Medtronic	
Study Title	Multi-center, Randomized, Parallel, Adaptive, Controlled Trial in Adult and Pediatric Patients with Type 1 Diabetes Using Hybrid Closed Loop System and Control (CSII, MDI and SAP) at Home
NCT Number	NCT02748018
Document Description	Clinical Investigation Plan (Version H)
Document Date	01-FEB-2024

Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	Multi-center, Randomized, Parallel, Adaptive, Controlled Trial in Adult and Pediatric Patients with Type 1 Diabetes Using Hybrid Closed Loop System and Control (CSII, MDI and SAP) at Home
Clinical Investigation Plan Identifier	CEP304DOC
Study Product Name	• MiniMed® 670G Pump labeled as MiniMed Insulin Pump - referred to as MiniMed Pump throughout the protocol • MiniMed 770G Pump labeled as MiniMed Insulin Pump - referred to as MiniMed Pump throughout the protocol • Guardian® Link (3) Transmitter • MiniMed Mobile Application referred to as the Mobile App in the protocol • CareLink Connect Application • Transmitter Charger • CONTOUR® NEXT LINK 2.4 by Ascencia Blood Glucose Meter - referred to as the Study Meter throughout this protocol) • Roche Accu-Chek Guide Link Meter -referred to as the Accu-Chek Guide Link study meter in this protocol • Guardian® Sensor (3), referred to as Guardian Sensor (3) throughout this protocol • One-Press Serter -referred to as the Serter throughout the protocol • Tester
Sponsor/Local Sponsor	USA: [redacted] Medtronic MiniMed (“Medtronic”) 18000 Devonshire St Northridge, CA 91325

	866.948.6633 Europe: [redacted] Medtronic International Trading Sarl. (“Medtronic”) Route du Molliau 31 Case Postale 1131 Tolochenaz Switzerland (+41) 21 803 80 84 Canada: Medtronic Canada ULC. 99 Hereford St. Brampton, Ontario, Canada L6Y 0R3 905 460 37211 Australia: [redacted] Medtronic Australasia Pty. Ltd 2 Alma Road Macquarie Park, NSW 2113 Australia (+61) 2 9857 9000 New Zealand: [redacted] Medtronic New Zealand Limited Level 3, Bldg 5, 666 Great South Road Penrose, Auckland 1051 New Zealand (+64) 9 9674600
Document Version	CEP304DOC, version H (Equivalent to Version H.1)
Version Date	01 Feb 2024

Confidentiality Statement

1. Investigator Agreement and Signature Page

Study Product Name	MiniMed 670G pump MiniMed 770G pump
Sponsor	Medtronic MiniMed
Clinical Investigation Plan Identifier	CEP304DOC
Version Number/Date	H/01-FEB-2024

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to comply with all applicable regulatory guidelines under which the study is being conducted, i.e., International Conference on Harmonization Guidelines on Good Clinical Practice (US only), United Stated Food and Drug Administration regulations (21 CFR Part 50, 21CFR Part 56, 21 CFR 812, etc.) (US only), United Stated Food and Drug Administration regulations (21 CFR Part 54 and part 11) (US and Europe), Health Canada Regulations (SOR/98-282 – Canada only), International Organization for Standardization (ISO 14155:2011 – Europe only). In Australia and New Zealand, the study will be carried out in conformity with the ethical principles of the Declaration of Helsinki, the requirements of ISO14155:2011 and with all the other local laws and regulations relevant to the use of new and approved medical devices in the country.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.

Investigator's Signature:	
Investigator's Name:	
Institution:	

Date:	

Table of Contents

2. Glossary

Term	Definition
A1C	Glycosylated hemoglobin
AE	Adverse Event
ADE	Adverse Device Effect
ASIC	Application Specific Integrated Circuit
BLE	Bluetooth Low Energy
BMI	Body Mass Index
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CGMS	Continuous Glucose Monitoring System
CL	Closed Loop
CSII	Continuous Subcutaneous Insulin Infusion
CV	Coefficient of Variation
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EC	Ethics Committee
EIS	Electrochemical Impedance Spectroscopy
ER	Emergency Room
EU MDR	European Medical Device Regulation
FDA	United States Food and Drug Administration

Term	Definition
FST	Frequent Sample Testing
GCRC	General Clinical Research Center
hCG	Human chorionic gonadotropin
HCL	Hybrid Closed Loop
HCP	Health Care Professional
HFE	Human Factors Engineer
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board
IV	Intravenous
JDRF	Juvenile Diabetes Research Foundation
LSL	Low Suspend Limit
MAGE	Mean Amplitude of Glycemic Excursions
MDD	Medical Device Directive
MDI	Multiple Daily Injections
MedDRA	Medical Dictionary for Regulatory Activities
NDC	National Drug Code
NGSP	National Glycohemoglobin Standardization Program
OC-RDC	Oracle Clinical Remote Data Capture
OLS	Clinical Online Store

Term	Definition
PC	Personal Computer
QC	Quality Control
RF	Radio Frequency
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Sensor Augmented Pump
SG	Sensor Glucose
SGV	Sensor Glucose Value
SMBG	Self-Monitoring of Blood Glucose
SR	Significant Risk
Tel-D	Telemetry-Diabetes
TLS	Transport Layer Security
TDD	Total Daily Dose
TGA	Therapeutic Goods Administration
TS	Technical Support
TSH	Thyroid-stimulating hormone
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

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3. Synopsis

Title	Multi-center, Randomized, Parallel, Adaptive Controlled Trial in Adult and Pediatric Patients with Type 1 Diabetes Using Hybrid Closed Loop System and Control (CSII, MDI and SAP) at Home
Clinical Study Type	Phase IV; Interventional
Product Name	Hybrid Closed Loop System
Sponsor	Medtronic MiniMed
Local Sponsor	[redacted] Medtronic MiniMed 18000 Devonshire St Northridge, CA 91325, USA [redacted] Medtronic International Trading Sarl. (“Medtronic”) Route du Molliau 31 Case Postale 1131 Tolochenaz, Switzerland Medtronic Canada ULC 99 Hereford St. Brampton, Ontario, Canada L6Y 0R3 [redacted] Medtronic Australasia Pty. Ltd 2 Alma Road Macquarie Park, NSW 2113 Australia

	(+61) 2 9857 9000 [redacted] Medtronic New Zealand Limited Level 3, Bldg 5, 666 Great South Road Penrose, Auckland 1051 New Zealand (+64) 9 9674600
Indication under investigation	Type 1 Diabetes
Investigation Purpose	The purpose of this study is to evaluate the safety and effectiveness of the Hybrid Closed Loop system (HCL) in adult and pediatric patients with type 1 diabetes in the home setting. A diverse population of patients 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 glycosylated hemoglobin (A1C). The following cohorts will be enrolled: 1) Cohort 1: Continuous Subcutaneous Insulin Infusion (CSII) or HCL; 2) Cohort 2: Multiple Daily Injections (MDI) or HCL and 3) Cohort 3: Sensor-Augmented Pump therapy (SAP) or HCL.
Product Status	***Investigational Devices*** ***MiniMed 670G US only – Subjects 2-6 years:*** ○ MiniMed 670G Pump labeled as MiniMed Insulin Pump (MMT-1780), referred to as MiniMed Pump throughout the protocol ○ Guardian® Link (3) Transmitter (MMT-7811) ○ Guardian® Sensor (3) (MMT-7020), referred to as Guardian Sensor (3) throughout this protocol ○ CONTOUR® NEXT LINK 2.4 by Ascencia Blood Glucose Meter (MMT-1152 or MMT-1352 in US) - referred to as the Study Meter

	throughout this protocol) ***MiniMed 770G Australia – Subjects 2-6 years:*** ○ MiniMed 770G Pump labeled as MiniMed Insulin Pump (MMT-1881, MMT-1891), referred to as MiniMed Pump throughout the protocol ○ Guardian® Link (3) Transmitter (MMT-7910W5, MMT-7911W) ○ MiniMed Mobile Application (MMT-6103 Android/6104 IOS)- referred to as the Mobile App in this protocol, Medical Device Data System exempt device ○ CareLink Connect Application (MMT-6113 Android/6114 IOS), Medical Device Data System exempt device ○ Roche Accu-Chek Guide Link Meter (Model 08116113186M) - referred to as the Accu-Chek Guide Link study meter in this protocol ○ Blue adapter (ACC-1003911) ○ Medtronic CareLink® Clinical Software (MMT-7338)– referred to as CareLink Clinical Medical Device Data System exempt device ***Non-Investigational/Exempt Devices*** ***MiniMed 670G US - Subjects 7 years and older:*** ○ MiniMed 670G Pump labeled as MiniMed Insulin Pump (MMT-1780), referred to as MiniMed Pump throughout the protocol ○ Guardian® Link (3) Transmitter (MMT-7811) ○ Transmitter Charger (MMT-7715) ○ CONTOUR® NEXT LINK 2.4 by Ascencia Blood Glucose Meter (MMT-1152 or MMT-1352 in US) - referred to as the Study Meter throughout this protocol) ○ Guardian® Sensor (3) (MMT-7020), referred to as Guardian Sensor (3) throughout this protocol ○ Tester (MMT-7736L) ○ Ketone Meter ○ One-Press Serter (MMT-7512) -referred to as the Serter throughout

	the protocol ○ Medtronic CareLink® Personal Therapy Management Software for Diabetes (MMT-7333) -– referred to as CareLink Personal for Clinical Research throughout this protocol; Class 1 exempt device ***MiniMed 670G Europe - Subjects 7 years and older:*** ○ MiniMed 670G Pump* labeled as MiniMed Insulin Pump (MMT-1781 or MMT-1782), referred to as MiniMed Pump throughout the protocol ○ Guardian® Link (3) Transmitter (MMT-7811) ○ Guardian® Sensor 3 (MMT-7020), referred to as Guardian Sensor (3) throughout this protocol ○ Ketone Meter ○ CONTOUR® NEXT LINK 2.4 by Ascencia Blood Glucose Meter (MMT-1151 and MMT-1152) - referred to as the Study Meter throughout this protocol) ○ Transmitter Charger (MMT-7715) ○ Tester (MMT-7736L)* ○ Medtronic CareLink® Personal Therapy Management Software for Diabetes (MMT-7333) -– referred to as CareLink Personal for Clinical Research throughout this protocol; CE Marked. ○ One-Press Serter (MMT-7512)-referred to as the Serter throughout the protocol ***MiniMed 670G Canada - Subjects 7 years and older:*** ○ MiniMed 670G Pump labeled as MiniMed Insulin Pump (MMT-1781 (pump) and MMT-1762KCN (kit)) , referred to as MiniMed Pump throughout the protocol ○ Guardian® Link (3) Transmitter (MMT-7811) ○ Guardian® Sensor (3) (MMT-7020), referred to as Guardian Sensor (3) throughout this protocol

	○ CONTOUR® NEXT LINK 2.4 by Ascencia Blood Glucose Meter (MMT-1151 and MMT-1152) - referred to as the Study Meter throughout this protocol) ○ Ketone Meter ○ Medtronic CareLink® Personal Therapy Management Software for Diabetes (MMT-7333WW) -– referred to as CareLink Personal for Clinical Research throughout this protocol; Medical Device Data System exempt device ○ One Press Serter (MMT-7512)- referred to as the Serter throughout the protocol ○ Transmitter Charger (MMT-7715) ○ Tester (MMT-7736L) ***MiniMed 670G All Geographies:*** ○ CareLink USB 2.4 GHz (MMT-7306) ***MiniMed 770G US Only – Subjects 2 years and older:*** ○ MiniMed 770G Pump labeled as MiniMed Insulin Pump (MMT-1880, referred to as MiniMed Pump throughout the protocol ○ MiniMed Mobile Application (MMT-6103 Android/6104 IOS)- referred to as the Mobile App in this protocol, (when available). ○ CareLink Connect Application (MMT-6113 Android/6114 IOS), (when available) ○ Roche Accu-Chek Guide Link Meter (Model 08116083022) -referred to as the Accu-Chek Guide Link study meter in this protocol ○ Blue adapter (ACC-1003911) ○ Medtronic CareLink® Clinical Software (MMT-7338) – referred to as CareLink Clinical; Class 1 exempt device ***MiniMed 770G Canada - Subjects 2 years and older:***

	○ MiniMed 770G Pump labeled as MiniMed Insulin Pump (MMT-1881, MMT-1891KCN and MMT-1891CRP (kit)), referred to as MiniMed Pump throughout the protocol ○ Guardian® Link (3) Transmitter (MMT-7911) ○ MiniMed Mobile Application (MMT-6103 Android/6104 IOS)- referred to as the Mobile App in this protocol, Medical Device Data System exempt device ○ CareLink Connect Application (MMT-6113 Android/6114 IOS), Medical Device Data System exempt device ○ Roche Accu-Chek Guide Link Meter (Model 08109222001) -referred to as the Accu-Chek Guide Link study meter in this protocol ○ Blue adapter (ACC-1003911) ○ Medtronic CareLink® Clinical Software (MMT-7338)– referred to as CareLink Clinical Medical Device Data System exempt device ***MiniMed 770G Australia – Subjects 7 years and older:*** ○ MiniMed 770G Pump labeled as MiniMed Insulin Pump (MMT-1881, MMT-1891), referred to as MiniMed Pump throughout the protocol ○ Guardian® Link (3) Transmitter (MMT-7910W5, MMT-7911W) ○ MiniMed Mobile Application (MMT-6103 Android/6104 IOS)- referred to as the Mobile App in this protocol, Medical Device Data System exempt device ○ CareLink Connect Application (MMT-6113 Android/6114 IOS), Medical Device Data System exempt device ○ Roche Accu-Chek Guide Link Meter (Model 08116113186M) - referred to as the Accu-Chek Guide Link study meter in this protocol ○ Blue adapter (ACC-1003911) ○ Medtronic CareLink® Clinical Software (MMT-7338)– referred to as CareLink Clinical Medical Device Data System exempt device ***MiniMed 770G New Zealand– Subjects 2 years and older:***

