control in individuals with T1DM. The pivotal clinical trial, which directly results in the United States Food and Drug Administration's (FDA) approval on September 28, 2016, investigated the safety of MiniMed™ 670G system and the effects of HCL Auto Mode on glycemic control in 124 patients (ages 14-75 years) with T1DM from 10 hospitals in the United States or Israel. In the CEP294 trial, the

study participants had a 2-week run-in period to learn the devices with HCL Auto Mode off followed by a 3-month study period with HCL Auto Mode on.

The trial results have shown that over 12,389 patient-days, no episodes of severe hypoglycemia or ketoacidosis were observed and 28 device-related adverse events (AEs) that were resolved at home [Bergenstal et al, 2016]. The trial has also demonstrated improved glucose outcomes from the HCL Auto Mode [Garg et al 2017]. From baseline run-in to the end of study phase, both adolescent and adult HbA1c levels decreased significantly from 7.7% to 7.1% and from 7.3% to 6.7%, respectively (both $P < 0.001$). The proportion of overall in-target (71–180 mg/dL) sensor glucose (SG) values increased from 60.4% to 67.2% ($P < 0.001$) in adolescents and from 68.8% to 73.8% ($P < 0.001$) in adults. The SG values in hyperglycemic (> 180mg/dL) and hypoglycemic (≤ 70mg/dL) ranges reduced significantly in both adolescents and adults. In particular, nighttime SG values in the hypoglycemic range (≤ 70mg/dL) reduced from 5.8% to 2.9% in adolescents and from 6.6% to 3.2% in adults. The variability of SG values during HCL Auto Mode decreased significantly compared with those at baseline.

In addition, the Guardian™ Sensor (3) of the MiniMed™ 670G system has also been shown to provide accurate glucose readings in the abdomen and arm of individuals (ages 14-75 years) of T1DM or T2DM [Christiansen et al, 2017]. The mean absolute relative difference between abdomen SG and the standard reference values was 9.4%, and 8.7% between arm SG and the standard reference values. The SmartGuard™ feature (Suspend Before Low) has also been tested in 40 individuals with T1DM [Choudhary et al, 2016]. The 40 individuals used the Suspend Before Low pump system for 4 weeks, and 2,322 suspend before low events were observed. No device-adverse event occurred during the study.

On January 26, 2018, FDA approved the expansion of the use of 670G system to include patients 7 to 13 years of age.

Although there are ample evidence supporting the clinical benefits, the MiniMed™ 670G system has not been evaluated in Chinese individuals with T1DM. Clinical trials to test the system in Chinese subjects is necessary to support National Medical Product Administration (NMPA) approval of the MiniMed™ 670G System.

4.2. Purpose

Obtain clinical data in Chinese patients to support product registration of the MiniMed™ 670G system with the National Medical Product Administration (NMPA) in China. The results from the study will be submitted to the NMPA for product registration.

5. Objectives and Endpoints

5.1. Objectives

5.1.1. Primary Objective(s)

To evaluate the safety, effectiveness and usability of the Medtronic MiniMed™ 670G system in Chinese patients with type 1 diabetes.

5.2. Endpoints

5.2.1. Primary Endpoint

Time in target range (% of SG): 70 mg/dL (3.9 mmol/L) ≤ SG ≤ 180 mg/dL (10 mmol/L)

The overall mean change in % of time in target range from run-in period to study period will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

5.2.2. Secondary Endpoints

- Time in hypoglycemic range (% of SG): SG < 70 mg/dL (3.9 mmol/L), 60 mg/dL (3.3 mmol/L) and 54 mg/dL (3.0 mmol/L)
- Time in hyperglycemic range: SG > 180 mg/dL (10 mmol/L), 250 mg/dL (13.9 mmol/L) and 350 mg/dL (19.4 mmol/L)
- Glucose variation: the standard deviation (SD) of SG and the glucose coefficient of variation (CV)
- Change of Total Daily Dose (TDD) of insulin and weight from baseline to EOS
- Time spent in Auto Mode (HCL) versus time spent in Manual Mode (open loop)
- Stratified by HbA1c Ranges (< 7%, 7 – 7.5%, 7.5 – 8%, > 8%)
    - Time in target range (% of SG): 70 mg/dL (3.9 mmol/L) ≤ SG ≤ 180 mg/dL (10 mmol/L)
    - Time in hypoglycemic range (% of SG): SG < 70 mg/dL (3.9 mmol/L), 60 mg/dL (3.3 mmol/L) and 54 mg/dL (3.0 mmol/L)
    - Time in hyperglycemic range: SG > 180 mg/dL (10 mmol/L), 250 mg/dL (13.9 mmol/L) and 350 mg/dL (19.4 mmol/L)

5.2.3. Safety

All adverse events will be collected from enrollment (i.e., time of consent) to study end including but not limited to:

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

5.2.4. Device Deficiencies

Descriptive summary will be used to characterize device deficiencies, which will be collected from enrollment (i.e., time of consent) to study end.

5.2.5. Subject Feedback

Descriptive summary will be used to characterize study questionnaire(s) results.

6. Study Design

This study is a multi-center, single arm study in insulin-requiring subjects with type 1 diabetes who are 14 years of age and older. The run-in period will be approximately up to 35 days long, followed by a study period that will be approximately up to 33 days in duration.

The study is anticipated to last no longer than 13 months from investigational center initiation to completion of all data entry and monitoring procedures. The study will target approximately 5 months to complete subject enrollment. Subjects can expect to participate for approximately 2-3 months including the run-in and study periods.

A total of up to 75 subjects (aged 14-75) will be enrolled at a minimum 2 investigational centers and up to 6 investigational centers (hospitals) in China to have at least 50 subjects who complete the study.

Overview of the Run-in and Study Periods:

Run-in Period :

After enrollment and passing Screening requirements, subjects will be trained on pump use as well as the use of Continuous Glucose Monitoring (CGM) with transmitters and sensors.

The run-in period will be used to allow subjects to become familiar with new study devices. During the run-in period study subjects will be using the Study Pump (MiniMed™ 670G) and CGM with only the Sensor Augmented Pump (SAP) function activated (i.e. SmartGuard™ features such as Suspend on Low and Suspend before Low will remain turned OFF).

All subjects will be trained on the study devices and diabetes management principles, such as the treatment of hyperglycemia and hypoglycemia. A training checklist consisting of review of the MiniMed™ 670G system features will be completed and collected for each subject to ensure competency. In addition, there will be training regarding access to oral glucose, oral carbohydrates or glucagon in case of hypoglycemia.

For study purposes, subjects will be instructed to perform SMBG if they are experiencing a severe hypoglycemic event, severe hyperglycemic event or Diabetic Ketoacidosis (DKA). As a precaution, subjects will be told that they should keep their own insulin pump supplies in a safe place and to have back up supplies on hand (such as insulin and syringe) in the event they are asked to revert back to their own therapy during the study or experience study pump issues (i.e. infusion set occlusion with high glucose).

Subjects will be instructed to insert glucose sensors only in the locations that are specified in the User Guide materials. Reminders will be given to subjects at each office visit. Information about sensor insertions will be collected on an electronic Case Report Form (eCRF) in the study database, i.e. insertion location.

Study Period :

The study period begins at Visit 4 in which subjects will begin using Auto Mode. The subject will have follow up visits after Auto Mode has been turned on to adjust insulin pump settings and then continue wearing the study devices until the end of the study period.

Manual Mode Settings

- High glucose alert limit recommend to be set at 300 mg/dL (16.7 mmol/L)
  - Alert Setting Options may be set per investigator discretion
- Low glucose alert limit recommend to be set at 70 mg/dL (3.9 mmol/L)
  - Subjects will be instructed to follow up with an SMBG confirmatory measurement when receiving a low alert
  - Alert Setting Options may be set per investigator discretion
- Predictive alerts and rate of change alerts are optional
- Consider setting the glucose target in the bolus wizard calculator to the same target as the Auto Mode (HCL algorithm), i.e. 120 mg/dL (6.7 mmol/L) or higher, based on investigator discretion.

Settings for Auto Mode:

- Auto Mode (HCL) basal rate target for the closed loop algorithm is factory set at 120 mg/dL (6.7 mmol/L)
- Auto Mode correction target is factory set at 150 mg/dL (8.3 mmol/L)
- The Temp target setting in the pump may be used when subject exercises. Temp Target Threshold is set to 150 mg/dL (8.3 mmol/L)
- Alarms that are fixed into system:
  - When SG at or below 50 mg/dL (2.8 mmol/L)
  - When SG at or above 300 mg/dL (16.7 mmol/L) for one hour
  - When SG at or above 250 mg/dL (13.9 mmol/L) for 3 hours
- High glucose alert limit (i.e. the setting for a high glucose alert threshold based on sensor reading) is recommended to be set at 300 mg/dL (16.7 mmol/L)
  - Alert setting options may be set per investigator discretion
- Low glucose alert limit (i.e. the setting for a low glucose alert threshold based on sensor reading) is recommended to be set at 70 mg/dL (3.9 mmol/L)
- Alert setting options may be set per investigator discretion
- Subjects will be instructed to follow up with an SMBG confirmatory measurement when receiving a low alert
- Insulin carbohydrate ratios may be adjusted throughout study.
- Active insulin time may also be adjusted.

Blood Glucose Monitoring Method:

- Accu-Chek™* Guide Link Study Meter

SMBG recommendations:
Subjects will be instructed to check their blood glucose at least 4-6 times per day and also before driving (as applicable) for diabetes self-management (SMBG), using the supplied Study Meter according to the

user guide. Occasionally, subjects may receive a notification if the pump needs a blood glucose (BG) measurement to enter or to stay in Auto Mode.

6.1. Duration

The study is anticipated to last no longer than 13 months from investigational center initiation to completion of all data entry and monitoring procedures. The study will target 5 months to complete subject enrollment. Subjects can expect to participate for approximately 2-3 months including the run-in and study periods.

6.2. Rationale

Although the performance and safety of the MiniMed™ 670G System has already been studied in subjects in the United States, an evaluation involving Chinese subjects is required to support NMPA approval of the system.

7. Product Description

7.1. Intended Population

The Chinese population of subjects with type 1 diabetes will be studied. The study population will have a large range for duration of diabetes and glycemic control, as measured by HbA1c.

7.2. General Overview of MiniMed 670G System Components and Consumables

Table 1. MiniMed™ 670G Insulin System Components and consumable materials

Device name	MDT Model number/ part number	China
MiniMed™ 670G Insulin Pump	MMT-1883	Investigational
Guardian™ Sensor (3)	MMT-7020	Investigational
Guardian™ Link (3) Transmitter	MMT-7911	Investigational
One-press Serter	MMT-7512	Investigational
Charger	MMT-7715	Investigational
Tester	MMT-7736L	Investigational
Blue adapter	ACC-1003910	Investigational
MiniMed Mobile Application	MMT-6101/6102	Investigational
CareLink™ For Clinical Research Software	MMT-7338	Non-investigational
FreeStyle Optium Neo Ketone Meter		Non-Investigational
Accu-Chek™* Guide Link Study Meter	MTR114	Investigational

7.3. Investigational Devices

The investigational devices used in the study will be described in this section. Instructions for intended use, including indications, contraindications, and precautions of the components used in this study, are provided in their respective user guides/instructions for use (IFU).

