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Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	Safety, Effectiveness and Usability Evaluation of the Hybrid Closed Loop (HCL) System in Type 1 Adult and Adolescent Subjects in Chinese Population
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0 01-JUL-2021	Not Applicable, New Document	[redacted]

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
BG	Blood Glucose
CGM	Continuous Glucose Monitoring
CIP	Clinical Investigation Plan
CV	Coefficient of Variation
DKA	Diabetic Ketoacidosis
eCRF	Electronic Case Report Form
EOS	End of Study
FDA	United States Food and Drug Administration
GA	Glycated Albumin
HbA1c	Glycosylated hemoglobin
HCL	Hybrid Closed Loop
ITT	Intention to Treat
IV	Intravenous
NMPA	National Medical Products Administration

PP	Per Protocol
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
T1DM	Type 1 Diabetes Mellitus
TDD	Total Daily Dose
UADE	Unanticipated Adverse Device Effect

3. Introduction

3.1 Background

3.1.1 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.

3.1.2 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.

3.2 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.

4. Study Objectives

4.1.1 Primary Objective(s)

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

5. Investigation Plan

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.

5.1 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.

5.2 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.

6. Determination of Sample Size

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 an expected ratio (1:5) between Adolescents (14-17 years) and Adults (≥ 18 years) to complete the study.

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.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

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

7.1.2 Clinical Investigation Plan (CIP) Deviations

All protocol deviations will be presented in the listings.

7.1.3 Analysis Sets

- Intention to Treat (ITT) Population
  The Intention to Treat (ITT) population will include all subjects who start the study period.

- Per Protocol (PP) Population
  The Per Protocol (PP) population will include all subjects who complete the study period and stay in Auto Mode ≥80% of study period and have no major deviations (e.g. protocol violation in eligibility).

- Efficacy Population
  The primary analysis will be performed on the ITT population. Sensitivity analysis will be performed on PP population.

- Safety Population
  The Safety Population will include all enrolled subjects.

7.2 General Methodology

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.

7.3 Center Pooling

Data will be pooled for analysis.

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

Data entry error or non-reasonable values will be resolved before data analysis. No imputation will be applied for the device data.

7.5 Adjustments for Multiple Comparisons

Not Applicable.

7.6 Demographic and Other 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.

7.7 Treatment Characteristics

Not Applicable.

7.8 Interim Analyses

Not Applicable.

7.9 Evaluation of Objectives

7.9.1 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).

$H_o: \mu \leq 0\%$

$H_a: \mu > 0\%$

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.

7.9.2 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)

7.9.3 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

7.9.4 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.

7.9.5 Subject Feedback

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

7.9.6 Exploratory Analysis

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

7.10 Safety Evaluation

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

7.11 Health Outcomes Analyses

Descriptive summary will be used to characterize data from questionnaires that are given to subjects to record feedback.

7.12 Changes to Planned Analysis

Not Appliable.

8. Validation Requirements

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

9. References

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.