	○ MiniMed 770G Pump labeled as MiniMed Insulin Pump (MMT-1881, MMT-1891), referred to as MiniMed Pump throughout the protocol ○ Guardian® Link (3) Transmitter (MMT-7910W5, MMT-7911W) ○ MiniMed Mobile Application (MMT-6103 Android/6104 IOS)- referred to as the Mobile App in this protocol, Medical Device Data System exempt device ○ CareLink Connect Application (MMT-6113 Android/6114 IOS), Medical Device Data System exempt device ○ Roche Accu-Chek Guide Link Meter (Model 08116113186M) - referred to as the Accu-Chek Guide Link study meter in this protocol ○ Blue adapter (ACC-1003911) ○ Medtronic CareLink® Clinical Software (MMT-7338)– referred to as CareLink Clinical Medical Device Data System exempt device
Europe Classification of devices by Rules according to Medical Device Directive (MDD)	• Infusion set: MDD, Annex IX, Rule 8, Class IIb • Insertion devices: MDD, Annex IX, Rule 12, Class I • Reservoirs: MDD, Annex IX, Rule 2, Class IIa • Insulin Pump: MDD, Annex IX, Rule 11, Class IIb • Transmitter: MDD, Annex X, Rule 10, Class IIa • Transmitter Charger: MDD, Annex IX, Rule 1, Class I • Sensor: MDD, Annex IX, Rule 8, Class III • Glucose Meter (Ascencia): In vitro diagnostic device, Annex II of the DIRECTIVE 98/79/EC, List B • Blood Glucose and Ketone Monitoring System: In vitro diagnostic device, Annex II of the DIRECTIVE 98/79/EC, List B
Europe Classification for Biocompatibility according to ISO EN 10993-1 Table 1 and 2 (Type of Body	• Infusion sets, Pump reservoirs: In compliance with ISO10993-1 and USP requirements for the use of insulin in the infusion sets. • Insulin Pump: In compliance with ISO10993-1 • Transmitter: In compliance with ISO10993-1 • Sensor: In compliance with ISO10993-1

contact/duration)	
Europe Device Nomenclature: GMDN (Global Medical Device Nomenclature)	• Reservoirs: 35838, Ambulatory insulin infusion pump reservoir • Infusion sets: 35833, Infusion Pump Administration Set • Insulin Pump: 35983, Insulin Infusion Pump • Transmitter: 44611, Interstitial-Fluid Glucose Monitoring System • Sensor: 59016 Subcutaneous Glucose Sensor • Transmitter Charger: 44611 Interstitial-Fluid Glucose Monitoring System • Serter: 45449, Injector Reset Device • Blood Glucose Meter: 30854 Glucose Meter Self-Testing
Primary Objective(s)	The purpose of this study is to evaluate the safety and effectiveness of the Hybrid Closed Loop system (HCL) in adult and pediatric patients with type 1 diabetes in the home setting.
Study Design	This is a 6 month, multi-center, randomized, parallel, adaptive study in type 1 diabetes with a 6 month continuation period. Up to 1500 subjects will be enrolled in order to have 1000 subjects who enter the study period. To date, 959 subjects have enrolled. Up to 70 investigational Centers in the US, Europe, Canada, Australia and New Zealand will be enrolled. For additional information on investigational sites and investigators, refer to information listed on public databases (e.g., clinicaltrials.gov). The study is anticipated to last no longer than 6.5 years from investigational center initiation to completion of all data entry and monitoring procedures. The study will target 54 months to complete subject enrollment. Subjects can expect to participate for approximately 7-8 months during the run-in period and study period, with a 6 month continuation period. The study will have three periods per Cohort: 1. Run-in Period: The run-in period can be up to 60 days. The run-in period will also be used for CGM data collection for approximately two weeks. Two consecutive 7-day sensors will be worn. If a sensor falls out, a replacement sensor should make up the difference for a total of 14 days of sensor wear (i.e. Monday Day 1

through next Sunday Day 14)

For example: If a sensor falls out on Day 4, a replacement sensor should be inserted. Once that replacement sensor has been worn for 7 days, a new sensor should then be inserted and worn for 3 days so that a total of 14 days of sensor wear is completed.

All patients will wear blinded CGM. Subjects will be expected to demonstrate sensor wear for approximately 14 days total between the two 7-day sensor wears (plus replacement sensor if needed). Subjects should be instructed to make 4-6 BG measurements per day. Sponsor may request a repeat of blinded CGM. Repeat of blinded CGM may occur if the following are not met:

- A minimum of 12 days of sensor wear have been self-reported to research staff
- A minimum of 2 blood glucose checks/day during the blinded CGM wear are confirmed on the subject's study BG meter.

If these requirements are not met then patient should repeat the entire 2 week blinded CGM data collection unless sponsor has approved that there was adequate data collection. An additional 21 days may be added to the run in visit window schedule if blinded CGM data collection needs to be repeated. Additional visits may also be allowed if needed.

2. Study Period: There will be a 6 month randomized study period with two arms: HCL system and Control. CSII and MDI control groups will undergo two blinded CGM collections during the study period.

   The first blinded CGM data collection during the study period will occur before the month three (see visit schedule) for approximately two weeks. Two consecutive 7-day sensors will be worn. If a sensor falls out, a replacement sensor should make up the difference for a total of 14 days of sensor wear. (i.e. Monday Day 1 through next Sunday Day 14)

   For example: If a sensor falls out on Day 4, a replacement sensor should be inserted. Once that replacement sensor has been worn for 7 days, a new sensor should then be inserted and worn for 3

	days so that a total of 14 days of sensor wear is completed. All patients will wear blinded CGM. Subjects will be expected to demonstrate sensor wear for approximately 14 days total between the two 7-day sensor wears (plus replacement sensor if needed). Subjects should be instructed to make 4-6 BG measurements per day. Sponsor may request a repeat of blinded CGM. The following should have occurred: • A minimum of 12 days of sensor wear have been self-reported to research staff • A minimum of 2 blood glucose checks/day during the blinded CGM wear are confirmed on the subject's study BG meter. If the above requirements are not met then patient should repeat the entire 2 week blinded CGM data collection unless the sponsor approves that there was adequate data collection. Additional visits may also be allowed if needed. No changes to the remaining visit schedule are needed. The second blinded CGM data collection during the study period will occur before the month six (see visit schedule) for approximately two weeks. Two consecutive 7-day sensors will be worn. If a sensor falls out, a replacement sensor should make up the difference for a total of 14 days of sensor wear. (i.e. Monday Day 1 through next Sunday Day 14) *For example: If a sensor falls out on Day 4, a replacement sensor should be inserted. Once that replacement sensor has been worn for 7 days, a new sensor should then be inserted and worn for 3 days so that a total of 14 days of sensor wear is completed.* All patients will wear blinded CGM. Subjects will be expected to demonstrate sensor wear for approximately 14 days total between the two 7-day sensor wears (plus replacement sensor if needed). Subjects should be instructed to make 4-6 BG measurements per day. 3. Continuation Period: There will be a 6 month continuation period during which time all subjects will use the HCL system.

	Enrollment Cohorts According to Treatment At Enrollment, subjects will be identified according to the type of treatment regimen they are currently on. Treatment regimen is defined as follows: • Cohort 1: CSII – subjects using pump (Medtronic or other pump systems) for at least 3 months at time of screening without concurrent use of real time CGM in the last 3 months. (Self-report acceptable.) Please note that alternatives to SMBG such as Freestyle Libre are not considered real time CGM and subjects who are using Freestyle Libre at time of Screening will be allowed to enroll in the study. During the study, however, subjects will not be allowed to use Freestyle Libre. • Cohort 2: Multiple Daily Injections (MDI) - Subjects using MDI with or without concurrent use of CGM for at least 3 months prior to Screening. (Self report is acceptable.) • Cohort 3: Sensor Augmented Pump (SAP) – subjects using pump for at least 3 months at time of screening with real time CGM use (Medtronic or other CGM systems) approximately 20% of the time (Self report acceptable). Subjects will use the Medtronic CGM starting at Visit 3, but they may use their own CGM until then. Sensor insertion placement will be according to User guide. Staged enrollment in the post approval study for Subjects 2-6 Years of Age: • Subjects 2-6 years of age will be allowed to enroll in the post approval study, once DMC has reviewed data from 10 subjects age 2-4 years who have completed participation in the study period of the CEP302 study and has given approval to enroll. In the US and Canada, subjects 2-80 years of age will be allowed to transition from the 670G system to the 770G system. The Run-In Period: Following successful screening, all subjects (CSII, MDI or SAP) will enter the run-in period and collect blinded CGM data while using their own diabetes therapy. Blinded CGM consists of using a Guardian Sensor (3) connected to a Guardian Link (3) transmitter. A total period of 2 weeks of CGM data will be collected. Note: Subjects 2-6 years of age will automatically enter the HCL arm at the end of the run-in period

Cohort 1: CSII

The Study Period: After completion of the run-in period, subjects with CSII therapy (minimum N= 280) will be randomized and placed into one of 2 different arms during the study period:

1. The HCL Arm will use the MiniMed System (i.e., using Auto Mode) for 6 months during the study period. There will be N=140 for the HCL arm.
2. The Control Arm will use the MiniMed Pump without CGM
    a. Blinded CGM (Guardian Link (3) Transmitter and Guardian Sensor (3)) will only be worn at baseline, 3 months, and 6 months (two weeks of sensors use). There will be N=140.

Cohort 2: MDI

The Study Period: After completion of the run-in period, subjects with MDI therapy (minimum of N=280) will be randomized and placed into one of 2 different arms during the study period:

1. The HCL Arm will use the MiniMed system (i.e., using Auto Mode) for 6 months during the study period. There will be N=140 for the HCL arm.
2. The Control Arm will be using their current insulin therapy (MDI).

    The Multiple Daily Injection (MDI) subjects will remain on MDI therapy with subjects using their own insulin for 6 months during the study period. The Sponsor will not provide insulin. Blinded CGM (Guardian Link (3) Transmitter and Guardian Sensor (3)) will only be worn at baseline, 3 months and 6 months (two weeks of sensors use). There will be N=140.

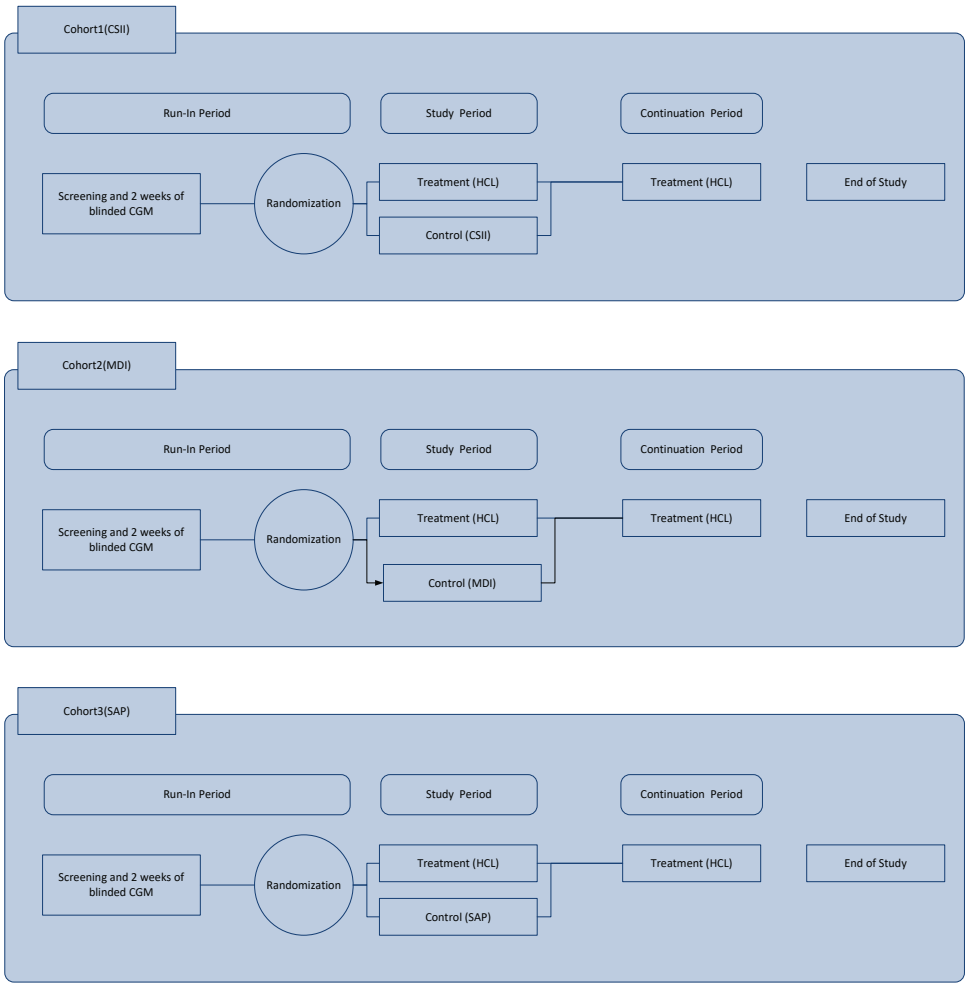
    MDI subjects who are currently using CGM, i.e. Dexcom or Medtronic Guardian Connect or who are currently using a SMBG alternative, i.e. Libre, will be allowed to enroll in the study and continue using their own device. There will be N=100

Cohort 3: SAP

The Study Period: After completion of the run-in period, subjects with SAP

	therapy (minimum N=280) will be randomized and placed into one of 2 different arms during the study period. Sensor insertion placement will be according to User guide: 1. The HCL Arm will use the MiniMed system (i.e., using Auto Mode) for 6 months during the study period. There will be N=140 for the HCL arm. 2. The Control Arm will be using SAP therapy using the MiniMed System. a. The Sensor Augmented Pump (SAP) subjects will use the MiniMed System (SAP without Low Management Suspend on Low, Low Management Suspend before low or Auto Mode) with Real Time CGM for the 6 month study period. There will be N=140. **The Continuation Period:** All subjects above will enter the continuation period for 6 months using the MiniMed system with Auto Mode on.