7.3.1. MiniMed™ 670G Insulin Pump

The MiniMed™ 670G Insulin Pump, version 5.2, is capable of continuous insulin delivery, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin. When used with the CGM components (Guardian™ Sensor (3), Guardian™ Link (3) Transmitter), the pump system is capable of continuous or periodic monitoring of glucose levels in the interstitial fluid under the skin and detection of possible low or high blood glucose episodes. The pump also displays SG values, storing this data so that it can be retrospectively analyzed to track patterns and improve diabetes management.

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

The pump may also be used as a simple pump without CGM or as a sensor augmented pump (SAP) without the SmartGuard™ features.

When Auto Mode is enabled on the MiniMed™ 670G insulin pump, the SG values received from the Guardian™ Link (3) Transmitter by the insulin pump will be used to automatically calculate the insulin dose. It will then deliver insulin to the patient, at five-minute intervals, to achieve glycemic control.

With the HCL system Auto Mode, subjects must still deliver bolus insulin for meals and corrections to the target SG level, as calculated by the insulin to carbohydrate ratio. This ratio is determined by the HCP/patient. In addition, the setting for active insulin must be programmed. Basal rates are set for period of open loop therapy.

When Auto Mode is not enabled, the user may enable the Low Management feature. Here, basal rate delivery will be suspended either when the SG reached a programmed low threshold (Suspend on Low) or before the SG value has reached the programmed low threshold (Suspend before Low).

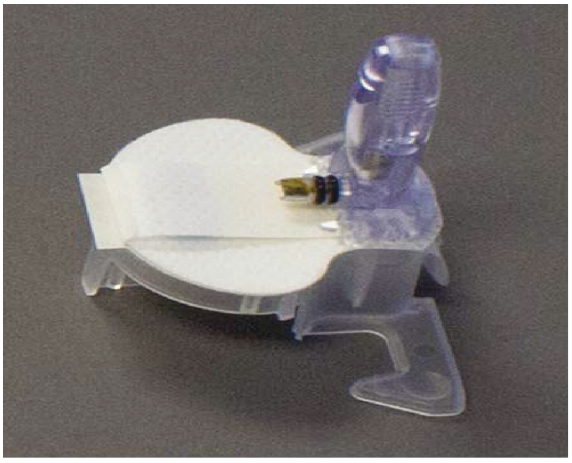
The MiniMed™ 670G Insulin Pump contains Bluetooth® Low Energy RF communication, which allows for connectivity to patients' smartphones, CGM transmitter and the blood glucose meter.

Figure 1. MiniMed™ 670G Insulin Pump

7.3.2. Guardian™ Sensor (3)

The Guardian™ Sensor (3) is a glucose sensor that contains one microelectrode with a thin coating of glucose oxidase beneath several layers of biocompatible membrane. The sensor is the latest generation of glucose sensors with design changes supporting improved accuracy. It is intended to penetrate the skin at a 90-degree angle. The sensor is tubeless and as a result has a smaller volume than previous Medtronic MiniMed sensors. An introducer needle penetrates the skin surface and provides support for the sensor microelectrode during insertion. The sensor continuously converts small amounts of glucose from the subject's interstitial fluid into an electronic signal that is received by a transmitter or recorder, the strength of which is proportional to the amount of glucose present in the blood. The electrode is composed of embedding, signal-conducting and insulating layers.

Figure 2. Guardian™ Sensor (3)



7.3.3. Guardian™ Link (3) Transmitter

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

In addition, the transmitter also contains the sensor calibration algorithm which converts the sensor signal to a SG value using calibration BG values from a meter relayed to the transmitter through the pump. The algorithm is designed to improve and optimize performance when paired with the sensors.

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

Figure 3. Guardian Link (3) Transmitter

7.3.4. One-press Serter

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

Figure 4. One-press Serter

7.3.5. Charger

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

Figure 5. Charger

7.3.6. Tester

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

Figure 6. Tester

7.3.7. Roche Accu-Chek™* Guide Link Meter

The Accu-Chek™* Guide Link Meter Blood Glucose Monitoring System is comprised of the Accu-Chek™* Guide Link Meter and Accu-Chek™* Guide Link test strips. This Blood Glucose Monitoring System is intended to quantitatively measure glucose in fresh capillary whole blood from the fingertip, palm, and upper arm as an aid in monitoring the effectiveness of glucose control. The Accu-Chek™* Guide Blood Glucose Monitoring System is intended for in vitro diagnostic single-patient use by people with diabetes. Transmission of data is via Bluetooth® Low Energy.

7.3.8. Blue adapter

The Blue Adapter is a USB accessory that allows for data uploads from the MiniMed™ 670G insulin pump to CareLink™ For Clinical Research via USB interface of the PC or Mac devices.

7.3.9. Mobile Application

The MiniMed Mobile Application, referred to as Mobile App in the protocol, is an optional accessory to the MiniMed™ 670G insulin pump and provides a secondary display and passive monitoring of pump data for users with compatible electronic devices. The Mobile App is available for both iOS and Android platforms.

7.4. Non-Investigational Devices

The non-investigational device used in the study will be described in this section. Instructions for intended use, including indications, contraindications, and precautions of the components used in this study, are provided in their respective user guides/instructions for use (IFU).

7.4.1. CareLink™ For Clinical Research Software

Medtronic CareLink™ For Clinical Research is an web-based system which allows the device data to be viewed and easily evaluated by the subject and his/her physician. A PC links to the Medtronic CareLink™ system via the Internet, which then allows subjects and investigational center staff to upload data from Medtronic MiniMed insulin pumps and third-party BG meters. The clinical support version of Medtronic CareLink™ For Clinical Research will be used by the investigational center staff and subjects. All references to CareLink™ For Clinical Research software are meant to imply the clinical support version of Medtronic

CareLink™ and throughout the protocol will be referred to as CareLink™ software. The data contained in CareLink™ For Clinical Research software is accessible to users using a standard browser, i.e., Microsoft® Internet Explorer, on an Internet enabled PC.

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

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

7.4.2. Abbott™* FreeStyle Optium Neo Blood Glucose & Ketone Monitoring System

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

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

7.5. Consumable devices

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

7.6. Insulin

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

7.7. Smartphone

Subjects will use their own Smartphone during this study.

7.8. Device Accountability

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

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

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

The labeling of commercial devices will be provided in accordance with local language requirements.

In China, all study devices will be labeled as per local regulations in China. Investigational devices will be labeled "Clinical trial use only" in accordance with NMPA Order No. 25.

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

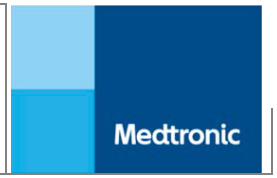


Table 2 Device Accountability Requirements

Device		Record on Site Received eCRF	Record Disbursement, Returned or Not Returned from Subject on Device Identification eCRF	Subject Return Device to Investigational Center	Record Returned or Not Returned on Site Returned eCRF	Site Return Device to Sponsor at Conclusion of Study
MiniMed™ 670G Insulin Pump (MMT-1883)		Yes	Yes	Yes	Yes	Yes
Guardian™ Sensor (3) (MMT-7020)		Yes	Yes	Yes (Unused only)	Yes (Unused only)	Yes (Unused only)
Kit (MMT-7910)	Guardian™ Link (3) Transmitter* (MMT-7911)	Yes	Yes	Yes	Yes	Yes
	One-press Serter (MMT-7512)*	Yes	Yes	Yes	Yes	Yes
	Charger (MMT-7715)*	Yes	Yes	Yes	Yes	Yes

	Tester (MMT-7736L)*	Yes	Yes	Yes	Yes	Yes
Accu-Chek™* Guide Link study meter (Model MTR114)		Yes	Yes	Yes	Yes	Yes
Blue adapter (ACC-1003910)		Yes	Yes	Yes	Yes	Yes
FreeStyle Optium Neo Ketone Meter		No	No	No	No	Yes (Unused only)

*Devices may be combined and distributed in kits.

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

7.8.1. Receipt and Inventory of Investigational Devices by Investigational Center

- Upon receipt of the study devices, investigational center staff take inventory of the shipment, making sure that information on the packing slips/invoices matches exactly the contents of the containers, as applicable, including:
    - Ship to Address
    - Reference Number
    - Device Type
    - Quantity
    - Quantity per package
    - Lot number (where applicable)
    - Serial number(where applicable)
- Ensure that devices and supplies received have not reached or exceeded their expiration date
- Sign and date the packing slips/invoices, noting any discrepancies, and file in appropriate study binder
- Notify the study monitor of any discrepancies
- Enter the study device information on the appropriate eCRFs in the study database, if applicable.

7.8.2. Storage of Study Devices at Investigational Center

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

7.8.3. Disbursement of Study Devices

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

- Date of disbursement
- Subject ID
- Lot number(s)

- Serial Number
- Reference Number
- Amount dispensed

7.8.4. Return or Disposal of Study Devices

After use by the subject, the investigational center is expected to accept and retain all devices as described in Table 2 and store them in a secure environment. If containers/units/devices are missing, the reasons should be documented in the applicable eCRF. If discrepancies between the amounts used by subjects and the amounts expected to be returned exist, the reasons should be documented in the applicable eCRF.

Requirements for return of devices by subjects to the investigational center and return of device by the investigational center to the sponsor are listed in Table 2. The devices that are being returned to the investigational center may be returned to the sponsor as subjects complete the study, at the EOS visit or upon sponsor request.

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

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

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

8. Selection of Subjects

8.1. Study Population

This study will enroll subjects between age of 14 and 75 years old, with a ratio (1:5) between Adolescents (14-17 years) and Adults (≥ 18 years).

A total of up to 75 subjects will be enrolled at minimum 2 investigational centers and up to 6 investigational centers (hospitals) in China considering potential drop outs. A maximum of 30 subjects will be enrolled at each investigational center. Sites with less than 6 subjects will be pooled into 'pseudo-sites' of at least 10 subjects per pseudo-site. Pseudo-sites will be pooled by ranking those sites with less than 6 subjects by site number and pooling those sites in order of site number until the number of subjects reaches at least 10.

8.2. Subject Enrollment

Subjects will be considered enrolled in the study upon signing the Informed Consent Form (ICF) and

assent form (if applicable).

A subject will be assigned a unique study subject identification (ID) via the eCRF, which is a 9-digit code (329XXXXXX). The first three numbers refer to the CIP number (329), the next three numbers refer to the investigational center number, and the last 3 numbers refer to the subject number assigned during Visit 1 (e.g., 329002001 is subject 001 from site 002).