Figure 1. Study Design



Subjects may be re-tested as per sponsor discretion.

Per Cohort (CSII, MDI or SAP), here are the numbers of subjects expected to enroll:

- A1C at time of screening:
  - N = 70 A1C > 8% for HCL Arm
  - N = 70 A1C ≤ 8% for HCL Arm
  - N = 70 A1C > 8% for Control Arm
  - N = 70 A1C ≤ 8% for Control Arm

- Age at time of screening:

N=Minimum number of eligible subjects for each age group within each treatment cohort			N= Minimum number of eligible Subjects for each age group and cohort	N= Minimum number of eligible subjects for each age group for study
Age Group	Cohort	N	N	N
2-6 years	CSII	No Minimum	No minimum	N =120
	SAP			
	MDI			
7 -13 years	CSII	No Minimum	No minimum	N=180
	SAP			
	MDI			
14-21 years	CSII SAP MDI	N=45	N=45	N=135
22-64 years	CSII SAP MDI	N=120	N=120	N=360
65-80 years	CSII	No Minimum	No minimum	N=150
	SAP			
	MDI			

Randomization

Table 1. Randomization

Treatment at Baseline	Randomization Options	Continuation
CSII	CSII	HCL
	HCL	
MDI	MDI	HCL
	HCL	
SAP	SAP	HCL
	HCL	

Note: Subjects 2-6 years of age will automatically enter the HCL arm at the end of the run-in period

[redacted]

	[redacted]
Inclusion/ Exclusion Criteria	**Inclusion Criteria:** Subjects will be considered for enrollment in the study if they meet all of the following criteria: 1. Subject is age 2-80 years at time of screening a. US, Canada, Australia and New Zealand: Subjects 2-80 years of age will be allowed to enroll in the post approval study. b. Europe: Only subjects ≥7 years of age are allowed to enroll in the post-market study. 2. Subjects who are 2-21 years are determined by the investigator to have the appropriate, requisite support (family, caregiver or social network) to successfully participate in this study 3. Subject must have a minimum daily insulin requirement (Total Daily Dose) of equal to or greater than 8 units/day 4. Subjects who are determined by the investigator to be psychologically sound in order to successfully participate in this study 5. Subject has been diagnosed with type 1 diabetes for at least three months **Note: Determination of classification for diabetes will be based on American Diabetes Association Clinical Practice Guidelines accounting for several patient characteristics such as: age of onset, patient's weight or BMI, history of diabetic ketoacidosis, history of therapy management, if available in the medical records.** 6. Subject must be on one of the following management therapies: a. Multiple daily injections defined by use of rapid analogue with meals and approved long acting analogue (e.g. detemir or glargine) with or without CGM b. Insulin pump therapy with or without CGM 7. Subject is willing to perform ≥ 4 finger stick blood glucose measurements daily

	8. Subject is willing to perform required study procedures 9. Subject is willing to wear the system continuously throughout the study for at least 80% of the time. 10. Subject is willing to upload data at least weekly from the study pump/meter, must have Internet access and a computer system that meets the requirements for uploading the study pump/meter for data collection 11. Subject must be willing to use the study glucose meter system (i.e. along with study meter strips). 12. If subject has celiac disease, it has been adequately treated as determined by the investigator 13. Subject with the diagnosis of 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, within 1 year of screening, will be included in the study with the consent of the Investigator 14. Subject is willing to take one of the following insulins and can financially afford to use either of the 2 insulin preparations throughout the course of the study (i.e. co-payments for insulin with insurance or able to pay full amount) a. Humalog® (insulin lispro injection) b. NovoLog® (insulin aspart) **Exclusion Criteria:** 1. Subject participated in any Closed Loop study in the past. 2. Subject is unable to tolerate tape adhesive in the area of sensor placement 3. Subject has any unresolved adverse skin condition in the area of sensor placement (e.g., psoriasis, rash, *Staphylococcus* infection) or area of infusion set placement 4. Women of child-bearing potential who have a positive pregnancy test at screening or plan to become pregnant during the course of the study 5. Subject is being treated for hyperthyroidism at time of screening 6. Subject has an abnormality (out of reference range) in thyroid-stimulating hormone (TSH) at time of screening visit. TSH is not required for subjects 2-13 years of age. 7. Subject has taken any oral, injectable, or IV glucocorticoids within 8 weeks from time of screening visit, or plans to take any oral, injectable, or IV

	glucocorticoids during the course of the study. 8. 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 9. Subject is currently abusing illicit drugs or marijuana 10. Subject is currently abusing prescription drugs 11. Subject is currently abusing alcohol 12. Subject is using pramlintide (Symlin), SGLT2 inhibitors, GLP agonists, biguanides, DPP-4 inhibitors or sulfonylureas at time of screening 13. Subject is using hydroxyurea at the time of screening or plans to use it during the study. 14. 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 15. Subject has a sickle cell disease, hemoglobinopathy; or has received red blood cell transfusion or erythropoietin within 3 months prior to time of screening 16. Subject plans to receive red blood cell transfusion or erythropoietin over the course of study participation 17. Subject diagnosed with current moderate to severe eating disorder such as anorexia or bulimia 18. Subject has been diagnosed with chronic kidney disease requiring dialysis or resulting in chronic anemia 19. Subjects who are currently being actively treated for cancer. 20. Subject who is designated as a research staff member for this study
Study Procedures and Assessments	Each subject's participation will be comprised of the following scheduled visits listed below over the course of approximately 8 months during the run-in period and study period, and for 6 months during the continuation period. • Telemedicine visits will be allowed to replace office visits if they do not involve collection of blood samples and device related procedures that require staff assistance **Early Withdrawal:**

Subjects who exit the study before the last scheduled study visit will complete all requirements that are listed for **Visit 13**, with the exception of c-peptide lab testing.

The schedule is planned as follows:

Screening and Run-In Period

All subjects will complete screening and the run-in period. This period must be completed in 60 days.

Visit 1: Screening Visit – Consent and Screening

Patients may re-screen once with Sponsor approval

Visit 2: Begin Run-in Period

- Placement of blinded sensor to be worn for 2 Weeks (each sensor is worn for 7 days)
- Study training, including instruction on procedures for wearing blinded CGM (i.e., insertion of sensor)

Visit 3: Begin MiniMed Pump (Except MDI Control)

- Occurs after 2-week blinded sensor wear, either immediately at the end of sensor wear or suggested to be within 14 days.
- The run-in period may be repeated a second time with Sponsor approval

Randomization

At **Visit 3** subjects (CSII, MDI or SAP Cohort) will be randomized into one of 2 arms:

- **HCL Arm**

  Note: Patients who are on SAP at baseline will start Medtronic CGM at this visit.

- **Control Arm**

  Note: Patients in SAP will receive and be trained on Medtronic CGM if they are randomized to the Control arm to ensure continuity with use of real time CGM.

Note: Subjects 2-6 years of age will automatically enter the HCL arm at the end

	of the run-in period To schedule **Visit 4**: • For subjects who have been on insulin pump therapy prior to screening for at least 3 months, Visit 4 should occur 3-30 days after Visit 3 • For subjects without pump therapy experience, the following should occur: • If randomized to the HCL arm, Visit 4 should occur 14-30 days after Visit 3 • If randomized to the MDI Control arm, Visit 4 should occur 1-7 days after Visit 3 The visit schedules for each of these Arms are as follows: **HCL Arm:** **Visit 4: Start CGM - Day 0** Start CGM with Guardian Sensor (3) (Note: SAP subjects will have already started CGM with Guardian Sensor (3) at Visit 3) **Visit 4A:** Follow up Telephone visit - 2-3 days after Visit 4 **Visit 5:** Follow up Office Visit - 7-21 days after Visit 4 Auto Mode is enabled and activated. Investigator sets carbohydrate to insulin ratios and active insulin time, and basal rates for open loop periods **Visit 6A:** Follow-up Telephone Visit (option of office visit) – 1 Day after Visit 5 **Visit 6B:** Follow-up Telephone Visit (option of office visit) - 2 Days after Visit 5 **Visit 6C:** Follow-up Telephone Visit - 5 Days (± 1 day) after Visit 5 **Visit 7A:** Follow up Office Visit - 14 Days (± 3 days) after Visit 5 **Visit 7B:** Follow-up Telephone Visit - 21 Days (± 3 days) after Visit 5 **Visit 7C:** Follow up Office Visit - 30 Days after Visit 5 (± 5 days) **Visit 7D:** Follow-up Telephone Visit - 45 Days (± 7 days) after Visit 5 **Visit 8:** Follow up Office Visit - 90 Days after Randomization (± 10 days) **Visit 9:** Follow up Office Visit - 180 Days after Randomization (± 10 days)

	○ End of Study Period and Start of Continuation period **Control Arm:** **a. CSII Cohort** **Visit 4:** Day 0: ○ Review pump settings **Visit 5:** Follow up Office Visit 7-21 days after Visit 4 ○ Insulin Pump adjustments **Visit 6A:** Follow up Telephone Visit - 1 Day after Visit 5 **Visit 6B:** Follow up Telephone Visit - 2 Days after Visit 5 **Visit 6C:** Follow up Telephone Visit - 14 Days (± 7 days) after Visit 5 **Visit 6D:** Follow up Office Visit - 30 Days after Visit 5 (± 7 days) **Visit 6E:** Follow-up Telephone Visit - 45 Days (± 7 days) after Visit 5 **Visit 7:** Follow up Office Visit - 76 days after Randomization (-14 days) ○ Blinded CGM Start ○ 14 days of sensor wear before 90 Day study period visit. Transmitter is not connected to study pump **Visit 8A:** Follow up Office Visit – 90 Days after Randomization (+14 days) ○ Blinded CGM Return **Visit 8B:** Follow up Office Visit - 166 days after Randomization (-14 days) ○ Blinded CGM Start ○ 14 days of sensor wear before 180 Day study period visit. Transmitter is not connected to study pump **Visit 9:** Follow up Office Visit – 180 Days after Randomization (+14 days) ○ Blinded CGM Return ○ End of Study Period and Start of Continuation period. ○ Start CGM with Guardian Sensor (3) **b. MDI Cohort** **Visit 4:** Day 0 **Visit 5:** Follow up Office Visit 7-21 days after Visit 4 **Visit 6A:** Follow up Telephone Visit - 1 Day after Visit 5

	Visit 6B: Follow up Telephone Visit - 2 Days after Visit 5 **Visit 6C:** Follow up Telephone Visit - 14 Days (± 7 days) after Visit 5 **Visit 6D:** Follow up Office Visit - 25 Days after Visit 5 (± 5 days) **Visit 6E:** Follow-up Telephone Visit - 35 Days (+1 days) after Visit 5 **Visit 7:** Follow up Office Visit - 76 days after Randomization (-2 days) ○ Blinded CGM Start ○ 14 days of sensor wear before 90 Day study period visit. **Visit 8A:** Follow up Office Visit – 90 Days after Randomization (+14 days) ○ Blinded CGM Return **Visit 8B:** Follow up Office Visit - 166 days after Randomization (-14 days) ○ Blinded CGM Start ○ 14 days of sensor wear before 180 Day study period visit. **Visit 9:** Follow up Office Visit – 180 Days after Randomization (+14 days) ○ Blinded CGM Return ○ End of Study Period and Start of Continuation period. ○ Start study pump **c. SAP Cohort:** **Visit 4:** Day 0 **Visit 4A:** Follow up Telephone visit - 2-3 days after Visit 4 **Visit 5:** Follow-up Office Visit - 7-21 days after Visit 4 ○ Pump and Sensor adjustments **Visit 6A:** Follow-up Telephone Visit (option of office visit) – 1 Day after Visit 5 **Visit 6B:** Follow-up Telephone Visit (option of office visit) - 2 Days after Visit 5 **Visit 6C:** Follow-up Telephone Visit 7 days after Visit 5 (±3 days) **Visit 7A:** Follow-up Telephone Visit - 14 Days after Visit 5 (± 3 days) **Visit 7B:** Follow-up Telephone Visit - 21 Days after Visit 5 (± 3 days) **Visit 7C:** Follow-up Office Visit - 30 Days after Visit 5 (± 5 days) **Visit 7D:** Follow-up Telephone Visit - 45 Days (± 7 days) after Visit 5 **Visit 8:** Follow-up Office Visit - 90 Days after Randomization (± 10 days)

	Visit 9: Follow-up Office Visit - 180 Days after Randomization (± 10 days) ○ End of Study Period and Start of Continuation period ○ Auto Mode is enabled and activated. **Continuation Period:** **HCL Arm:** **Visit 10:** Follow up Office Visit – 1 to 14 days after Visit 9 **Visit 11:** Follow up Office Visit – 15 to 30 days after Visit 9 **Visit 12:** Follow up Office Visit - 270 Days after Randomization (+/- 21 days) **Visit 13:** Follow up Office Visit - 365 Days after Randomization (+/- 21 days) ○ End of Continuation Period and End of Study **Control Arm** **a. CSII Cohort:** **Visit 10A:** Follow up Telephone visit - 2-3 days after sensor start **Visit 10B:** Follow up Office Visit 7-21 days after Visit 9 ○ Auto Mode is enabled and activated. **Visit 10C:** Follow up Telephone Visit (option of office visit) – 1 Day after Visit 10B **Visit 10D:** Follow up Telephone Visit (option of office visit) – 2 Days after Visit 10B **Visit 10E:** Follow-up Telephone Visit – 5 Days (± 1 day) after Visit 10B **Visit 11A:** Follow up Office Visit - 14 Days after Visit 10B (±3 days**)** **Visit 11B:** Follow-up Telephone Visit - 21 Days (±3 days**)** after Visit 10B **Visit 11C:** Follow up Office Visit - 30 Days after Visit 10B (±5 days) **Visit 11D:** Follow-up Telephone Visit - 45 Days (±7 days**)** after Visit 10B **Visit 12:** Follow up Office Visit - 270 Days after Randomization (+/- 21 days) **Visit 13:** Follow up Office Visit - 365 Days after Randomization (+/- 21 days) ○ End of Continuation Period and End of Study

	b. MDI Cohort: **Visit 9A:** Follow up Office Visit – 14-30 days after Visit 9 ○ Start CGM with Guardian Sensor (3) ○ This visit should occur between 14 and 30 days after pump start. **Visit 10A:** Follow up Telephone visit - 2-3 days after sensor start **Visit 10B:** Follow up Office Visit 7-21 days after Visit 9A ○ Patient has been wearing CGM for at least 4 days before enabling Auto Mode ○ Auto Mode is enabled and activated. **Visit 10C:** Follow up Telephone Visit (option of office visit) – 1 Day after Visit 10B **Visit 10D:** Follow up Telephone Visit (option of office visit) – 2 Days after Visit 10B **Visit 10E:** Follow-up Telephone Visit – 5 Days (± 1 day) after Visit 10B **Visit 11A:** Follow up Office Visit - 14 Days after Visit 10B (±3 days) **Visit 11B:** Follow-up Telephone Visit – 21 Days (± 3 day) after Visit 10B **Visit 11C:** Follow up Office Visit - 30 Days after Visit 10B (± 5 days) **Visit 11D:** Follow-up Telephone Visit – 45 Days (± 7 day) after Visit 10B **Visit 12:** Follow up Office Visit - 270 Days after Randomization (+/- 21 days) **Visit 13:** Follow up Office Visit - 365 Days after Randomization (+/- 21 days) ○ End of Continuation Period and End of Study **c. SAP Cohort:** **Visit 10A:** Follow up Telephone Visit (option of office visit) – 1 Day after Visit 9 **Visit 10B:** Follow up Telephone Visit (option of office visit) – 2 Days after Visit 9 **Visit 10C:** Follow-up Telephone Visit – 5 Days (± 1 day) after Visit 9

Visit 11A: Follow up Office Visit - 14 Days after Visit 9 (±3 days)

Visit 11B: Follow-up Telephone Visit – 21 Days (± 3 day) after Visit 9

Visit 11C: Follow up Office Visit - 30 Days after Visit 9 (±5 days)

Visit 11D: Follow-up Telephone Visit – 45 Days (± 5 day) after Visit 9

Visit 12: Follow up Office Visit - 270 Days after Randomization (+/- 21 days)

Visit 13: Follow up Office Visit - 365 Days after Randomization (+/- 21 days)

- End of Continuation Period and End of Study

Safety Success Criteria

In order to achieve safety success, the following study success criteria must be met for the HCL Arm by the end of the study:

Table 2. Safety Success Criteria

Adverse Event	Reference	Reference Rate > 25 years old	Reference Rate 15-25 years old	Reference Rate <15 years old	Study Success Criteria
DKA events per 100 patient years	STAR 3 Bergenstal et. al	SAP arm: 0.68 Control arm: 0	SAP arm: 2.7 Control arm: 3.6	SAP arm: 2.2 Control arm: 0	≤ 4 events per 100 patient years with HCL arm
	530 G Adult inhome study CEP 266 (MDT on file)	1.27	3.4	N/A	
	530 G Pediatric inhome study CEP 287 (MDT on file)	N/A	N/A	0	
	Type 1 exchange Weinstock et. al	4.8	N/A	N/A	
	Type 1 exchange Cengiz et. al	N/A	9.9	9.9	
Severe hypoglycemia per 100 patient years	STAR 3 Bergenstal et. al	SAP arm: 16.5 Control arm: 20.9	SAP arm: 5.4 Control arm: 3.9	SAP arm: 10.2 Control arm: 3.6	≤ 8 events per 100 patient years with HCL arm
	530 G Adult inhome study CEP 266 (MDT on file)	0.85	0	N/A	
	530 G Pediatric inhome study CEP 287	N/A	N/A	1.42	

	<table><tr><td></td><td>(MDT on file)</td><td></td><td></td><td></td><td></td></tr><tr><td></td><td>Type 1 exchange Weinstock et. al</td><td>11.8</td><td>N/A</td><td>N/A</td><td></td></tr><tr><td></td><td>Type 1 exchange Cengiz et. al</td><td>N/A</td><td>6.2</td><td>6.2</td><td></td></tr></table> Descriptive summary (i.e. not statistically powered) for severe hypoglycemia and DKA events rates will be performed between the HCL and control arms for each age group (< 15 years, 15-25 years, and > 25 years), as well as the overall event rates. Severe hypoglycemia and DKA event rates were taken from the following 1. Richard Bergenstal et.al: Effectiveness of Sensor-Augmented Insulin-Pump Therapy in Type 1Diabetes.New England Journal of Medicine, 2010; 363:311-20 2. Weinstock et. al: Severe hypoglycemia and diabetic ketoacidosis in adults with type 1 diabetes: results from the T1D Exchange clinic registry. J Clin Endocrinol Metab. 2013 Aug;98(8):3411-9. 3. Cengiz et. al: Severe hypoglycemia and diabetic ketoacidosis among youth with type 1 diabetes in the T1D Exchange clinic registry. Pediatr Diabetes. 2013 Sep;14(6):447-54. 4. MDT on file: Statistical Analysis Plan (SAP) for CEP304, 056-F286 **Safety monitoring/risk analysis details are outlined in Section 14.**
Study Stopping Rules for Entire Study	The study will be stopped if DMC determines that there are significant safety issues. (See DMC section.) Note: If it is decided to withdraw patients from participation in the study or if the study is stopped, subjects will be followed-up in accordance with standard practice.
Subject Stopping Rules	1. One episode of DKA or 2 episodes of severe hypoglycemia will result in withdrawal of subject from study, regardless of which arm or period they are in. 2. The first episode of Severe Hypoglycemia may lead to withdrawal, if it is secondary to subject non-compliance or other individual safety concerns: ○ Subject is not using the bolus wizard ○ Subject is not checking blood glucose using finger sticks ○ Subject is non-compliant with sensor wear ○ Subject is not following protocol procedures
Statistics	Effectiveness endpoints will be evaluated during the 6 month study period by individual Cohort (CSII, MDI or SAP), stratified by A1C;

	• Group 1: Baseline A1C > 8% • Group 2: Baseline A1C ≤ 8% The comparison of HCL **arm** vs. Control **arm** will be performed. For SG-based comparison between HCL vs Control analyses, two weeks of CGM data collected at 3 month visit and 6 month visits will be used. ***Primary Effectiveness Endpoints – Co-Primary Endpoints:*** • Group 1: Baseline A1C > 8%: Change in A1C (ΔA1C) The primary effectiveness endpoint for the baseline A1C > 8% is the change in A1C from baseline to the end of the six-month treatment period, defined as A1C measured at the six-month treatment visit minus A1C measured at the randomization visit. The goal is to show superiority of the HCL Arm compared to the Control Arm in reducing A1C from baseline to end of six-month treatment period. • Group 2: Baseline A1C ≤ 8%: Time in Hypoglycemic Range The primary effectiveness endpoint for the baseline A1C ≤ 8% is the time with sensor glucose (SG) below 70 mg/dL (3.9 mmol/L) during the six-month study period. The goal is to show superiority of the HCL Arm compared to the Control Arm in reducing time in hypoglycemic range. : ***Key Secondary Effectiveness Endpoints*** • Group 1: Baseline A1C > 8%: Time in Hypoglycemic Range The key secondary effectiveness endpoint for the baseline A1C > 8% is the time with SG below 70mg/dL (3.9 mmol/L) during the six-month study period. The goal is to show non-inferiority of the HCL Arm compared to the Control Arm in reducing time in hypoglycemic range. • Group 2: Baseline A1C ≤ 8%: Change in A1C (ΔA1C) The key secondary effectiveness endpoint for the baseline A1C ≤ 8% is the change in A1C from baseline to end of six-month treatment period, defined as A1C measured at the six-month treatment visit minus A1C measured at the randomization visit. The goal is to show non-inferiority of the HCL Arm compared to the Control Arm in reducing A1C from baseline to end of six-month treatment period.

	Other Secondary Effectiveness Endpoints The other secondary effectiveness endpoints are hierarchically ordered and will be evaluated in the fixed sequence from endpoint 1 to 5 during the first 6 months of study phase. • Group 1 + Group 2: Time in Hypoglycemic Range during Night The first secondary effectiveness endpoint is the time with SG below 70 mg/dL (3.9mmol/L) during Night. The goal is to show superiority of the HCL Arm compared to the Control Arm reducing time in hypoglycemic range during night. • Group 1 + Group 2: Time in Hypoglycemic Range during Day and Night The endpoint of time in hypoglycemic range below 70 mg/dL (3.9mmol/L) will be evaluated for superiority in the combined Groups. The goal is to show superiority of the HCL Arm compared to the Control Arm in reducing time in hypoglycemic range. • Group 1 + Group 2: Time in Target Range 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) during Night The endpoint of time in target range measures the time with SG in target range 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) during Night. The goal is to show superiority of the HCL Arm compared to the Control Arm in improving the time in target range • Group 1 + Group 2: Time in Target Range 70mg/dL (3.9mmol/L)– 180 mg/dL (10.0mmol/L) during Day and Night The endpoint of time in target range measures the time with SG in target range 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) during Day and Night. The goal is to show superiority of the HCL Arm compared to the Control Arm in improving the time in target range • Group 1 + Group 2: Change in A1C The endpoint of change in A1C will be evaluated for superiority in the combined Groups. The goal is to show superiority of the HCL Arm compared to the Control Arm in reducing A1C from baseline to end of six-month treatment period.

Primary Safety Endpoints:

The primary safety endpoint is the event rate of severe hypoglycemia and DKA from both Groups (1 & 2) during the first 6 months of study phase and second 6 months of continuation phase. The descriptive summary statistics will be presented by number of event and event rate (100 patient years) for severe hypoglycemia and DKA **separately**.

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

- Diabetic ketoacidosis (DKA)
- Severe hypoglycemia
- Severe hyperglycemia
- Serious adverse events (SAEs)
- Unanticipated adverse device effects (UADEs)

[redacted]

[redacted]

4. Introduction

4.1 Background

Provisional studies employing closed loop technology have shown a reduction in both hypoglycemia and hyperglycemia, as well as glycemic variability. Previous studies have evaluated prototype versions of the Medtronic closed-loop insulin delivery systems in pediatric patients, as well as adolescents and young adults. Researchers at the Yale University School of Medicine studied the performance of both a hybrid closed-loop algorithm and a fully closed loop algorithm using the Medtronic MMT-715 insulin pump, the Medtronic Sof-sensor and MiniLink transmitter and a control algorithm running on a laptop computer [Weinzimer et al, 2008]. Seventeen subjects between the ages of 13 and 20 years participated in the study with eight subjects undergoing testing with a fully closed-loop algorithm, and the remaining nine subjects being evaluated using the hybrid closed-loop algorithm. This study demonstrated that a fully closed loop artificial pancreas using an external glucose sensor is feasible and effective in adolescents with type 1 diabetes.

The Type 1 Diabetes TrialNet Study Groups used this same system to evaluate inpatient hybrid closed-loop control (HCL) initiated shortly after the diagnosis of type 1 diabetes [Diabetes Research in Children Network Study Group, 2013]. Forty eight subjects between the ages of 7.8 and 37.7 years participated in the intensive treatment group and received inpatient HCL followed by outpatient sensor augmented pump therapy. Forty six of the 48 subjects were less than 18 years old. The study found that inpatient HCL safely initiated soon after the diagnosis of type 1 diabetes resulted in the rapid decrease in blood glucose levels within 24 hours of initiation and that while using HCL, about 80% of the glucose levels were in the target range of 71mg/dL -180 mg/dL, with minimal hypoglycemia.

Medtronic has completed 7 phases in the HCL Feasibility Study (CEP 273) with a total of 71 subjects enrolled. In this Feasibility study, the closed loop system was stressed by artificially inducing sensor error as well as inducing physiologic stress such as exercise and administration of meals without bolus. The Feasibility study provided data which was used to develop the device algorithm that is being tested in this study.