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

8.3. Inclusion Criteria

General Inclusion Criteria

1. Subject is age 14- 75 years at time of Screening.
2. Subject has 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.

Study-specific inclusion criteria

3. Subject is willing to perform ≥ 4 finger stick BG measurements daily.
4. Subject is willing to perform required sensor calibrations.
5. Subject is willing to wear the system continuously throughout the study.
6. Subject must have a minimum daily insulin requirement (Total Daily Dose) of greater than or equal to 8 units.
7. Subject has a Glycosylated hemoglobin (HbA1c) less than 10% (as processed by the investigational center lab or their contracted Local Lab) at time of Screening visit.
8. Subject 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. Prior labs in the last 6 months are sufficient.
9. Subject has been on pump therapy for greater than 6 months prior to screening (with or without CGM experience).
10. Subject is willing to upload data from the study pump and meter at home.
11. If subject has celiac disease, it has been adequately treated as determined by the investigator.
12. Subject has been taking and is willing to take one of the following insulins throughout the course of the study:
    - Humalog™* (insulin lispro injection)
    - NovoLog™* (insulin aspart)
13. Subject must be able to carbohydrate count or willing to learn how to carbohydrate count for the study.

8.4. Exclusion Criteria

1. Subject 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. Subject has been hospitalized or has visited the ER in the 6 months prior to Screening resulting in a **primary diagnosis** of uncontrolled diabetes.
3. Subject has had DKA in the 6 months prior to Screening.
4. Subject is unable to tolerate tape adhesive in the area of sensor placement.
5. Subject has any unresolved adverse skin condition in the area of sensor placement (e.g., psoriasis, dermatitis herpetiformis, rash, Staphylococcus infection).
6. Subject is a female of child-bearing potential who has a positive pregnancy test at Screening or plans to become pregnant during the course of the study.
7. Subject is a female who is sexually active and able to conceive should be excluded if they are not using an effective method of contraception and do not agree to continue using an effective method of contraception for the duration of the study as determined by investigator.
8. Subject has had any of the following cardiovascular events within 1 year of screening: myocardial infarction, unstable angina, coronary artery bypass surgery, coronary artery stenting, transient ischemic attack, cerebrovascular accident, angina, congestive heart failure, ventricular rhythm disturbances or thromboembolic disease.
9. Subject is being treated for hyperthyroidism at time of Screening.
10. Subject has a diagnosis of adrenal insufficiency.
11. Subject has taken any oral, injectable, or intravenous (IV) glucocorticoids within 8 weeks from time of Screening, or plans to take any oral, injectable, or IV glucocorticoids during the course of the study.
12. Subject is actively participating in an investigational study (drug or device) wherein he/she has received treatment from an investigational study drug or investigational study device in the last 2 weeks. (Please note participation in an observational study is acceptable.)
13. Subject is currently abusing illicit drugs.
14. Subject is currently abusing alcohol.
15. Subject is using pramlintide (Symlin), DPP-4 inhibitor, liraglutide (Victoza or other GLP-1 agonists), metformin, canagliflozin (Invokana or other SGLT2 inhibitors) at time of Screening.
16. Subject has a history of visual impairment which would not allow subject to participate in the study and perform all study procedures safely, as determined by the investigator.
17. Subject has elective surgery planned that requires general anesthesia during the course of the study.
18. Subject has a sickle cell disease, hemoglobinopathy; or has received red blood cell transfusion or erythropoietin within 3 months prior to time of Screening
19. Subject plans to receive red blood cell transfusion or erythropoietin over the course of study participation.
20. Subject diagnosed with current eating disorder such as anorexia or bulimia
21. Subject has been diagnosed with chronic kidney disease that results in chronic anemia.
22. Subject has a hematocrit (Hct) that is below the normal reference range of lab used. Prior labs in the last 6 months are sufficient.
23. Subject is on dialysis.
24. Subject has an estimated glomerular filtration rate (eGFR) of < 30.
25. Subject has a pediatric BMI category of underweight (less than the 5th percentile) as defined by Centers for Disease Control (CDC) (https://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html)
26. Subject is a member the research staff involved with the study.

9. Study Procedures

9.1. Study Timeline

Visit Schedule:

Run-in Period Visits: To be completed approximately up to 35 days

- Visit 1: Screening (Office):
  - Consent
  - Collect demographic and baseline characteristics:
    - Age
    - Gender
    - Race
    - Ethnicity
    - Height and Weight
  - Obtain prior Medical History
  - Collect concomitant medications
  - Labs (pregnancy test [if applicable], HbA1c, TSH, Hct, GA and eGFR)
  - Screening Requirements

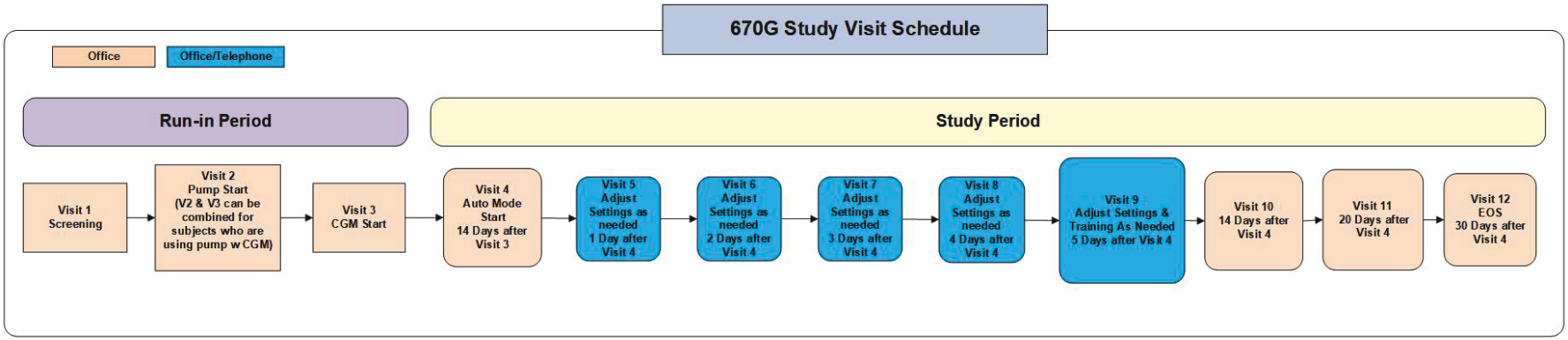
- Visit 2: Run-in Period Start - Visit 2 (Office): 2 - 7 days after Visit 1
  - *Eligibility has been confirmed including labs*
  - **All eligible subjects**:
    - Start study pump; provide pump training
    - Collect questionnaire(s)
    - Collect information about food consumed in last 24 hours (food log)
  - Subjects who are using pump **with** CGM at Screening:
    - Visits 2 and 3 may be combined
    - Start CGM, provide CGM training
    - Start CGM run-in (2 weeks)
    - Install Mobile App to Smartphone (if applicable)
    - System is set Manual Mode (Sensor Augmented Pump only): **SmartGuard™ features should not be activated**

- Visit 3: Start CGM 0-7 days after Visit 2
  - Subjects who are using pump **without** CGM at Screening:
  - Start CGM, provide CGM Training
    - Recommend that this visit take place 5-7 days after Visit 2
    - Start CGM run-in (2 weeks)
    - Install Mobile App to Smartphone (if applicable)
    - System is set Manual Mode (Sensor Augmented Pump only): **SmartGuard™ features should not be activated**

Study Period Visits:

- Visit 4 (Office): 14 days after Visit 3 (+7 days)
  - Turn on Auto Mode
- Visit 5 (Office/ Telephone): 1 days after Visit 4 Office or telephone visit
  - Adjust settings as needed
- Visit 6 (Office/ Telephone): 2 days after Visit 4 Office or telephone visit
  - Adjust settings as needed
- Visit 7 (Office/ Telephone): 3 days after Visit 4 Office or telephone visit
  - Adjust settings as needed
- Visit 8 (Office/ Telephone): 4 days after Visit 4 Office or telephone visit
  - Adjust settings as needed
- Visit 9 (Office/ Telephone): 5 days after Visit 4 Office or telephone visit
  - Adjust Settings as needed
  - Provide training as needed
- Visit 10 (Office) – 14 days after Visit 4 (±3 days)
- Visit 11 (Office) – 20 days after Visit 4 (±3 days)
- Visit 12 (Office) – 30 days after Visit 4 (±3 days)
  - Remove Mobile App from Smartphone (if applicable)
  - Collect questionnaire(s)
  - Collect lab test for GA
  - End of Study

Figure 7. Visit Schedule Flowchart



9.2. Schedule of Events

Each subject's participation will be comprised of the scheduled visits listed in Section 9.1 and additional unscheduled visits (at office or phone) over the course of approximately 2-3 months during the run-in period and study period. Refer to Table 3 for Visit Details.

Table 3. Visit Details

	Run-in Period			Study Period					
O= Office **T= Telephone**	**Visit 1 (O)**	**Visit 2 (O)**	**Visit 3 (O)**	**Visit 4 (O)**	**Visit 5,6 and 7 (O/T)**	**Visit 8 and 9 (O/T)**	**Visit 10 (O)**	**Visit 11 (O)**	**Visit 12 (O)**
Things to do (General):									
Administer Informed Consent/Assent (if applicable)	x								
Assess Subject Eligibility	x								
Measure subject height and weight	x								x
Obtain demographic and baseline characteristics according to CRF questions: • Age • Gender • Race • Ethnicity • Height and Weight Note: BMI will be calculated automatically in the study database, based on height and weight measurements entered.	x								
Obtain prior Medical History, including type 1 diabetes and date of diagnosis	x								
Collect concomitant medication data	x								
Collect food log (subject's dietary/food intake within the last 24 hours)		x							
Obtain blood sample(s) to complete required screening lab tests • Pregnancy test for females of child-bearing age (if applicable) will be tested at investigational center lab or their contracted Local Lab	x								

	Run-in Period			Study Period					
O= Office **T= Telephone**	**Visit 1 (O)**	**Visit 2 (O)**	**Visit 3 (O)**	**Visit 4 (O)**	**Visit 5,6 and 7 (O/T)**	**Visit 8 and 9 (O/T)**	**Visit 10 (O)**	**Visit 11 (O)**	**Visit 12 (O)**
• HbA1c will be tested at investigational center lab or their contracted Local Lab • TSH will be tested at investigational center lab or their contracted Local Lab if no historical lab is on record (Prior labs in the last 6 months are sufficient) § If TSH level is out of range, Free T3 and Free T4 will be tested § Subject may be included with TSH out of range as long as: – Free T3 is low or within the normal reference range – Free T4 is within the normal reference range § TSH, including Free T3 and Free T4, may be repeated once within 14 days of screening for values that are out of reference range • Hematocrit will be tested at investigational center lab or their contracted Local Lab if no historical lab is on record (Prior labs in the last 6 months are sufficient) • eGFR of <30 (refer to GFR calculator from National Kidney Foundation website)									
Obtain blood sample to complete Glycated Albumin (GA) lab test	x								x
Confirm subject eligibility, including lab results, **prior** to moving forward with any study procedures		x							
Enroll subjects in CareLink™ and upload the study pump - Refer to CareLink™ Site Enrollment Instructions		x							