A pivotal trial with 120 subjects was completed in February 2016. This was a single arm study evaluating the safety of the MiniMed 670G HCL system in subjects 14-75 years of age, for 3 months in the home setting. The pediatric pivotal study for the HCL system was conducted as an at-home, multi-center study, which enrolled 162 participants ages 2-13 years of age. Patients were recruited at 11 centers (10 in the United States, 1 in Israel). The study was identical in design to the young adult/adult pivotal study.

Study results in the pediatric study mirrored data from the pivotal trial of the system in adults and adolescents (14 and above), showing patients spent more time in euglycemic range, experienced less glycemic variability,

had less exposure to hypoglycemia and hyperglycemia and significantly reduced HbA1c compared to baseline data where they used sensor-augmented pumps without SmartGuard™ automation activated. No episodes of severe hypoglycemia or diabetic ketoacidosis and no serious device-related adverse events were reported.

The MiniMed 770G Insulin Pump is equivalent in function to the MiniMed 670G insulin pump, with the exception of telemetry. While the MiniMed 670G insulin pump communicates on the basis of Tel-D (telemetry-diabetes) radio frequency (RF) technology, the MiniMed 770G pump contains BLE (Bluetooth Low Energy) RF communication, which allows for connectivity to patients' smartphones, CGM transmitter and an BLE RF enabled blood glucose meter. For detailed information on the MiniMed 770G pump, see Section 7.5.

4.2 Purpose

The purpose of this study is to evaluate the safety and effectiveness of the Hybrid Closed Loop system (HCL) in adult and pediatric patients with type 1 diabetes in the home setting. A diverse population of patients 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 glycosylated hemoglobin (A1C). The following cohorts will be enrolled:

1) Cohort 1: Continuous Subcutaneous Insulin Infusion (CSII) or HCL;

2) Cohort 2: Multiple Daily Injections (MDI) or HCL and

3) Cohort 3: Sensor-Augmented Pump therapy (SAP) or HCL.

5. Objectives and/or Endpoints

5.1 Objectives

5.1.1 Primary Objective(s)

The purpose of this study is to evaluate the safety and effectiveness of the Hybrid Closed Loop system (HCL) in adult and pediatric patients with type 1 diabetes in the home setting.

5.2 Endpoints – General Considerations

All endpoints are hierarchically ordered and will be evaluated in the fixed sequence from primary endpoints to

secondary endpoints. Unless the primary endpoints hypotheses are rejected, secondary endpoints will not be tested.

Effectiveness endpoints will be evaluated during the 6 month study period by individual Cohort (CSII, MDI or SAP), stratified by A1C;

- Group 1: Baseline A1C > 8%
- Group 2: Baseline A1C ≤ 8%

The comparison of HCL **arm** vs. Control **arm** will be performed. For SG-based comparison between HCL vs Control analyses, two weeks of CGM data collected at 3 month visit and 6 month visits will be used.

5.2.1 Co-Primary Effectiveness Endpoints

The primary effectiveness endpoints consist of one-primary endpoint for each group.

Group 1: Baseline A1C > 8%: Change in A1C (ΔA1C)

- The primary effectiveness endpoints for the baseline A1C > 8% group is change in A1C from baseline to end of six-month treatment period, defined as A1C measured at the six-month treatment visit minus A1C measured at the randomization visit. The goal is to show superiority of the HCL Arm compared to the Control Arm in reducing A1C from baseline to end of six-month treatment period.
- The hypothesis is mathematically expressed as:

  H0: μ(HCL) ≥ μ(Control)

  Ha: μ(HCL) < μ(Control)

  where μ(HCL) is the mean of change in A1C (%) with the HCL Arm, μ(Control) is the mean of change in A1C (%) with the Control Arm.

Group 2: Baseline A1C ≤ 8%: Time in Hypoglycemic Range

- The primary effectiveness endpoint for the baseline A1C ≤ 8% group is the time with SG below 70 mg/dL (3.9mmol/L) during the six-month study period, defined as percentage of SG below 70 mg/dL (3.9mmol/L) out of total number of available SG readings. The goal is to show superiority of the HCL Arm compared to the Control Arm in reducing daily time in hypoglycemic range.
- The hypothesis is mathematically expressed as:

H0: μ(HCL) ≥ μ(Control)

Ha: μ(HCL) < μ(Control)

where μ(HCL) is the subject mean of time with SG below 70 mg/dL (3.9 mmol/L) in the HCL Arm, μ(Control) is the subject mean of time with SG below 70 mg/dL (3.9 mmol/L) in Control Arm

5.2.2 Secondary Effectiveness Endpoints

Key Secondary Effectiveness Endpoints

Group 1: Baseline A1C > 8%: Time in Hypoglycemic Range

- The key secondary effectiveness endpoint for the baseline A1C > 8% group is the time with SG below 70 mg/dL (3.9mmol/L) during the six-month study period, defined as percentage of SG below 70 mg/dL (3.9mmol/L) out of total number of available SG readings. The goal is to show non-inferiority (with a non-inferiority margin of 2%) of the HCL Arm compared to the Control Arm.
- The hypothesis of non-inferiority is mathematically expressed as:

  H0: μ(HCL) ≥ μ(Control) + 2%

  Ha: μ(HCL) < μ(Control) + 2%

  where μ(HCL) is the subject mean of time with SG below 70 mg/dL (3.9 mmol/L) in the HCL Arm, μ(Control) is the subject mean of time with SG below 70 mg/dL (3.9 mmol/L) in the Control Arm

Group 2: Baseline A1C ≤ 8%: Change in A1C (ΔA1C)

- The key secondary effectiveness endpoint for the baseline A1C ≤ 8% group is change in A1C from baseline to end of six-month treatment period, defined as A1C measured at the six-month treatment visit minus A1C measured at the randomization visit. The goal is to show non-inferiority (with a non-inferiority margin of 0.4%) of the HCL Arm compared to the Control Arm in reducing A1C from baseline to end of six-month treatment period.
- The hypothesis of non-inferiority is mathematically expressed as:
- H0: μ(HCL) ≥ μ(Control) + 0.4%
- Ha: μ(HCL) < μ(Control) + 0.4%
- where μ(HCL) is the mean of change in A1C (%) with the HCL Arm, μ(Control) is the mean of change in A1C (%) with the Control Arm.

Rest of Secondary Effectiveness Endpoints

1. Group 1 + Group 2: Time in Hypoglycemic Range during Night

The secondary effectiveness endpoint is the time with SG below 70 mg/dL (3.9mmol/L) during Night. The goal is to show superiority of the HCL Arm compared to the Control Arm reducing time in hypoglycemic range during night . The hypothesis is mathematically expressed as:

H0: μ(HCL) ≥ μ(Control)

Ha: μ(HCL) < μ(Control)

where μ(HCL) is the subject mean of time with SG below 70 mg/dL (3.9 mmol/L) in the HCL Arm during night, μ(Control) is the subject mean of time with SG below 70 mg/dL (3.9 mmol/L) in the Control Arm during the night.

2. Group 1 + Group 2: Time in Hypoglycemic Range during Day and Night

The endpoint of time in hypoglycemic range below 70 mg/dL (3.9mmol/L) will be evaluated for superiority in the combined Groups during day and night. The goal is to show superiority of the HCL Arm compared to the Control Arm in reducing time in hypoglycemic range. The hypothesis is mathematically expressed as:

H0: μ(HCL) ≥ μ(Control)

Ha: μ(HCL) < μ(Control)

where μ(HCL) is the subject mean of time with SG below 70 mg/dL (3.9 mmol/L) in the HCL Arm, μ(Control) is the subject mean of time with SG below 70 mg/dL (3.9 mmol/L) in the Control Arm.

3. Group 1 + Group 2: Time in Target Range 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) during Night

The endpoint of time in target range measures the time with SG in target range 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) during Night. The goal is to show superiority of the HCL Arm compared to the Control Arm in improving the time in target range. The hypothesis is mathematically expressed as:

H0: μ(HCL) ≤ μ(Control)

Ha: μ(HCL) > μ(Control)

where μ(HCL) is the subject mean of time with SG between 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) range in the HCL Arm during Night, μ(Control) is the subject mean daily time with SG between 70mg/dL

(3.9mmol/L) – 180 mg/dL (10.0mmol/L) range in the Control Arm.

4. Group 1 + Group 2: Time in Target Range 70mg/dL (3.9mmol/L)– 180 mg/dL (10.0mmol/L) during Day and Night

The endpoint of time in target range measures the time with SG in target range 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) during Day and Night. The goal is to show superiority of the HCL Arm compared to the Combined Control group in improving the time in target range. The hypothesis is mathematically expressed as:

$H0: \mu(HCL) \leq \mu(Controls)$

$Ha: \mu(HCL) > \mu(Controls)$

where μ(HCL) is the subject mean of time with SG between 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) range in the HCL Arm during Day and Night, μ(Control) is the subject mean daily time with SG between 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) range in the Control Arm

5. Group 1 + Group 2: Change in A1C

The endpoint of change in A1C will be evaluated for superiority in the combined groups. The goal is to show superiority of the HCL Arm compared to the Control Arm in reducing A1C from baseline to end of six-month treatment period. The hypothesis is mathematically expressed as:

$H0: \mu(HCL) \geq \mu(Control)$

$Ha: \mu(HCL) < \mu(Control)$

where μ(HCL) is the mean of change in A1C (%) with the HCL Arm, μ(Control) is the mean of change in A1C (%) with the Control Arm.

5.2.3 Safety Endpoint

The primary safety endpoint is the event rate of severe hypoglycemia and DKA from both Groups (1 & 2) during the first 6 months of study phase and second 6 months of continuation phase. The descriptive summary statistics will be presented by number of event and event rate (100 patient years) for severe hypoglycemia and DKA **separately**.

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

- Diabetic ketoacidosis (DKA)
- Severe hypoglycemia
- Severe hyperglycemia

- Serious adverse events (SAEs)
- Unanticipated adverse device effects (UADEs)

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6. Study Design

This is a 6 month, multi-center, randomized, parallel, adaptive study in type 1 diabetes with a 6 month continuation period. Up to 1500 subjects will be enrolled in order to have 1000 subjects who enter the study period. To date, 959 subjects have enrolled. Up to 70 investigational Centers in the US, Europe, Canada, Australia and New Zealand will be enrolled. For additional information on investigational sites and investigators, refer to information listed on public databases (e.g., clinicaltrials.gov).

The study will have three periods per Cohort:

1. Run-in Period: The run-in period can be up to 60 days.

   The run-in period will also be used for CGM data collection for approximately two weeks. Two consecutive 7-day sensors will be worn. If a sensor falls out, a replacement sensor should make up the difference for a total of 14 days of sensor wear (i.e. Monday Day 1 through next Sunday Day 14)

   > *For example: If a sensor falls out on Day 4, a replacement sensor should be inserted. Once that replacement sensor has been worn for 7 days, a new sensor should then be inserted and worn for 3 days so that a total of 14 days of sensor wear is completed.*

   All patients will wear blinded CGM. Subjects will be expected to demonstrate sensor wear for approximately 14 days total between the two 7-day sensor wears (plus replacement sensor if needed). Subjects should be instructed to make 4-6 BG measurements per day. Sponsor may request a repeat of blinded CGM. Repeat of blinded CGM may occur if the following are not met:

   - A minimum of 12 days of sensor wear have been self-reported to research staff
   - A minimum of 2 blood glucose checks/day during the blinded CGM wear are confirmed on the subject's study BG meter.

   If these requirements are not met then patient should repeat the entire 2 week blinded CGM data collection unless sponsor has approved that there was adequate data collection. An additional 21 days may

be added to the run in visit window schedule if blinded CGM data collection needs to be repeated. Additional visits may also be allowed if needed.

2. Study Period: There will be a 6 month randomized study period with two arms: HCL system and Control. CSII and MDI control groups will undergo two blinded CGM collections during the study period.

   The first blinded CGM data collection during the study period will occur before the month three (see visit schedule) for approximately two weeks. Two consecutive 7-day sensors will be worn. If a sensor falls out, a replacement sensor should make up the difference for a total of 14 days of sensor wear. (i.e. Monday Day 1 through next Sunday Day 14)

   > *For example: If a sensor falls out on Day 4, a replacement sensor should be inserted. Once that replacement sensor has been worn for 7days, a new sensor should then be inserted and worn for 3 days so that a total of 14 days of sensor wear is completed.*

   All patients will wear blinded CGM. Subjects will be expected to demonstrate sensor wear for approximately 14 days total between the two 7-day sensor wears (plus replacement sensor if needed). Subjects should be instructed to make 4-6 BG measurements per day. The following should have occurred:

   - A minimum of 12 days of sensor wear have been self-reported to research staff
   - A minimum of 2 blood glucose checks/day during the blinded CGM wear are confirmed on the subject's study BG meter.

   If the above requirements are not met then patient should repeat the entire 2 week blinded CGM data collection unless the sponsor approves that there was adequate data collection. Additional visits may also be allowed if needed. No changes to the remaining visit schedule are needed.

   The second blinded CGM data collection during the study period will occur before the month six (see visit schedule) for approximately two weeks. Two consecutive 7-day sensors will be worn. If a sensor falls out, a replacement sensor should make up the difference for a total of 14 days of sensor wear. (i.e. Monday Day 1 through next Sunday Day 14).

   > *For example: If a sensor falls out on Day 4, a replacement sensor should be inserted. Once that replacement sensor has been worn for 7 days, a new sensor should then be inserted and worn for 3 days so that a total of 14 days of sensor wear is completed.*

   All patients will wear blinded CGM. Subjects will be expected to demonstrate sensor wear for approximately 14 days total between the two 7-day sensor wears (plus replacement sensor if needed). Subjects should be instructed to make 4-6 BG measurements per day.

3. Continuation Period: There will be a 6 month continuation period during which time all subjects will use the HCL system.

Enrollment Cohorts According to Treatment

At Enrollment, subjects will be identified according to the type of treatment regimen they are currently on. Treatment regimen is defined as follows:

- Cohort 1: CSII – subjects using pump (Medtronic or other pump systems) for at least 3 months at time of screening without concurrent use of real time CGM in the last 3 months. (Self-report acceptable.) Please note that alternatives to SMBG such as Freestyle Libre are not considered real time CGM and subjects who are using Freestyle Libre at time of Screening will be allowed to enroll in the study. During the study, however, subjects will not be allowed to use Freestyle Libre.
- Cohort 2: Multiple Daily Injections (MDI) - Subjects using MDI with or without concurrent use of CGM for at least 3 months prior to Screening. (Self report is acceptable.)
- Cohort 3: Sensor Augmented Pump (SAP) – subjects using pump for at least 3 months at time of screening with real time CGM use (Medtronic or other CGM systems) approximately 20% of the time. (Self report acceptable.) Subjects will use the Medtronic CGM starting at Visit 3, but they may use their own CGM until then. Sensor insertion placement will be according to User guide.

Staged enrollment for Subjects 2-6 Years of Age:

- Subjects 2-6 years of age will be allowed to enroll in the post approval study, once DMC has reviewed data from 10 subjects age 2-4 years who have completed participation in the study period of the CEP302 study and has given approval to enroll

In the US and Canada, subjects 2-80 years of age will be allowed to transition from the 670G system to the 770G system.

The Run-In Period: Following successful screening, all subjects (CSII, MDI or SAP) will enter the run-in period and collect blinded CGM data while using their own diabetes therapy. Blinded CGM consists of using a Guardian Sensor (3) connected to a Guardian Link (3) transmitter. A total period of 2 weeks of CGM data will be collected.

Cohort 1: CSII

The Study Period: After completion of the run-in period, subjects with CSII therapy (minimum N= 280) will be randomized and placed into one of 2 different arms during the study period:

1. The HCL Arm will use the MiniMed system (i.e., using Auto Mode) for 6 months during the study

period. There will be N=140 for the HCL arm.

2. The Control Arm will use the MiniMed Pump without CGM.
    a) Blinded CGM (Guardian Link (3) Transmitter and Guardian Sensor (3)) will only be worn at baseline, 3 months, and 6 months (two weeks of sensors use). There will be N=140.

Cohort 2: MDI

The Study Period: After completion of the run-in period, subjects with MDI therapy (minimum of N=280) will be randomized and placed into one of 2 different arms during the study period:

1. The HCL Arm will use the MiniMed system (i.e., using Auto Mode) for 6 months during the study period. There will be N=140 for the HCL arm.
2. The Control Arm will be using their current insulin therapy (MDI)

    The Multiple Daily Injection (MDI) subjects will remain on MDI therapy with subjects using their own insulin for 6 months during the study period. The Sponsor will not provide insulin. Blinded CGM (Guardian Link (3) Transmitter and Guardian Sensor (3)) will only be worn at baseline, 3 months, and 6 months (two weeks of sensors use). There will be N=140.

    MDI subjects who are currently using CGM, i.e. Dexcom or Medtronic Guardian Connect or who are currently using a SMBG alternative, i.e. Libre, will be allowed to enroll in the study and continue using their own device. There will be N=100

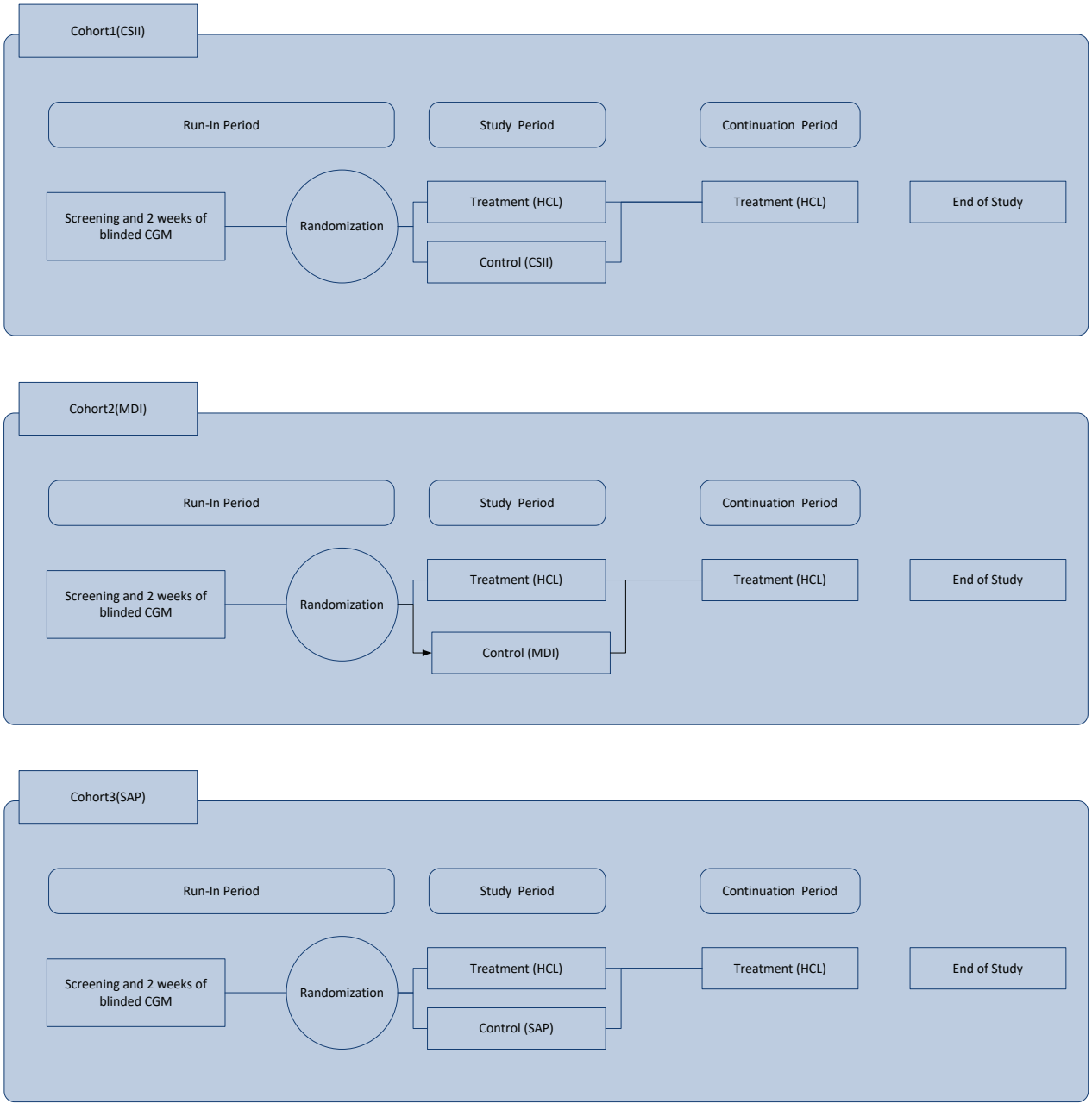
Cohort 3: SAP

The Study Period: After completion of the run-in period, subjects with SAP therapy (minimum N= 280) will be randomized and placed into one of 2 different arms during the study period. Sensor insertion placement will be according to User guide:

1. The HCL Arm will use the MiniMed system (i.e., using Auto Mode) for 6 months during the study period. There will be N=140 for the HCL arm.
2. The Control Arm will be using SAP therapy using the MiniMed System.
    a) The Sensor Augmented Pump (SAP) subjects will use the MiniMed System (SAP without Low Management Suspend on Low, Low Management Suspend before low or Auto Mode) with Real Time CGM for the 6 month study period. There will be N=140.

The Continuation Period: All subjects above will enter the continuation period for 6 months using the MiniMed system with Auto Mode on.

Figure 2. Study Design



Subjects may be re-tested as per sponsor discretion.

Per Cohort (CSII, MDI, or SAP), here is the numbers of subjects expected to enroll:

- A1C at time of screening:
  - N = 70 A1C > 8% for HCL Arm
  - N = 70 A1C ≤ 8% for HCL Arm
  - N = 70 A1C > 8% for Control Arm
  - N = 70 A1C ≤ 8% for Control Arm

- Age at time of screening:

N=Minimum number of eligible subjects for each age group within each treatment cohort			**N= Minimum number of eligible Subjects for each age group and cohort**	**N=Minimum number of eligible subjects for each age group for study**
Age Group	Cohort	N	N	N
2-6 years	CSII SAP MDI	No Minimum	No minimum	N= 120
7 -13 years	CSII SAP MDI	No Minimum	No minimum	N= 180
14-21 years	CSII SAP MDI	N= 45	N=45	N=135
22-64 years	CSII SAP MDI	N= 120	N=120	N=360
65-80 years	CSII SAP MDI	No Minimum	No minimum	N=150

Table 3. Randomization

Treatment at Baseline	Randomization Options	Continuation
CSII	CSII	HCL
	HCL	
MDI	MDI	HCL
	HCL	
SAP	SAP	HCL
	HCL	

Note: Subjects 2-6 years of age will automatically enter the HCL arm at the end of the run-in period

Table 4. Site Enrollment (approximate schedule from Protocol approval)

Month Enrollment Timelines	Actual Site Enrollment (per month)	Site Enrollment Timelines
Month 1-48	April 2017 to March 2021	37
Month 49-52	April 2021 to July 2021	45

Table 5. Subject Enrollment at 2-3 month intervals (approximate schedule from first enrollment)

Month Enrollment Timelines	Actual Month Intervals	Subject Enrollment Timelines
Month 1-43	May 2017 to December 2020	930
Month 44 -50	January 2021 to June 2021	1080

Month Enrollment Timelines	Actual Month Intervals	Subject Enrollment Timelines
Month 51-56	July 2021 to December 2021	1120*

**1120 subject enrollment to target 1000 subjects who enter the study period*

Table 6. Milestone Table

Major Milestone	Estimated time required to achieve milestone (approximate schedule from study protocol approval)
Protocol Approval / Device Launch	
First site enrolled	30 days
First subject enrolled	70 days
First subject completed	15 months
Last site enrolled	52 months
Last subject enrolled	55 months – 57 months (target 54 months)
Last subject completed	69 months (or sooner based on last subject enrolled)
Final report submitted	75 months

6.1 Duration

The study is anticipated to last no longer than 6.5 years from investigational center initiation to completion of all data entry and monitoring procedures. The study will target 54 months to complete subject enrollment. Subjects can expect to participate for approximately 7-8 months during the run-in period and study period, with a 6 month continuation period.

6.2 Rationale

As remote monitoring may play an important role in the pediatric population, we have added this capability with the MiniMed 770G system and are introducing this approved device to enhance subject compliance. In the US and Canada subjects 2-80 years of age will be allowed to transition from the 670G system to the 770G system. In Australia, the MiniMed 770G system is investigational for 2-6 years of age.

7. Product Description

7.1 General

None of the devices used in this study contain tissues of animal origin, nor derivatives rendered non-viable. The devices do not incorporate, as an integral part, a substance which if used separately, may be considered to be a medicinal product as defined in Annex I point 7.4, 1st paragraph of Directive 93/42/EEC.

The sensor contains human serum albumin. The human serum albumin serves to protect the enzyme in the chemistry stack from subsequent processes and layers. Human serum albumin is immobilized via crosslinking and is not liable to act on the human body.

7.2 Intended Population

A diverse population of patients 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 glycosylated hemoglobin (A1C). They will be enrolled in the study regardless of their prior diabetes regimen, including using Multiple Daily Injections (MDI), Continuous Subcutaneous Insulin Infusion (CSII) or Sensor-Augmented Pump therapy (SAP).

7.3 Names and Intended Use of Devices

Table 7. MiniMed 670G System Components*

Device name	MDT Model number/ part number	US	Canada	Europe
MiniMed 670G Pump (closed loop algorithm)	MMT-1780 (US) MMT-1781 (pump) and MMT-1762KCN (kit) (Canada) MMT-1781 and MMT-1782 (Europe)	Age 7-80: Non-Investigational Age 2-6: Investigational	Licensed (age ≥7 years)	CE marked (age ≥7 years)
Guardian Link (3) Transmitter	MMT-7811	Age 7-80: Non-Investigational Age 2-6: Investigational	Licensed (age ≥7 years)	CE marked
Transmitter Charger	MMT-7715	Non-Investigational	Licensed	CE marked
Tester	MMT-7736L	Non-Investigational	Licensed	CE marked*
Guardian Sensor (3)	MMT-7020	Age 7-80: Non-Investigational Age 2-6: Investigational	Licensed	CE marked
One-Press Serter	MMT-7512	Non-Investigational	Exempt	CE marked
CareLink USB 2.4 GHz	(MMT- 7306)	Non-Investigational	Licensed	CE marked
Medtronic CareLink® Personal Therapy Management Software	MMT-7333	Exempt	Exempt**	CE marked

Device name	MDT Model number/ part number	US	Canada	Europe
Paradigm Reservoir	MMT-332A	Cleared	Licensed	CE marked
MiniMed Silhouette Infusion Set	e.g. MMT-368	Cleared	Licensed	CE marked
MiniMed Sil Serter	MMT-385	Cleared	Exempt	CE marked
MiniMed Quick Set Infusion Set	e.g. MMT-386	Cleared	Licensed	CE marked
MiniMed Mio Infusion Set	e.g. MMT-923	Cleared	Licensed	CE marked
MiniMed Sure-T Infusion Set	e.g. MMT-864	Cleared	Licensed	CE marked
MiniMed Quick-Serter	MMT-305	Cleared	Exempt	CE marked
Ketone Meter		Cleared	Licensed	CE marked
Contour Next Link 2.4 by Ascencia Meter	MMT-1152 or MMT-1352 (US) MMT-1151 (Canada) MMT-1151 and MMT-1152 (Europe)	Age 7-80: Non-Investigational Age 2-6: Investigational	Licensed	CE marked

* For detailed information on the characteristics materials, see device instructions for use.