	Run-in Period			Study Period					
O= Office T= Telephone	**Visit 1 (O)**	**Visit 2 (O)**	**Visit 3 (O)**	**Visit 4 (O)**	**Visit 5,6 and 7 (O/T)**	**Visit 8 and 9 (O/T)**	**Visit 10 (O)**	**Visit 11 (O)**	**Visit 12 (O)**
Provide subjects with study reference materials. Review EZ reference guide		x							
Disburse the MiniMed™ 670G pump		x							
Start study pump • SmartGuard™ features remain turned OFF		x							
Disburse the Guardian Link (3) transmitter		x (as applicable)	x						
Disburse Guardian Sensor (3) sensors		x (as applicable)	x				x	x	
Disburse the Study Meter		x							
Disburse the Ketone Meter		x							
Disburse the Blue adapter		x							
Disburse study supplies as needed		x	x	x	As needed	As needed	x	x	
Instruct subjects to have access to oral glucose, oral carbohydrates or glucagon and instruct subjects to keep these supplies available at all times (as needed)		x							
Adjust pump settings as needed: • Determine carbohydrate to insulin ratios (may differ by mealtime) • Adjust active insulin time • Adjust basal rate settings for time periods spent in Manual Mode • Adjust insulin sensitivity as needed		x	x	x	As needed	As needed	As needed	As needed	
Install Mobile App on subject's Smartphone (if applicable)		x	x						
Collect general HCL training information from training checklist (e.g., MiniMed™ 670G system features and training time)		x	x	x					
Collect/Assist with the Questionnaires		x							x
Schedule the next visit date and time	x	x	x	x	x	x	x	x	

	Run-in Period			Study Period					
O= Office T= Telephone	**Visit 1 (O)**	**Visit 2 (O)**	**Visit 3 (O)**	**Visit 4 (O)**	**Visit 5,6 and 7 (O/T)**	**Visit 8 and 9 (O/T)**	**Visit 10 (O)**	**Visit 11 (O)**	**Visit 12 (O)**
Upload the study pump during office visit (as applicable)		x	x	x	x	x	x	x	x
Enter eCRFs into the study database as appropriate	x	x	x	x	x	x	x	x	x
Collect study devices from subjects upon exit from study									x
Things to do (General Instructions/Training/Review)									
Train subjects on CareLink™ - Refer to Subject CareLink™ Uploading Instructions		x							
Instruct subjects on carbohydrate counting since subjects will need to carbohydrate count in order to use the study device		x	As needed	As needed	As needed	As needed	As needed	As needed	
Print and review CareLink™ Reports				x	x	x	x	x	x
Review surveillance report in Medtronic Box and recommend to review with subjects as necessary							x	x	x
Train subjects on sensor guidelines: • Self-insert Guardian Sensor (3) per user guide and connect to Guardian Link (3) Transmitter • Sensor must be calibrated to ensure correct operation. • If there are any calibration problems with the sensor, the sensor may be replaced to ensure correct operation. • The investigator or qualified research staff will provide recommendations whether or not the SG low and high alerts should be turned on or off and, if they are turned on, at which threshold they should be set. • Subjects, with assistance from their parent(s)/guardian(s) where applicable, should replace the sensor after 7 days of use or as events dictate throughout the course of the study.		x (as applicable)	x						

	Run-in Period			Study Period					
O= Office **T= Telephone**	**Visit 1 (O)**	**Visit 2 (O)**	**Visit 3 (O)**	**Visit 4 (O)**	**Visit 5,6 and 7 (O/T)**	**Visit 8 and 9 (O/T)**	**Visit 10 (O)**	**Visit 11 (O)**	**Visit 12 (O)**
• Transmitter should be re-charged between uses									
Instruct subjects that blood testing is required every time BG is greater than 300 mg/dL (16.7mmol/L), as measured by the study meter Blood ketone testing: • If ketone testing occurred, the results should be entered into the CareLink™ Logbook at least weekly prior to Monday morning. • In the event the blood ketone meter is not used to collect ketone values, urine ketones must be measured and entered into CareLink™ instead.		x	x	x	x	x	x	x	
Instruct subjects to place the sensor in a location that is approved for placement as per the user guide.		x	x	x	x	x	x	x	
Instruct subjects to wear sensors continuously throughout the study, as compliance to sensor wear with pump CGM will be a condition for continued study participation		x	x	x	x	x	x	x	
Remind subject to bring in both study meter and ketone meter at each required office visit.		x	x	x	x	x	x	x	
Instruct subjects to verify appropriate meter operation for both the study meter and the ketone meter. The respective user guides should be consulted to determine frequency of control solution testing.		x							
Inform subjects that observation by Sponsor may occur at any time during the study		x							
Perform applicable quality control (QC) testing (Accu-Chek™* Guide study meter). Shake control solution bottle well prior to use.		x							

	Run-in Period			Study Period					
O= Office **T= Telephone**	**Visit 1 (O)**	**Visit 2 (O)**	**Visit 3 (O)**	**Visit 4 (O)**	**Visit 5,6 and 7 (O/T)**	**Visit 8 and 9 (O/T)**	**Visit 10 (O)**	**Visit 11 (O)**	**Visit 12 (O)**
Train subjects on use of Accu-Chek™* Guide study meter • Subject will be instructed to wash his/her hands thoroughly with warm, soapy water, rinse and dry before testing blood glucose • Consider best practice to use "second drop" technique, express first drop and wipe away, express second drop for meter BG testing • Subjects will be instructed to use only the Accu-Chek™* Guide study meter during the course of the study to perform SMBG measurements		x							
Instruct subjects to check their blood glucose at least 4-6 times each day (before meals and bedtime) for diabetes self-management (SMBG), using the supplied Accu-Chek™* Guide Link study meter. Subject compliance with SMBG (according to the user guide) will be encouraged.		x	As needed	As needed	As needed	As needed	As needed	As needed	
Instruct subjects to always base their diabetes therapy decisions on a confirmatory finger stick (per user guide).		x	x	x	x	x	x	x	
Instruct subjects regarding the use of the BG meter to make treatment decisions: • When a Calibrate Now alert is received: Instruct subjects to clear the alert and use the BG meter to calibrate the sensor before using the sensor glucose to make treatment decisions • When a BG required alert is received:		x							

	Run-in Period			Study Period					
O= Office **T= Telephone**	**Visit 1 (O)**	**Visit 2 (O)**	**Visit 3 (O)**	**Visit 4 (O)**	**Visit 5,6 and 7 (O/T)**	**Visit 8 and 9 (O/T)**	**Visit 10 (O)**	**Visit 11 (O)**	**Visit 12 (O)**
Instruct subjects to clear the alert and enter a BG meter reading before using the sensor glucose to make treatment decisions • When symptoms are present: If subject's sensor glucose readings are different than symptoms (e.g., if subject is feeling low when sensor glucose reading is not low), a BG meter reading should be used to confirm blood glucose. If subject's sensor glucose readings continue to be different from symptoms, the study doctor should be called.									
Instruct subjects to consider avoiding the use of products containing Acetaminophen. • If medications containing Acetaminophen are taken: • Instruct subjects to use additional BG meter readings (they are not to calibrate with those readings) to verify their glucose levels • Instruct subjects to consider exiting Auto Mode		x (as applicable)	x	x	x	x	x	x	
Things to ask about									
Provide subjects with the opportunity to bring up study-related questions and concerns.	x	x	x	x	x	x	x	x	x
Ask subjects about the occurrence of adverse events • Record adverse events on the appropriate eCRF, if subject reports health status changes that result in a new medical condition or deterioration of an existing		x	x	x	x	x	x	x	x

	Run-in Period			Study Period					
O= Office **T= Telephone**	**Visit 1 (O)**	**Visit 2 (O)**	**Visit 3 (O)**	**Visit 4 (O)**	**Visit 5,6 and 7 (O/T)**	**Visit 8 and 9 (O/T)**	**Visit 10 (O)**	**Visit 11 (O)**	**Visit 12 (O)**
medical condition, such as sickness or glycemic problems. • Instruct subject to call the investigational center to report any changes to their health status (see adverse event definition). • Ask subjects about number of days missed at work or school, record on applicable CRF									
Ask subjects about device performance issues and if they called the 24 -Hour Technical Support (TS) 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
Pump Training - General									
Instruct subjects on the use of the study pump; provide Pump User Guide, Getting Started Guide, etc.		x							
Instruct/remind subjects that they must upload the MiniMed 670G pump to CareLink™. • Uploading may occur daily/weekly based on sponsor instruction		x	x	x	x	x	x	x	x
Verify that the pump is set Manual Mode (Sensor Augmented Pump only) SmartGuard™ features should not be activated		x							
Instruct subjects that the low glucose alert limit (low glucose threshold alert based on sensor glucose reading) is recommended to be set at 70 mg/dL (3.9 mmol/L)		x (as applicable)	x	x					
Instruct subjects that the high glucose alert limit (high glucose threshold alert based on sensor glucose reading) is recommended to be set at 300 mg/dL (16.7 mmol/L)		x (as applicable)	x	x					
Pump Training - Auto Mode Instructions									

	Run-in Period			Study Period					
O= Office **T= Telephone**	**Visit 1 (O)**	**Visit 2 (O)**	**Visit 3 (O)**	**Visit 4 (O)**	**Visit 5,6 and 7 (O/T)**	**Visit 8 and 9 (O/T)**	**Visit 10 (O)**	**Visit 11 (O)**	**Visit 12 (O)**
Instruct subjects to turn Auto Mode ON.				x					
Instruct subjects on the Auto Mode feature of the pump as well as specific considerations regarding Auto Mode • Instruct subjects to ensure the Auto Mode feature is turned ON and remain ON throughout the course of the study. It is recommended that Auto Mode should be switched OFF in the study pump or that subjects switch to manual injections if: • Hospital admission is needed for any reason • Glucose is persistently elevated (i.e. above 300 mg/dL (16.7mmol/L)) • Illness that prevents ability to ingest fluids due to nausea and vomiting • Subject experiences an occlusion alarm where glucose becomes elevated and the subject is not able to address the occlusion by changing the infusion set. • Subject experiences an episode of severe hypoglycemia • Subject experiences an episode of DKA				x	As needed	As needed	As needed	As needed	
Instruct subjects that they should not assume that Auto Mode is able to prevent all hypoglycemia or all hyperglycemia including diabetic ketoacidosis.				x	As needed	As needed	As needed	As needed	
Instruct subjects to consistently look for the presence of the "Blue Shield" on the pump, which indicates that they are in Auto Mode.				x	x	x	x	x	

9.3. Subject Consent

ICF and assent (if applicable per site specific requirement) will be obtained in accordance with the NMPA Order No. 25. Prior to entry into the study, the Ethics Committee (EC)- and Medtronic-approved ICF and assent form will be presented to each subject and their legally authorized representative or guardian (if applicable) to review and sign as applicable. Subjects and their legally authorized representative/ guardian will be offered the opportunity to review these documents away from the investigational center.

The following will be provided to or explained to the subject or legally authorized representative/ guardian 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 inthe study. Every attempt will be made to answer subject's or their legally authorized representative/or guardian's questions during the informed consent process. The language used shall be as non-technical as possible and must be understandable to the subject or legally authorized representative/ guardian.

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

The consenting process must be documented in the subject's source documents. The ICF and assent will include a dated signature of the subject or legal representative/guardian acknowledging their participation in the study is voluntary. In addition, it will include a dated signature of the principal investigator or an authorized designee responsible for conducting the informed consent and assent process. The subject or their legally authorized representative/ guardian will receive copies of the fully executed documents. A subject's participation in study procedures cannot begin before the consent process has been properly executed.

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

Medtronic will revise the written ICF and assent 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 EC. After approval by the EC, a copy of this information must be provided to the participating subjects, and the informed consent and assent process as described above needs to be repeated.

If the ICF and assent is amended during the course of the study, the EC will determine:

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

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

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

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

9.4. Assessment of Safety

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

9.5. Medical Oversight

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

9.5.1. Medical Staff

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

9.5.2. Qualification

The investigator (or designee) will need to have one of the following qualifications: Endocrinology fellowship or management in patients with diabetes in a clinical practice. The provider must be qualified to treat diabetic emergencies.

9.5.3. Experience

Investigator (or designee) must also have at least one-year experience in managing type 1 patients in his/her practice.

9.6. Safety Monitoring/Risk Analysis

9.6.1. Glucose Monitoring Risk

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

9.6.2. Hypoglycemic/Hyperglycemic Risk

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

9.6.3. Calibration of CGM Risk

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

9.6.4. Reuse Risk

All study devices will be single patient use.

9.6.5. Sterilization Risk

The following devices will be supplied sterilized:

- Infusion sets
- Insulin reservoirs
- Glucose sensors

9.6.6. Misuse Risk

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

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

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

9.6.8. HbA1c Risk

An investigational center lab or their contracted local laboratory will be used for HbA1c testing.

9.7. Glucose and Glycemia Measurements

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

9.7.1. Daily BG

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 manufactures user guide.

9.7.2. Sensor Glucose Values

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

9.7.3. HbA1c

Collected at screening for exclusion criteria.

9.7.4. Blood Ketone Values

Blood ketones will be measured by all subjects using the FreeStyle Optium Neo ketone meter when certain conditions are met. The control solution test will be performed following the manufacturer's user guide. The investigational center staff will be trained on the use of the FreeStyle Optium Neo ketone meter per the manufacturer's instructions. All ketone measurements will be entered by study subjects into the Log Book section of the CareLink™ software.

Note: In the event the blood ketone meter is not used by subjects to collect ketone values, urine ketones should be measured and entered appropriately into the CareLink™ software as urine ketones.

9.8. Recording Data

Data will be captured on eCRFs using Oracle Clinical Remote Data Capture's (OC-RDC) module. Original eCRFs will not be considered as source data and supporting documentation will be required. The food log and subject questionnaires on paper are considered source data, then source data is transferred to an eCRF.

Electronic device data will be collected from the study pump using CareLink™ 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. These data files will be sent to the sponsor electronically using the internet and a secure cloud-based site (Box).

Laboratory results will be recorded on eCRFs.

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

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

9.9. Deviation Handling

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

- Investigational center disqualification
- Notification to the regulatory authorities/EC 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 EC, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the the change does not affect the scientific soundness of the plan or the rights, safety, and welfare of the subjects.

Deviations related to instructions provided to study subjects :

As subjects may not follow the instructions perfectly (e.g. SMBG, system use, sensor use, etc.), no study deviation will be given unless the site staff did not train the subjectappropiately.

9.9.1. Documenting Requirements for Study Deviations

9.9.1.1. Unplanned CIP Deviations

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

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

CIP deviations should be reported as follows:

a) To the EC for notification/acknowledgement,
b) To the sponsor and, if required;
c) To the regulatory agency, if required

9.9.1.2. Minor or Administrative CIP Deviations

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

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

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

9.9.2. 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. Any deviations from the CIP will be documented in the clinical study report.

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

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

- Failure to obtain informed consent and assent (if applicable), i.e., there is no documentation of informed consent
- Informed consent and assent (if applicable) obtained after initiation of study procedures
- Continued study participation of a subject who did not meet all inclusion/exclusion criteria
- Performing study procedure not approved by the EC
- Failure to inform EC and sponsor of reportable AEs (see Section 11.4)

- Investigational study device dispensed without obtaining informed consent and assent (if applicable)

Reporting of all other study deviations should comply with EC policies and/or local laws and must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation. Reporting of deviations must comply with EC policies, local laws, and/or regulatory agency requirements. Refer to Investigator Reports, Table 6 for specific deviation reporting requirements and timeframes for reporting to Medtronic, EC, and/or regulatory agency (if applicable).

9.9.3. 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.

9.10. Subject Withdrawal or Discontinuation

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

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

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

- In the opinion of the investigator, the subject's health or safety would be compromised by continuing in the study
- In the opinion of the investigator, it is in the subject's best interest to discontinue participation in the study
- The subject is found to no longer meet all inclusion criteria, or is found to meet one or more exclusion criteria
- The subject fails to comply with one or more study requirements
- The subject is lost to follow up
- During the course of the study, subject begins participation in another investigational study (drug or device).
- During the course of the study, subject begins abusing illicit drugs.
- During the course of the study, subject begins abusing alcohol.

- During the course of the study, subject begins using pramlintide (Symlin), DPP-4 inhibitors, liraglutide (Victoza or other GLP-1 agonists), metformin, canagliflozin (Invokana or other SGLT2 inhibitors).
- During the course of the study, 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 course of the study, subject is taking oral, injectable, or IV glucocorticoids
- During the study, (female) subject becomes pregnant.
- During the study, the subject experiences one severe hypoglycemic episode
- During the study, the subject experiences one episode of DKA
- During the study, subject has a cardiovascular event or any vascular event such as stroke.

Lost to Follow-up

In the case that the subject is determined to be lost to follow-up, details of a minimum of two attempts and the method of attempt (e.g., one letter and one phone record or two letters) to contact the subject must be recorded. In addition, the requirements set by the governing EC for subjects lost to follow-up must be followed.

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

Upon exiting from the study, no further study data will be collected or study visits will occur for the subject. All data available through the time of the subject's exit will be used for analysis. In the event of study exit, the investigator should discuss with the subject the plans for future care and treatment. The investigator should explain that the subject will continue to receive standard medical care. Alternative treatment, such as medication options or follow-up through standard of care procedures instead of study procedures, and medical consequences should also be discussed. Source documentation of this conversation recommended. The investigator must notify the subject of any significant new findings that may become available during the course of the study, which are pertinent to the safety and well-being of the subject.

9.11. Stopping Rules

9.11.1. Subject Stopping Rules

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

9.11.2. Stopping Rules for Entire Study

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

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

1. Site will notify the sponsor within approximately 24 hours of receiving knowledge of the event.
2. CEC is to review and adjudicate the event.
3. CEC will provide recommendation to the sponsor on the following:
    a) If enrollment and the study may continue
    b) If enrollment should be stopped, while already enrolled subjects are allowed to continue in study
    c) If the entire study must be stopped, including subjects who have already received study devices.

10. Risks and Benefits

10.1. Potential Risks

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 should be removed and another placed in a new location. • In case of hyperglycemia secondary to infusion set occlusion, remove current infusion set and replace with new infusion set and give correction insulin if needed with syringe. • Follow the provided user guides for insulin pump management. • Training prior to study on device use and diabetes management principles and told to call with problems.
Risks with Insulin Administration and Pumps	**Prevention and Mitigation**
Risks with the use of an insulin infusion pump may include the risk of malfunction of the components of the system (pump, software, infusion set and reservoir) as well as the risk of use error during use of the system. Device deficiencies or use errors can result in administration of too much or too little insulin which can lead to the following clinical consequences: • Hypoglycemia • Hyperglycemia • Diabetic ketoacidosis • Severe hypoglycemia with or without associated seizure, coma or death • Kinked cannula leading to hyperglycemia • Infusion set disconnection from pump leading to hyperglycemia • Subject removes the reservoir from the pump but forgets to disconnect the infusion set from the body which results in hypoglycemia or severe hypoglycemia • Dislodged cannula leading to hyperglycemia	Prevention and mitigation include: • Follow the provided user guides & instructions for insulin pump management which includes information on infusion set change. • Training prior to study on device use and diabetes management principles and told to call with problems. • Check SMBG 4-6 times a day and also before driving (as applicable). Instructed to have glucose on hand for hypoglycemia • Change infusion set if suspected catheter occlusion or administer insulin with syringe for persistent hyperglycemia especially if ketones develop.

• A pump error may lead to under delivery or over-delivery of insulin • Battery failure – no insulin delivered • 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 Auto Mode feature where sensor glucose 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. • Training prior to study on device use and diabetes management principles. • Check SMBG 4-6 times a day. • Alternative method of managing glucose levels should 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. • Training prior to study on device use and diabetes management principles. • Check SMBG 4-6 times a day. • Instructed to have glucose on hand for hypoglycemia
Risk with Sensors	**Prevention and Mitigation**
Risks with Sensors may include: • Skin irritation or reaction to adhesives • Bruising • Discomfort • Redness • Bleeding • Excessive bleeding due to anticoagulants • Pain • Rash • Infection • Irritation from tapes used with glucose-sensing products • Raised bump • Appearance of a small "freckle-like" dot where needle was inserted • Allergic reaction • Syncopal episode secondary to needle insertion • Soreness or tenderness • Swelling at insertion site • Sensor fracture, breakage or damage • Minimal blood splatter associated with sensor needle removal • Residual redness associated with adhesive and/ or tapes • Scarring • Scab • Blister • Itchiness • Inflammation • Anxiety • Incorrect sensor glucose reading results in incorrect diabetes management • Subject over-treating secondary to alarms which can result in	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 should be removed and another placed in a new location • Base diabetes management on fingerstick readings and not sensor glucose values.