** Determined to be a Medical Device Data System by the Medical Device Directorate and as such not subject to the Canadian Medical Device Regulations.

Table 8 MiniMed 770G System Components*

Device name	MDT Model number/part number	US	Canada	Australia	New Zealand
MiniMed 770G Pump (closed loop algorithm)	MMT-1890 (US Kit) MMT-1880 (US Pump) MMT-1881 (Canada Pump) MMT-1891KCN, MMT-	Age 2-80: Non-Investigational	Licensed (age 2-80 years)	Age 2-6: Investigational Age 7-80: Non-Investigational	Age 2-80: Non-Investigational

Device name	MDT Model number/part number	US	Canada	Australia	New Zealand
	1891CRP (Canada Kit)				
Guardian Link (3) Transmitter	MMT-7911 (US GST5C) MMT-7910 (US GST5C Kit) MMT-7911 (Canada Transmitter) MMT-7910W4, MMT-7911WW (Canada Kit)	Age 2-80: Non-Investigational	Licensed (age 2-80 years)	Age 2-6: Investigational Age 7-80: Non-Investigational	Age 2-80: Non-Investigational
Accu-Chek Guide Link Meter Blood Glucose Monitoring System	08116083022 (US) 08109222001 (Canada)	Age 2-80: Non-Investigational	Licensed (age 2-80 years)	Age 2-6: Investigational Age 7-80: Non-Investigational	Age 2-80: Non-Investigational
Transmitter Charger	MMT-7715	Non-Investigational	Licensed	Age 2-6: Investigational Age 7-80: Non-Investigational	Age 2-80: Non-Investigational
Tester	MMT-7736L	Non-Investigational	Licensed	Age 2-6: Investigational Age 7-80: Non-Investigational	Age 2-80: Non-Investigational
Guardian Sensor (3)	MMT-7020	Non-Investigational	Licensed	Age 2-6: Investigational Age 7-80: Non-Investigational	Age 2-80: Non-Investigational
One-Press Serter	MMT-7512	Non-Investigational	Exempt	Age 2-6: Investigational Age 7-80: Non-Investigational	Age 2-80: Non-Investigational
Blue adapter	ACC-1003911	Not a medical device	N/A	N/A	N/A
Medtronic Mobile Application	MT-6104 (iOS) MMT-6103 (Android)	Class II Exempt	Exempt**	Age 2-6: Investigational Age 7-80: Non-Investigational	Age 2-80: Non-Investigational

Device name	MDT Model number/part number	US	Canada	Australia	New Zealand
CareLink Connect Application	MMT-6114 (iOS) MMT-6113 (Android)	Class II Exempt	Exempt**	Age 2-6: Investigational Age 7-80: Non-Investigational	Age 2-80: Non-Investigational
Medtronic CareLink® Clinical Software	MMT-7338	Class I Exempt	Exempt**	Age 2-6: Investigational Age 7-80: Non-Investigational	Age 2-80: Non-Investigational
Paradigm Reservoir	MMT-332A	Cleared	Licensed	Age 2-6: Investigational Age 7-80: Non-Investigational	Age 2-80: Non-Investigational
MiniMed Silhouette Infusion Set	MMT-368	Cleared	Licensed	Age 2-6: Investigational Age 7-80: Non-Investigational	Age 2-80: Non-Investigational
MiniMed Sil Serter	MMT-385	Cleared	Exempt	Age 2-6: Investigational Age 7-80: Non-Investigational	Age 2-80: Non-Investigational
MiniMed Quick Set Infusion Set	eMMT-386	Cleared	Licensed	Age 2-6: Investigational Age 7-80: Non-Investigational	Age 2-80: Non-Investigational
MiniMed Mio Infusion Set	MMT-923	Cleared	Licensed	Age 2-6: Investigational Age 7-80: Non-Investigational	Age 2-80: Non-Investigational
MiniMed Sure-T Infusion Set	MMT-864	Cleared	Licensed	Age 2-6: Investigational Age 7-80: Non-Investigational	Age 2-80: Non-Investigational
MiniMed Quick-Serter	MMT-305	Cleared	Exempt	Age 2-6: Investigational Age 7-80: Non-Investigational	Age 2-80: Non-Investigational

Device name	MDT Model number/part number	US	Canada	Australia	New Zealand
Ketone Meter	HMS – Ketone Meter	Cleared	Licensed	Age 2-6: Investigational Age 7-80: Non-Investigational	Age 2-80: Non-Investigational

* For detailed information on the characteristics materials, see device instructions for use.

** Determined to be a Medical Device Data System by the Medical Device Directorate and as such not subject to the Canadian Medical Device Regulations.

7.4 MiniMed 670G Insulin Pump

The MiniMed 670G Insulin Pump 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 continuous glucose values, storing this data so that it can be retrospectively analyzed to track patterns and improve diabetes management. These features are similar to the commercially available Medtronic sensor-enabled system (e.g. MiniMed 530G System (P120010) in the US, MiniMed 640G and Veo System OUS, which has the threshold suspend feature).

The MiniMed 670G Insulin Pump also includes the closed loop algorithm as part of the SmartGuard™ collection of features that may be enabled by the user. SmartGuard is comprised of Manual Mode Low Management, which includes the suspend on low feature (suspends insulin delivery when a pre-set low SG threshold is reached), the suspend before low feature (enables insulin to suspend 30 minutes before a pre-set low SG threshold is reached) and 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 without the SmartGuard features.

When Auto Mode is enabled on the MiniMed 670G insulin pump, the sensor glucose (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, subjects must still deliver bolus insulin for meals as calculated by the insulin to carbohydrate ratio. This ratio is determined by the Health Care Professional (HCP)/patient. In addition, the

setting for active insulin must be programmed. Basal rates are set for 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 SGV has reached the programmed low threshold (Suspend before Low).

Figure 3. MiniMed 670G Insulin Pump

7.5 MiniMed 770G Insulin Pump

The MiniMed 770G Insulin Pump is equivalent in function to the MiniMed 670G insulin pump, with the exception of telemetry. While the MiniMed 670G insulin pump communicates on the basis of Tel-D (telemetry-diabetes) radio frequency (RF) technology, the MiniMed 770G pump contains BLE (Bluetooth Low Energy) RF communication, which allows for connectivity to patients' smartphones, CGM transmitter and an BLE RF enabled blood glucose meter.

The pump 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 continuous glucose values, storing this data so that it can be retrospectively analyzed to track patterns and improve diabetes management. These features are similar to the commercially available Medtronic sensor-enabled system (e.g. MiniMed 530G System (P120010) in the US, MiniMed 640G and Veo System OUS, which has the threshold suspend feature).

The MiniMed 770G Insulin Pump also includes the closed loop algorithm as part of the SmartGuard™ technology 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 pump without CGM or as a sensor augmented pump without the SmartGuard features.

When Auto Mode is enabled on the MiniMed 770G insulin pump, the sensor glucose (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 this system, users must still deliver bolus insulin for meals as calculated by the insulin to carbohydrate ratio. This ratio is determined by the Health Care Professional (HCP)/patient. In addition, the setting for active insulin must be programmed. Basal rates are set for 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 has reached the programmed low threshold (Suspend before Low).

7.6 Guardian® Sensor (3)

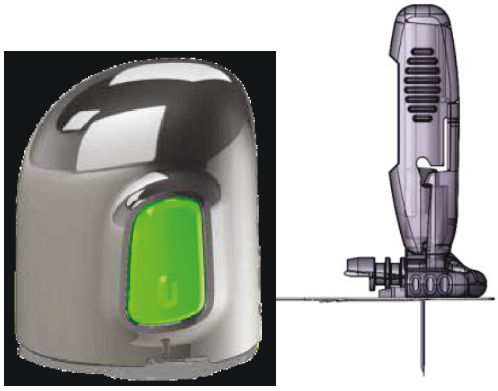
The Guardian Sensor (3) , referred to as Guardian Sensor (3) in this protocol, is a product that contains a microelectrode with a thin coating of glucose oxidase beneath several layers of biocompatible membrane. The sensor represents the next generation in the Enlite sensor family with design changes in the engineering reports for improved accuracy. It is intended to penetrate the skin at a 90-degree angle and is shorter and thinner than the previous generation of MiniMed sensors. An introducer needle penetrates the skin surface and provides support for the sensor microelectrode during insertion. The electrode tubing maintains the electrode structure by providing support during and after subcutaneous 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.

7.7 One-Press Serter

The One-Press Serter , referred to as the Serter (Figure 4) 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 and Guardian Sensor (3)

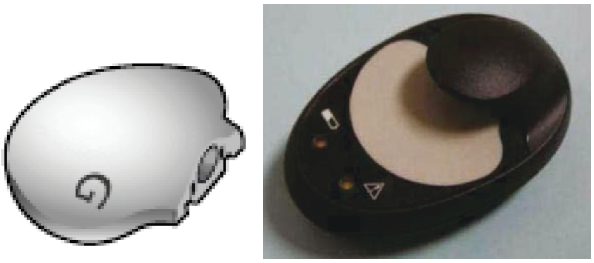


7.8 Guardian Link (3) Transmitter

The Guardian Link (3) Transmitter has the same housing and sensor interface as the MiniLink transmitter. However, the internal electronics and firmware of the Guardian Link (3) Transmitter are new. Like the MiniLink transmitter, the Guardian Link (3) Transmitter reads the electronic signal generated by the sensor. In addition, the transmitter contains a custom Application Specific Integrated Circuit (ASIC), which enables 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 SGV using calibration blood glucose values from a meter relayed to the transmitter through the pump. The transmitter transmits the calculated glucose data to the pump via RF technology. The new algorithm is designed to improve and optimize performance when paired with the Guardian Sensor (3). Some elements of the new calibration logic include prompting the user to calibrate when needed, referred to as "Smart Cal," instead of strictly scheduled time-based calibration requirements.

Figure 5. Transmitter and Transmitter Charger



7.9 Transmitter Charger

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

7.10 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.

7.11 CONTOUR® NEXT LINK 2.4 by Ascencia RF-Enabled Blood Glucose Meter

A CONTOUR Next Link by Ascencia RF-Enabled Blood Glucose Meter, referred to as the Study Meter throughout protocol, will be provided to study participants for use with the MiniMed 670G Insulin Pump. The meter measures a subject's capillary blood glucose level using the CONTOUR NEXT Strips by Ascencia, which is then used to calibrate the pump. The MiniMed 670G Insulin Pump uses the calibration point in the real-time algorithm which calculates the SGVs that are displayed to the subject. The result of the finger stick (capillary SMBG) reading performed is entered into the MiniMed 670G Insulin Pump and can be stored in its memory as a glucose point. The MiniMed 670G Insulin Pump asks the user every time if the user wants to use the linked meter BG for calibration. If yes is selected, the glucose value will be stored in memory as a calibration point. This meter has a remote bolus feature that will not be operational during the closed loop system.

7.12 Accu-Chek Guide Link Bluetooth Enabled Meter by Roche

The Accu-Chek Guide Link Meter Blood Glucose Monitoring System for use with the 770G 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.

7.13 CareLink® Personal For Clinical Research Software and CareLink® Clinical Software

Medtronic CareLink® Personal For Clinical Research Therapy Management Software for Diabetes and CareLink® Clinical are both internet-based software systems which allow the device data to be viewed and easily evaluated by the subject and his/her physician. A PC is used to access the Medtronic CareLink® system via the Internet, which then allows subjects and investigational center staff to upload data from Medtronic MiniMed insulin pumps and a range of system-supported, third-party BG meters. CareLink® Personal For Clinical Research Therapy Management Software for Diabetes, the clinical support version of Medtronic CareLink® Personal software, and the CareLink® Clinical allows retrospective review of device data and was developed for use by the investigational center staff and subjects. The CareLink® Clinical software allows the investigational center staff to manage, create, and link the subject's account. For the purposes of this study, all references to CareLink® Personal For Clinical Research software in this document relate to the clinical support version of Medtronic CareLink® Personal Therapy Management Software for Diabetes. The data contained in CareLink® Personal For Clinical Research software and CareLink® Clinical software is accessible to users using a standard browser, i.e., Microsoft® Internet Explorer, on an Internet enabled PC.

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

- The internet to the web server;

- Web server to the application server;
- Application server to the database server.

The CareLink® Clinical software supports both Bluetooth® Low Energy pumps and non- Bluetooth® Low Energy pumps, while the CareLink® Personal For Clinical Research software only support non- Bluetooth® Low Energy pumps.