hyperglycemia or hypoglycemia • Anxiety associated with insertion	
Risks with Transmitter	**Prevention and Mitigation**
Risks with Transmitter may include: • Skin irritation or reaction to adhesives • Bruising • Discomfort • Redness • Pain • Rash • Infection • Irritation from tapes used with glucose-sensing products • Raised bump • Allergic reaction • Soreness or tenderness • Residual redness associated with adhesive and/ or tapes • Scarring • Scab • Blister • Itchiness • Inflammation	Prevention and mitigation include: • Follow the provided user guides. • Training on proper use of the transmitters.
Risks with Serter	**Prevention and Mitigation**
Risks with Serters may include: • Improper insertion may lead to device performance issue or hyperglycemia	Prevention and mitigation include: • Follow the provided user guides for insertions and care of device. • Training on proper use of the Serter and skin preparation prior to insertion.
Risks with Finger Sticks	**Prevention and Mitigation**
Risks with frequent finger stick testing may include: • Potential risks associated with frequent meter testing of blood glucose and blood ketones include discomfort and ecchymosis at tips of fingers • Potential risks associated with finger stick testing include discomfort and bruising	Prevention and mitigation include: • Follow the provided user guides for use of the study meter with fingerstick testing. • Training on proper use of the meter and fingerstick testing.
Risk with Closed Loop Therapy	**Prevention and Mitigation**
Risks with Closed Loop may include:	Prevention and mitigation include:

• Hypoglycemia
• Severe hypoglycemia
• Hyperglycemia
• Diabetic ketoacidosis User Entry Error
  ○ Patient administering boluses by entering false carb doses leading to hypoglycemia or hyperglycemia
  ○ Patient entering false glucose values for any reason leading to hypoglycemia and hyperglycemia
  ○ Patient entering false BG values for calibration leading to hypoglycemia or hyperglycemia
• Sensor failure resulting from patient failure to calibrate leading to hypoglycemia or hyperglycemia
• Sensor over-reading resulting in hypoglycemia
• Sensor under-reading resulting in hyperglycemia
• Sensor missed transmission, or any other fault resulting in no SG value, leading to hyperglycemia or hypoglycemia
• Voluntary insulin delivery (with the pump or with a syringe) immediately prior to entering Auto Mode may result in severe hypoglycemia despite shutting down insulin delivery by the algorithm
• Hypoglycemia related to patient taking insulin via injection while in Closed Loop (Auto Mode)
• Hypoglycemia or hyperglycemia related to entering or exiting Closed Loop (Auto Mode)
• Insulin over-delivery due to potential interference from acetaminophen
• Cyber security hacking into pump
	• Follow the provided user guides for insulin pump management.
	• Training prior to study on device use and diabetes management principles and told to call with problems.
	• Check SMBG 4-6 times a day.
	• Instructed to have glucose on hand for hypoglycemia
	• Subjects will be instructed to consider avoiding the use of products containing acetaminophen
	• If acetaminophen is taken, subjects will be instructed to use additional BG meter readings (they are not to calibrate with those readings) to verify their glucose levels.
	• If acetaminophen is taken, subjects should consider exiting Auto Mode
	• Pump has cybersecurity encryptions to prevent hacking.

Risks with hyperglycemia may include • Diabetic ketoacidosis Symptomatic ketosis • Cardiovascular event	Prevention and mitigation include: • Follow the provided user guides for insulin pump management.

• Dehydration • Potassium and sodium imbalance • Shock • Altered mental status • Coma Acidosis	• Training prior to study device use and diabetes management principles. • Check SMBG 4-6 times a day.
Risks with hypoglycemia may include: • Seizure • Coma • Altered mental status • Loss of consciousness • Cardiovascular event • Death • Risk of rebound hyperglycemia with ketosis	Prevention and mitigation include: • Follow the provided user guides for insulin pump management. • Training prior to study device use and diabetes management principles. • Check SMBG 4-6 times a day. • Instructed to have glucose on hand for hypoglycemia
Risk with Acetaminophen Use	**Prevention and Mitigation**
Potential risks with acetaminophen may include: • False elevation of sensor glucose readings. The level of inaccuracy depends on the amount of acetaminophen active in subject's body and may be different for each subject	Prevention and mitigation include: • Follow the user guide • Subjects should be instructed to consider avoiding the use of products containing acetaminophen • If acetaminophen is taken, subjects should use additional BG meter readings (they are not to calibrate with those readings) to verify their glucose levels • Subjects should consider exiting Auto Mode
Risks related to blood glucose meter use	**Prevention and Mitigation**
Risks with blood glucose meter use • Inaccurate blood glucose or no results	Prevention and mitigation include: • Follow the provided user guides for use of the study meter • Training on proper use of the meter

10.2. Potential Benefits

The main benefit of this study is that patients may experience improved glucose control. Otherwise subjects should not expect to benefit from participation in this study; however, they may gain increased awareness of emerging technologies for diabetes management as a result of their participation.

10.3. Risk-Benefit Rationale

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

11. Adverse Events Assessments

11.1. Adverse Events

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

11.2. Definitions and Classification of Adverse Events

Medtronic uses the definitions provided in NMPA (former CFDA) Order No. 25, ISO 14155:2011 and 21 CFR 812 for AE definitions. ISO14155:2011 definitions are used for AE classifications while expedited reporting to local authorities/EC should be done based on local definitions of local regulations. 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. Medtronic follows MEDDEV 2.7/3 revision 3 guidelines for classifying causality levels; but will apply these causality definitions across all events, not only serious adverse events and definitions have been adapted accordingly.

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 his or her self, was unable to verbalize his or her needs, and was incoherent, disoriented and/or combative.

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

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

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

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

- Arterial blood pH less than (<) 7.30 or serum bicarbonate less than (<) 15mEq/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 14155-2011)

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

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

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

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

Adverse Event (AE) (NMPA (former CFDA) Order No.25 Article 93)

The medical events with disadvantages occurred during the clinical trials, no matter whether they are related to investigational medical devices or not.

Adverse Device Effect (ADE) (ISO 14155-2011)

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

Note 1: 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: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Serious Adverse Event (SAE) (ISO 14155-2011)

Adverse event that

- Led to a death
- Led to a serious deterioration in the health of the subject, that either resulted in
  1. a life-threatening illness or injury, or
  2. a permanent impairment of a body structure or a body function, 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
- Led to foetal distress, foetal death or a congenital abnormality or birth defect

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

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

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

Serious Adverse Device Effect (SADE) (ISO 14155-2011)

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

Serious Adverse Event (SAE) (NMPA (former CFDA) Order No.25 Article 93)

Any untoward medical occurrence during the clinical trial: results in death or serious deterioration in health; life-threatening diseases or injuries; causing permanent damage to the body structure or function; requires hospitalization or prolongation of hospitalization; requires medical operations or intervention for preventing from persistent or significant disability/incapacity; results in fetal distress, fetal death, or congenital anomaly/birth defect.

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

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

11.3. Reporting of Adverse Events

The investigator or designee will record ALL AEs while the subject is enrolled in the clinical study. Each AE needs to be assessed for its device or procedure relatedness. A device related AE is associated with the use of the study device (e.g. infection of sensor site or infusion set occlusion resulting in DKA). A procedure related AE is associated with testing related to the study procedures specified in the CIP (e.g. IV insertion pain).

Examples of device or procedure related AEs include:

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

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

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

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

Narratives gathered from completed questionnaires will not provide the basis of an AE report however could lead to discussions that result in the identification of a reportable AE.

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

11.4. Notification of Adverse Events

Sponsor Notification:

The investigational center staff must report all AEs to Medtronic in a timely manner. All Severe Hypoglycemia, Severe Hyperglycemia, DKA, SAE, and SADE should be reported as soon as possible (desired within 24 hours of investigator or study coordinator awareness) to Medtronic. Refer to Table

4 below for Investigator Reporting Requirements. For the previously mentioned events, the AE eCRF will be completed with all known details as soon as possible, this will serve as notification to Medtronic. If the study database cannot be accessed due to technical problems, contact the sponsor via email at dl.diabetesclinicalresearchsafety@medtronic.com and provide the known details of the event. Once the access issue has been corrected, the event should be entered onto an AE eCRF.

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

11.5. Expedited Safety Reporting Requirements

Documentation of GCP office and EC 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 EC reporting requirements.

Table 4. Investigator Reporting Requirements for AE and Device Deficiencies

For the following events, reporting requirements are: • **Serious Adverse Events (SAE)**	
Investigators shall immediately adopt appropriate therapeutic measures for subjects, and simultaneously report to the management department of medical device clinical study in investigational center in written form. Management department of medical device clinical study shall report to:	
Medtronic	Immediately
Local food and drug regulatory authority and health and family planning competent authority of the province, autonomous region and municipality directly under the central government where the investigational center locates	Within 24 hours
EC	Within 24 hours/ per EC's requirements
For the following events, reporting requirements are: • **All other AEs** • **All Device Deficiencies**	
Investigators shall record all the AEs and device deficiencies occurred during the clinical study. Investigators shall analyze the reasons for the events with Medtronic and document the analysis result in written report, including the comments of continuing, suspending or terminating study, which shall be reported to the EC through management department of medical device clinical study in investigational center for review.	
To Medtronic	Submit in a timely manner

	after the investigator first learns of the event.
To EC	Per EC's requirements

NOTE: In case there is/are additional AE reporting requirement(s) and/or process(es) (e.g. internal hospital policy or province regulatory authority instruction, etc.), these specific AE reporting requirement and process must be documented in a separate cover.

Table 5. Sponsor Reporting Requirements for AE and Device Deficiencies

For the following events, reporting requirements are: • **Serious Adverse Events (SAE)** • **Device Deficiencies with SADE potential**	
Medtronic submits to:	
The food and drug regulatory authorities and health and family planning competent authorities at the same level	Within 5 working days upon being informed
Other investigational center and investigators participating in the study	As per local reporting requirement
EC	Timely report to EC of the clinical Research institution through management department of medical device clinical study

NOTE: In case there is/are additional AE reporting requirement(s) and/or process(es) (e.g. internal hospital policy or province regulatory authority instruction, etc.), these specific AE reporting requirement and process must be documented in a separate cover.

11.6. Causality Assessment

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

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

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

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

- **Not related:** relationship to the device or procedures can be excluded when:
  - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures
  - the event has no temporal relationship with the use of the investigational device or the procedures;
  - the event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
  - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
  - the event involves a body-site or an organ not expected to be affected by the device or procedure;
  - the event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
  - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
  - harms to the subject are not clearly due to use error;
  - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
- **Unlikely:** the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but a relationship to the device cannot be completely ruled out.
- **Possible:** the relationship with the use of the investigational device is weak. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed should also be classified as possible.
- **Probable**: the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause.
- **Causal relationship:** the event is associated with the investigational device or with procedures beyond reasonable doubt when:
  - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
  - the event has a temporal relationship with investigational device use/application or procedures;
  - the event involves a body-site or organ that
    - the investigational device or procedures are applied to;
    - the investigational device or procedures have an effect on;
  - the event follows a known response pattern to the medical device (if the response pattern is previously known);
  - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible);
  - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
  - harm to the subject is due to error in use;

- the event depends on a false result given by the investigational device used for diagnosis, when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

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

11.7. Anticipated or Unanticipated

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

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

12. Data Review Committees

12.1. Clinical Events Committee

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

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

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

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

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

Refer to Section 9.11.2 for Stopping Rules for Entire Study.

13. Device Deficiencies and Troubleshooting

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

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

All device deficiencies reported directly to the investigational center staff by a subject should either be reported to the TS by the subject or investigational center staff. In addition, an eCRF should also be completed by the investigational center staff for each reported device deficiency.

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

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

Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. *NOTE: Device deficiencies include malfunctions, use errors, and inadequate labeling.* (ISO 14155:2011 section 3.15)
	Any unreasonable risk caused by a medical device in normal use during clinical trial that may endanger human health or life safety, such as label error, quality issues, malfunction and etc. (NMPA Order No.25 Article 93)

14. Statistical Design and Methods

14.1. General Considerations

All data collected from the time of screening until the end of the study will be collected either on eCRFs, subject questionnaires or electronically by downloading the various devices. Data and analysis will be summarized in a Clinical Study Report. For China, the Clinical Study Report will be compliant with NMPA 2016 No. 58 Announcement Annex 5 "Template of Clinical Trial Report of Medical Devices".

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

There will be no interim analysis perform during the study so therefore there are no criteria and/ reasons for trial termination based on statistics.

14.2. Subject Disposition

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

14.3. Subject Demographics and Baseline Characteristics

Subject characteristics, including age, gender, race, ethnicity, length of type 1 diabetes 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. Sample Size and Power

Based on US pivotal study outcome, the estimated difference of the TIR from run-in period to study period to be expected 5.3%. A sample size of 50 will achieve greater than 80% power to detect simple superiority using a one-sided t-test with a standard deviation of 13.0% at the significance level (alpha) of 0.025.

This study will enroll subjects between age of 14 and 75 years old, with a ratio (1:5) between Adolescents (14-17 years) and Adults (≥ 18 years).

A total of up to 75 subjects will be enrolled at minimum 2 investigational centers and up to 6 investigational centers (hospitals) in China considering potential drop outs. A maximum of 30 subjects will be enrolled at each investigational center. Sites with less than 6 subjects will be pooled into 'pseudo-sites' of at least 10 subjects per pseudo-site. Pseudo-sites will be pooled by ranking those sites with less than 6 subjects by site number and pooling those sites in order of site number until the number of subjects reaches at least 10.

14.5. Analysis Populations and Handling of Missing Data, Error

Data entry error or non-reasonable values will be resolved before data analysis. No imputations will be done for missing data.

The primary study population is the Intention to Treat (ITT) population, which consists of subjects who entering study period.

The Per Protocol (PP) population is defined as subjects who stay in Auto Mode ≥80% of Study Period and have no major deviations.

The safety population consists of all enrolled subjects.

14.6. Statistical Model and Analyses of Study Endpoints

14.6.1. Primary Endpoints

Time in target range (% of SG): 70 mg/dL (3.9 mmol/L) ≤ SG ≤ 180 mg/dL (10 mmol/L)

The overall mean change in % of time in target range from run-in period to study period will be estimated and compared by a simple superiority paired test and a significance level of 0.025 (one-sided).

Ho: $\mu \leq 0\%$

Ha: $\mu > 0\%$

Where μ is the mean of change in % of time in target range (1-month - baseline). The null hypothesis will be rejected if the one-sided 97.5% lower confidence limit of the mean change in % of time in target range is greater than 0%.

- Pass/Fail Criteria

  The study pass/fail criteria is based on statistical hypothesis of the primary endpoint. The study will be considered as success when the evaluation criteria meets the predefined threshold.

- Justification for Exclusion of Particular Information from the testing of the Hypothesis

  Not Applicable.

14.6.2. Secondary Endpoints

- Time in hypoglycemic range (% of SG): SG < 70 mg/dL (3.9 mmol/L), 60 mg/dL (3.3 mmol/L) and 54 mg/dL (3.0 mmol/L)
- Time in hyperglycemic range: SG > 180 mg/dL (10 mmol/L), 250 mg/dL (13.9 mmol/L) and 350 mg/dL (19.4 mmol/L)
- Glucose variation: the standard deviation (SD) of SG and the glucose coefficient of variation (CV)
- Change of Total Daily Dose (TDD) of insulin and weight from baseline to EOS
- Time spent in Auto Mode (HCL) versus time spent in Manual Mode (open loop)
- Stratified by HbA1c Ranges (< 7%, 7 – 7.5%, 7.5 – 8%, > 8%)
  - Time in target range (% of SG): 70 mg/dL (3.9 mmol/L) ≤ SG ≤ 180 mg/dL (10 mmol/L)
  - Time in hypoglycemic range (% of SG): SG < 70 mg/dL (3.9 mmol/L), 60 mg/dL (3.3 mmol/L) and 54 mg/dL (3.0 mmol/L)
  - Time in hyperglycemic range: SG > 180 mg/dL (10 mmol/L), 250 mg/dL (13.9 mmol/L) and 350 mg/dL (19.4 mmol/L)

14.7. Safety

All adverse events will be collected from enrollment (i.e., time of consent) to study end including but not limited to:

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

14.8. Device Deficiencies

Descriptive summary will be used to characterize device deficiencies, which will be collected from enrollment (i.e., time of consent) to study end.

14.9. Subject Feedback

Descriptive summary will be used to characterize study questionnaire(s) results.

14.10. Exploraroty Analysis

The change of Glycated Albumin (GA) from baseline to EOS will be analyzed.

14.11. Probability Analysis of Success

Since MiniMed™ 670G Insulin Pump has been evaluated in previous clinical studies and has demonstrated the overall mean change in % of time in target range from run-in period to study period, significantly higher than 0%. The probability of success is high.

14.12. Probability Analysis of Failure

Since MiniMed™ 670G Insulin Pump has been evaluated in previous clinical studies and has demonstrated the overall mean change in % of time in target range from run-in period to study period, significantly higher than 0%. The probability of failure is low.

15. Ethics

15.1. Statement(s) of Compliance

This study is a pre-market clinical trial for product registration in China. The study will be conducted in accordance with the laws and regulations of China, including any future applicable laws and regulations in China.

This CIP, any subsequent amendments to this CIP, the ICF and assent, subject materials and any form of subject recruitment information (e.g. advertisements) relating to this study will be approved by the responsible EC in accordance with NMPA Order No.25 and local regulatory requirements as applicable. The investigational center will not initiate any subject activities until EC approval has been granted, the sponsor has cleared the investigational center to begin the study, and the investigational center staff has been appropriately trained to conduct the study.

Regulatory Compliance

To protect the rights and welfare of patients, this clinical study will be conducted in compliance with the latest version of the Declaration of Helsinki ,the Clinical Trial Agreement and CIP, the laws and regulations of China including Good Clinical Practice for Medical Devices (NMPA Order No. 25), Announcement of NMPA on Filing of Medical Device Clinical Trial (2015, No.87) and also including applicable data protection laws. Investigational centers will also comply with any additional EC requirements, as applicable.

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

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

The clinical trial filing will be completed prior to conduct of this study per the requirement of the Announcement of NMPA on Filing of the Medical Device Clinical Trial (2015, No. 87).

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 EC, 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.

This clinical study will be conducted in subjects below 18 years of age (vulnerable population) therefore, the clinical investigations shall follow the additional EC procedures and national regulations where applicable.

Regulatory Submission

Sponsor should be responsible for filing the study to Shanghai Municipal Food and Drug Administration after EC approval of the current version of the CIP and fully executed Clinical Trial Agreement..

In countries where submission to the regulatory authority is required per local law, no patients will be enrolled in the clinical study until the particular regulatory authority has approved the current CIP of the clinical study and other documents as required according to the local requirements.

If the regulatory authority imposes any additional requirements (e.g. safety reports, progress reports etc.), Medtronic will prepare the required documents and send them to the respective authority.

Sponsor's Support

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

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

15.2. Investigator's Responsibilities

This study will be conducted at the investigational centers where all study-related activities will be performed and will be led by a PI.An investigator means an individual member of the investigation site team designated and supervised by the principal investigator at an investigation site to perform critical clinical-investigation-related procedures or to make important clinicalinvestigation-related decisions.

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

- Conduct of the investigation in accordance with the signed Form of Investigator Statement for clinical investigations of medical devices, CIP, applicable regulations set forth in NMPA Order No.25 and other applicable NMPA regulations and any conditions of approval imposed by the reviewing EC or NMPA regulatory requirements
- Conduct of investigation in accordance to regulations from NMPA to meet responsibilities with respect to protect human subjects and ensuring the integrity of the data from clinical investigations. The regulations is also intended to clarify NMPA's expectations concerning the investigator's responsibility:
    - To supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other third parties, and

  - 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
- 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 and assent are met in accordance with NMPA
- 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 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, to include
  - all relevant correspondence with another investigator (if applicable), an EC, the sponsor, a monitor, or NMPA (if applicable), including required reports.
  - records of receipt, use, or disposition of study devices
  - records of each subject's case history and exposure to the device
  - the CIP, with documents showing the dates of and reasons for each deviation from the CIP
  - Any other records the NMPA 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, NMPA and the reviewing EC, 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 NMPA and EC, if applicable
  - 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 and assent (if applicable)
- any further information requested by the NMPA and EC about any aspect of the investigation

- Permitting NMPA or other regulatory authorities to inspect and copy any records pertaining to the investigation including, in certain situations, those which identify subjects
- Meeting with the monitor to discuss study progress and findings and review source documentation and study files
- 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 Delegated Task List, are permitted to consent subjects, receive, dispense, dispose of and return investigational products, conduct subject visits, insert devices and enter data on eCRFs. These tasks may be delegated by the investigator. However, the investigator is ultimately responsible to ensure investigational center staff are qualified and perform the tasks that have been delegated to them correctly. In addition the investigator is responsible for the conduct of investigational center in the execution of the clinical trial.

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

16. Study Administration

16.1. Training of Clinical Staff

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

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

16.2. Monitoring

Monitoring visits may be conducted at the start, during and at the closure of the clinical study in accordance with Medtronic SOPs and the Monitoring Plan. At minimum, it will be verified whether signed and dated ICFs and assent form (if applicable)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. Monitoring will be done according to sponsor SOPs and the Monitoring Plan for this clinical study.

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 and the Clinical Study Manager. This accessibility is of particular importance for reviewing data in the eCRF. Direct access to subject medical files for source data verification will need to be granted and prepared prior to any monitoring visits.

16.2.2. Audits and Investigational Center Inspections

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

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

16.2.3. Investigational Center Disqualification

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

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

A written statement fully documenting the reasons for such a termination will be provided to sponsor, the EC and other regulatory authorities, as required.

16.3. Data Management

16.3.1. Data Collection

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

16.3.1.1. Electronic Case Report Forms (eCRFs)

The investigator must ensure accuracy, completeness and timeliness of the data reported in the eCRFs and in all other required reports. Data reported on the eCRFs which are derived from source documents, such as subject medical records, must be consistent with the source documents and the discrepancies need to be justified in a documented rationale.

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

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

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

16.3.1.2. Food Log and Subject Questionnaires

The food log and subject questionnaires will be collected on paper that will be kept at the investigational center. The investigator, or designated investigational center staff, will then copy the data from food log and enter the answers of the subject on the paper questionnaires into OC-RDC system. It is important that the investigator or designated investigational center staff verifies questionnaires for completeness.

16.3.1.3. CareLink™ For Clinical Research 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/meter data will be uploaded in CareLink™ 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 IDs to prevent subject's identification by the sponsor.

16.3.2. Time Windows for Completion and Submission of eCRFs

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

16.3.3. Data Review and Processing

The leading investigational center will be accountable for data management and analysis about the data from each clinical research institution in a centralized manner according to local regulations and study requirements. Medtronic will oversee all data management functions and provide support if necessary.

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

Collected data will be reviewed for completeness, correctness and consistency.. 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 hospital/clinic file, laboratory reports, and data collected on the food log, CareLink™ software data, 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.

16.4.1. Quality Audits

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

16.5. Confidentiality

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

16.6. Liability

Subjects will be properly compensated for their participation in the study. Refer to the ICF on the details. In addition, refer to CTA for subject's compensation and indemnification.

Medtronic maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a clinical study insurance statement/certificate will be provided to the EC.

Finance information will be documented in Clinical Trial Agreement.

16.7. Responsibilities of All Parties

Investigator responsibilities will be included in Clinical Trial Agreement and subject responsibilities will be available in ICF. Sponsor will undertake all the responsibilities of the sponsor as required per NMPA regulations.

16.8. CIP Amendments

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

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

16.9. Records and Reports

16.9.1. 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
- IB and/or User guide
- Medtronic and EC-approved Patient ICF and assent form (if applicable)
- EC 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 Delegated Task List
- Training documentation of all investigational center staff
- Subject screening log and/or Subject ID log
- Signed, dated and fully executed subject ICFs and assent forms (if applicable)
- Source documentation
- Fully executed eCRFs and corrections
- Report of AEs and Device Deficiencies
- Device accountability records
- CIP Deviation/ CIP Non Compliance, if any
- Clinical Bulletins (if applicable)- A brief official update or summary of current study news on a matter of immediate interest and high importance to investigational center surrounding the CIP.
- Current signed and dated curriculum vitae (CV) of PI (and key study team members if required per local requirements)
- Study reports

16.9.2. Investigator Reporting Responsibilities

Table 6. Investigator Reporting Requirements

Report	Submit to	Description/Constraints
AEs	Sponsor, EC, and regulatory authority, where applicable	Refer to Section 11 for reporting requirements.
DDs	Sponsor, EC, and regulatory authority, where applicable	Refer to Section 11 and 13 for reporting requirements.
Withdrawal of EC approval (either suspension or termination)	Sponsor	An investigator shall report to the sponsor a withdrawal of approval by the reviewing EC of the investigator's part of an investigation.
Study deviations	Management department of medical device clinical study then they will submit to sponsor and EC	Any deviation from the clinical investigational plan shall be recorded together with the explanation of the deviation. Protocol deviation that may affect the subjects' rights and interests, safety, health or the scientificity of clinical trials, including deviation regarding requests and reports. Refer to Section 9.9 for Deviation Handling.

Report	Submit to	Description/Constraints
Failure to obtain informed consent and assent prior to investigational device use	Sponsor and EC	Informed consent and assent shall be obtained in writing and documented before a subject is enrolled into the clinical investigation. *(Adapted from ISO 14155:2011)*
Progress report	Management department of medical device clinical study then they will submit to sponsor and EC (if needed per EC requirements)	Provide progress report, including safety summary and deviations, if required by local law or EC. (ISO 14155:2011) During the clinical trials, the investigators should notify sponsor and report to the EC in a timely manner by promptly reporting the progress report to the medical device clinical trial administration department of the investigational centers, including the safety summary and deviation report.
Final report	Management department of medical device clinical study then they will submit to sponsor and EC (if needed per EC requirements	Upon completion of multi-center clinical trials, investigators of all investigational centers shall issue brief summary of clinical trials, respectively, and submit it to coordinating investigator together with eCRFs upon review as required for coordinating investigator to summarize and complete summary report. *(NMPA order No.25 Article 29（7）)* Investigators should, in accordance with the design requirements of the clinical trial protocol, verify and validate the safety and effectiveness of investigational medical devices, and complete the Clinical Trial Report. As for multi-center clinical trials, the Clinical Trial Report should contain the Summaries of Clinical Trial of all sub-centers. *(NMPA order No.25 Article 83)* The Clinical Trial Report should be signed and dated by the investigators, and submitted to the sponsor after being reviewed, commented, dated and sealed by medical device clinical trial administration department of clinical trials institutions. For multi-center clinical trial, the clinical trial summary of each center should be signed and dated by the investigators of respective center and submitted to the leading investigational center after being reviewed, dated and sealed by the investigational center's clinical trial administration department. *(NMPA order No.25 Article 86)*

Report	Submit to	Description/Constraints
Other	Sponsor, EC and NMPA	An investigator shall, upon request by a reviewing EC, NMPA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation.

16.10. Record Retention

The sponsor and investigator will retain all records and documents pertaining to this study. They will be available for inspection by the appropriate regulatory agencies. In addition, the investigator will retain the source documents from which the information entered on the eCRF was derived. These records are to be retained in a secure storage facility maintained by the investigational center for 10 years after completion of the study or termination of the study, whichever is longer. The investigator should not dispose of these records without the approval of the sponsor. The sponsor shall keep the clinical data indefinitely.

16.11. Suspension or Early Termination

Sponsor or regulatory agency 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, Medtronic shall promptly inform the investigators of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing EC and the study subjects.

16.11.1. Early Investigational Center Suspension or Termination

Sponsor, EC, or a regulatory agency may decide to suspend or prematurely terminate an investigational center (e.g. in case of expiring approval of the reviewing EC, non-compliance to the CIP or lack of enrollment). The medical device clinical trial management departments of clinical trial institutions should be notified within 5 days with the rationale in writing. 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 EC 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, EC and department of food and drug administration of the concerned province, region and municipality.

The suspended clinical studies cannot be resumed without permission from EC. Upon completion of clinical studies, the applicant shall send written notice to the management of food and drug administration of the concerned province, autonomous region and municipality.

16.11.2. 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 (unless subject is allowed to keep them per country requirement), receive appropriate treatment and follow-up.

16.12. Study Close Out

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

16.13. Publication and Use of Information

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

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

17. References

Medtronic, Inc. CEP294: Safety Evaluation of the Hybrid Closed Loop (HCL) System in Type 1 Diabetes. CEP294DOC, 2018.

Bergenstal RM, Garg S, Weinzimer SA, Buckingham BA, Bode BW, Tamborlane WV, Kaufman FR. Safety of a Hybrid Closed-Loop Insulin Delivery System in Patients With Type 1 Diabetes. JAMA. 2016 Oct 4;316(13):1407-1408.

Garg SK, Weinzimer SA, Tamborlane WV, Buckingham BA, Bode BW, Bailey TS, et al. Glucose Outcomes with the In-Home Use of a Hybrid Closed-Loop Insulin Delivery System in Adolescents and Adults with Type 1 Diabetes. Diabetes Technol Ther. 2017 Mar;19(3):155-163.

Christiansen MP, Garg SK, Brazg R, Bode BW, Bailey TS, Slover RH, et al. Accuracy of a Fourth-Generation Subcutaneous Continuous Glucose Sensor. Diabetes Technol Ther. 2017 Aug;19(8):446-456.

Choudhary P, Olsen BS, Conget I, Welsh JB, Vorrink L, Shin JJ. Hypoglycemia Prevention and User Acceptance of an Insulin Pump System with Predictive Low Glucose Management. Diabetes Technol Ther. 2016 May;18(5):288-91.

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

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

18. Appendices

18.1. Names and Addressess

18.1.1. Investigational Centers and Investigators

At the time this CIP was finalized, a list of the names and addresses of the participating Investigational Centers and investigators that were identified are presented below (additional investigational Centers may be identified, if needed) . Refer to ClinicalTrials.gov for the names and address of the participating Investigational Centers and investigators.

The Investigational Centers are medical institutions which are qualified for conducting clinical studies by the regulatory department of NMPA and the Administrative Department of Health under the State Council.

Table 7: Investigational Centers and Investigators List

Investigational Center Number	Name of Investigational Center	Investigator	Title	Contact information
001	Chinese PLA General Hospital	Dr. Yiming Mu	Chief Physician	No.28 Fuxing Road, Haidian District, Beijing
002	Nanjing Drum Tower Hospital The Affiliated Hospital of Nanjing University Medical School	Dr. Yan Bi	Chief Physician	No.321 Zhongshan Road, Nanjing
003	Shanghai General Hospital	Dr. Yongde Peng	Chief Physician	No.100 Haining Road, Hongkou District
004	The First Affiliated Hospital, Sun Yat-sen University	Dr. Yanbing Li	Chief Physician	No.58 Zhongshan Er Road, Guangzhou

18.1.2. EC

At the time of this CIP was finalized, a list of the names and addresses of the ECs were not identified.

18.1.3. Monitors Contact Information

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

[redacted]

Clinical Research Monitor, MC2 Global Monitoring

Medtronic

Room 1903, T1, Raffles Plaza, No.3 Section 4,

Renmin South Road, Wuhou District,

Chengdu, Sichuan, China

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

18.1.4. Sponsor's and Local Sponsor's Staff Contact

A list of sponsor's and local sponsor's staff will be kept separate from the CIP and provided to the investigators. The sponsor will maintain an updated list.

18.2. Labeling and IFUs of Devices

The current labeling and IFU for the investigational devices will be provided to the investigators under a separate cover.

18.3. Sample Consent Materials

Samples of the consent and assent forms/materials will be provided in a separate cover.

18.4. Appendix E: Relevant Qualification Document(S) Of The Sponsor/Local Sponsor(Agent)

Relevant qualification document(s) of the sponsor/local sponsor(agent) will be provided under a separate cover.

19. Version History

Version	Summary of Changes	Author(s)/Title
A	Not Applicable, New Document.	[redacted]
B	• Updated Investigator Statement signature lines to align with CFDA Order No. 25 template • Updated picture of Guardian™ Link (3) Transmitter • Updated name and model number of CareLink™ • Added trademark for Bluetooth® Low Energy; removed reference of abbreviations of BLE • Revised study procedures for uploading of study devices (as study meter transmits to the study pump via Bluetooth® Low Energy communication) • Added collection of GA under study procedures and visit schedule to correlate with Exploratory analysis • Corrected cross reference for Investigator Reporting Requirements table	[redacted]
C	• Increased sample size • Corrected duration of run-in period • Updated software of MiniMed™ 670G Insulin Pump • Unscheduled visits (at office or phone call) added to Schedule of Events • Updated pregnancy test to be drawn as a lab test • Updated TSH and hematocrit, if not available at screening, will be tested at investigational center lab or their contracted Local Lab • Added assenting(if applicable) in CIP • Updated Ethics • Updated Suspension or Early Termination	[redacted]