7.14 CareLink USB 2.4 GHz

The CareLink USB is an accessory to the CareLink Personal Therapy Management Software that facilitates wireless communication between a personal computer and devices employing the Medtronic proprietary RF technology. The device is only intended to transfer data, it does not have any diagnostic or therapeutic function/benefit.

7.15 Blue Adapter

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

7.16 Medtronic Mobile Application

The MiniMed Mobile Application is an optional accessory to the MiniMed 770G 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.

7.17 Carelink Connect Application

The CareLink Connect App is an optional accessory which receives pump data wirelessly from the CareLink server. The CareLink Connect App provides a mirroring display of the MiniMed Mobile App screen, for remote

monitoring by a care partner (e.g., care giver or health care provider). The CareLink Connect App is not designed to monitor the performance of the insulin pump nor for direct monitoring of pump data. As a mirroring display, the app can provide notifications to the care partner via the user interface.

7.18 Ketone Meter

The Ketone Meter measures both blood glucose (sugar) and blood ß-Ketone. In this study, the meter will only be used to collect ß-Ketone data, which will be collected for reporting and review (see Investigator/Coordinator binder for details) and as described in the body of this study protocol. This particular meter will be used because it is the only commercially available meter which allows quantification of blood ß-Ketone levels and is the preferred patient method of testing over urine testing.

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

7.19 Infusion sets

- Quick Set Infusion sets
- Silhouette Infusion sets
- Sure-T Infusion sets
- Mio Infusion sets

Note: Medtronic may incorporate additional infusion sets into this clinical study as they become commercially available. Instructions for the devices used in this study are provided in their respective manuals. All infusion sets provided to subjects must be approved or cleared for use with MiniMed Pump for Humalog and Novolog.

7.20 Reservoirs

Patients are instructed to change their reservoir every 2 to 3 days. All reservoirs provided to subjects must be approved or cleared for use with the MiniMed pump for Humalog and Novolog.

7.21 Infusion Set Serter Devices

The following infusion set type has a corresponding serter device.

- Quick-Serter™ (MMT-305)
- Sil-Serter™ (MMT-385)

The devices are indicated for single patient multi use, i.e. a patient uses the same serter every 2 to 3 days to insert a new infusion set as described in the IFU. All infusion set serter devices provided to subjects must be approved or cleared for use with the MiniMed pump for Humalog and Novolog.

7.22 Insulin

Patients will use their own rapid-acting analogue insulin (novolog, humalog) during this study.

7.23 Supplies

Study pump, study meters and sensors are supplied with additional, commercially available materials i.e., reservoirs, infusion sets, alcohol wipes, meter supplies, tape, etc. free of charge.

7.24 Packaging

In Europe, all devices will be labeled in accordance with local language requirements.

Labeling for the study devices will be provided under separate cover. Investigational devices will be labeled in accordance to their regulatory requirements.

7.25 Product Training Requirements

Training of the investigational center staff on the conduct of the study and system being studied will be initiated before the protocol is implemented. All participating physicians and coordinators will be familiarized with the system. Specific investigational center staff will be trained on each of the system's components. Training will contain both lecture and hands-on experience.

Trained product support personnel may be present at the training and study follow-up visits to provide technical support.

Trained personnel may also give technical support via the local support service, e.g. Medtronic 24HR Technical Support.

7.26 Product Receipt and Tracking

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
- 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 their expiration date.

Sign and date the packing slips/invoices, noting any discrepancies, and file in appropriate study binder.

Notify the study Monitor of any discrepancies.

Enter the study device information on the appropriate eCRF in the study database.

7.27 Device Disbursement

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 (see Table 8 for details). Documentation may include:

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

7.28 Product Storage

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

7.29 Product Return

After use by the subject, the investigational center is expected to accept and retain all devices as described in Table 9 and store them in a secure environment. If containers/units/devices are missing, document the reasons in the eCRF. If discrepancies between amounts used by subjects and amounts expected to be returned exist, document the reasons in the eCRF.

All devices, as described in Table 9, will be returned by subjects to the investigational center and then to the Sponsor. Serialized devices provided to the investigational center may be returned as subjects complete the study, at the end of study or upon sponsor request. The quantity received by the investigational center and the quantity returned to sponsor should be equal. The investigational center will provide details of the disposition of all unreturned serialized devices (excluding the Study Meter and Ketone Meter) in the eCRF.

Used glucose sensors are not expected to be returned by subjects to the investigational center and therefore are not expected to be returned to the sponsor. Other unused consumable devices (i.e., infusion sets, alcohol wipes, Study Meter supplies, tape, etc.), supplies or materials may be returned to the sponsor or retained by investigational center for educational purposes only, or 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. This would include glucose sensors, meter

testing strips and supplies, infusion sets and adhesive tape.

All study devices that were required to be entered into the study database are required to be accounted for as described herein prior to return to sponsor or at the end of the study.

7.30 Product Accountability

Good clinical research practice requires that investigators and research teams ensure accurate accountability for any investigational device used in a research trial. It is expected that all investigational devices will be used in

the manner intended during the study, that they will be stored under appropriately controlled conditions with controlled access and that they will be used only by (on) subjects who have consented to participate in the research study.

Any investigational device being used in clinical research must be strictly accounted for and will not be shipped to any site unless all of the necessary approvals (e.g. Regulatory, IRB/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 Center) and/or disposal

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

Table 9. Device Accountability Requirements (U.S. Sites)

Device	Site Receipt (packing slip and eCRF)	Disbursement to Subject (eCRF)	Device Disposition at Conclusion of Study	Record Device Disposition (eCRF)
MiniMed 670G Insulin Pump (MMT-1780)	Yes	Yes	Return to Sponsor	Yes
MiniMed 770G Insulin Pump	Yes	Yes	Return to Sponsor	Yes

Device	Site Receipt (packing slip and eCRF)	Disbursement to Subject (eCRF)	Device Disposition at Conclusion of Study	Record Device Disposition (eCRF)
(MMT-1880)				
CONTOUR® NEXT LINK 2.4 by Ascencia Blood Glucose Meter(MMT-1152 or MMT-1352)	Yes	Yes	Dispose or return unused to Sponsor	Yes
Accu-Chek Guide Link Meter Blood Glucose Monitoring System (08116083022)	Yes	Yes	Return to Sponsor	Yes
Guardian Sensor (3) (MMT-7020) – for 670G only	Yes	Yes	Dispose or return unused to Sponsor	Yes
Guardian Sensor (3) (MMT-7020) – for 770G only	Yes	No	Dispose or return unused to Sponsor	No
One-Press Serter (MMT-7512)	No	No	Dispose or return unused to Sponsor	No
Guardian Link (3) Transmitter (MMT-7811) for 670G only	Yes	Yes	Return to Sponsor	Yes
Guardian Link (3) Transmitter (MMT-7910) for 770G only	Yes	Yes	Return to Sponsor	Yes
Tester (MMT-7736L)	No	No	Dispose or return unused to Sponsor	No
Transmitter Charger (MMT-7715)	No	No	Dispose or return unused to Sponsor	No
CareLink USB 2.4 GHz (MMT-7306)	No	No	Dispose or return unused to Sponsor	No
Ketone Meter	No	No	Dispose or return unused to Sponsor	No

Devices may be combined and distributed in kits.

Table 10. Device Accountability Requirements (European Sites)

Device	Site Receipt (packing slip and eCRF)	Disbursement to Subject (eCRF)	Device Disposition at Conclusion of Study	Record Device Disposition (eCRF)
MiniMed 670G Insulin Pump (Europe MMT-1781, and MMT-1782)	Yes	Yes	Return to Sponsor	Yes
CONTOUR® NEXT LINK 2.4 by Ascencia Blood Glucose Meter (MMT-1352, Europe: MMT-1151, MMT-1152)	Yes	Yes	Dispose or return unused to Sponsor	Yes
Guardian Sensor (3) (MMT-7020)	No	No	Dispose or return unused to Sponsor	No
Guardian Link (3) Transmitter (MMT-7811)	Yes	Yes	Return to Sponsor	Yes
Tester (MMT-7736L)	No	No	Dispose or return unused to Sponsor	No
One-Press Serter (MMT-7512)	No	No	Dispose or return unused to Sponsor	No
Transmitter Charger (MMT-7715)	No	No	Dispose or return unused to Sponsor	No
CareLink USB 2.4 GHz (MMT-7306)	No	No	Dispose or return unused to Sponsor	No
Ketone Meter	No	No	Dispose	No

Devices may be combined and distributed in kits.

Table 11. Device Accountability Requirements (Canadian Sites)

Device	Site Receipt (packing slip and eCRF)	Disbursement to Subject (eCRF)	Device Disposition at Conclusion of Study	Record Device Disposition (eCRF)
MiniMed 670G Insulin Pump (Canada MMT-1781 (pump))	Yes	Yes	Return to Sponsor	Yes
MiniMed 770G Insulin Pump (Canada MMT-1881)	Yes	Yes	Return to Sponsor	Yes
CONTOUR® NEXT LINK 2.4 by Ascencia Blood Glucose Meter (Canada MMT-1351 or MMT-1352)	Yes	Yes	Dispose or return unused to Sponsor	Yes
Accu-Chek Guide Link Meter Blood Glucose Monitoring System (08109222001)	Yes	Yes	Return to Sponsor	Yes
Guardian Sensor (3) (MMT-7020) – for 670G only	Yes	Yes	Dispose or return unused to Sponsor	Yes
Guardian Sensor (3) (MMT-7020) – for 770G only	Yes	No	Dispose or return unused to Sponsor	No
Guardian Link (3) Transmitter (MMT-7811WW), 670G only.	Yes	Yes	Return to Sponsor	Yes
Guardian Link (3) Transmitter (MMT-7911) 770G only	Yes	Yes	Return to Sponsor	Yes
Tester (MMT-7736L)	No	No	Dispose or return unused to Sponsor	No
One-Press Serter (MMT-7512)	No	No	Dispose or return unused to Sponsor	No
Transmitter Charger (MMT-7715)	No	No	Dispose or return unused to Sponsor	No

Device	Site Receipt (packing slip and eCRF)	Disbursement to Subject (eCRF)	Device Disposition at Conclusion of Study	Record Device Disposition (eCRF)
CareLink USB 2.4 GHz (MMT-7306)	No	No	Dispose or return unused to Sponsor	No
Ketone Meter	No	No	Dispose	No

Devices may be combined and distributed in kits.

Table 12. Device Accountability Requirements (Australian Sites)

Device	Site Receipt (packing slip and eCRF)	Disbursement to Subject (eCRF)	Device Disposition at Conclusion of Study	Record Device Disposition (eCRF)
MiniMed 770G Insulin Pump (MMT-1881, MMT-1891)	Yes	Yes	Return to Sponsor	Yes
Accu-Chek Guide Link Meter Blood Glucose Monitoring System (08116113186M)	Yes	Yes	Return to Sponsor	Yes
Guardian Sensor (3) (MMT-7020C5) – for 770G only	Yes	No	Dispose or return unused to Sponsor	No
Guardian Link (3) Transmitter (MMT-7910WS, MMT-7911W) 770G only	Yes	Yes	Return to Sponsor	Yes
Tester (MMT-7736L)	No	No	Dispose or return unused to Sponsor	No
One-Press Serter (MMT-7512)	No	No	Dispose or return unused to Sponsor	No

Device	Site Receipt (packing slip and eCRF)	Disbursement to Subject (eCRF)	Device Disposition at Conclusion of Study	Record Device Disposition (eCRF)
Transmitter Charger (MMT-7715)	No	No	Dispose or return unused to Sponsor	No
CareLink USB 2.4 GHz (Austalia, New Zealand)	No	No	Dispose or return unused to Sponsor	No
Ketone Meter	No	No	Dispose	No

Devices may be combined and distributed in kits.

Table 13. Device Accountability Requirements (New Zealand Sites)

Device	Site Receipt (packing slip and eCRF)	Disbursement to Subject (eCRF)	Device Disposition at Conclusion of Study	Record Device Disposition (eCRF)
MiniMed 770G Insulin Pump (MMT-1881, MMT-1891)	Yes	Yes	Return to Sponsor	Yes
Accu-Chek Guide Link Meter Blood Glucose Monitoring System (08116113186M)	Yes	Yes	Return to Sponsor	Yes
Guardian Sensor (3) (MMT-7020C5) – for 770G only	Yes	No	Dispose or return unused to Sponsor	No
Guardian Link (3) Transmitter (MMT-7910WS, MMT-7911W) 770G only	Yes	Yes	Return to Sponsor	Yes
Tester (MMT-7736L)	No	No	Dispose or return unused to Sponsor	No

Device	Site Receipt (packing slip and eCRF)	Disbursement to Subject (eCRF)	Device Disposition at Conclusion of Study	Record Device Disposition (eCRF)
One-Press Serter (MMT-7512)	No	No	Dispose or return unused to Sponsor	No
Transmitter Charger (MMT-7715)	No	No	Dispose or return unused to Sponsor	No
CareLink USB 2.4 GHz (ACC-1003911D)	No	No	Dispose or return unused to Sponsor	No
Ketone Meter	No	No	Dispose	No

Devices may be combined and distributed in kits.

8. Selection of Subjects

8.1 Study Population

A diverse population of patients 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 glycosylated hemoglobin (A1C).

8.2 Subject Enrollment

Subjects will be considered enrolled in the study upon signing the Informed Consent/Assent form(s).

8.3 Inclusion Criteria

Subjects will be considered for enrollment in the study if they meet all of the following criteria:

1. Subject is age 2-80 years at time of screening

a. US, Canada, Australia and New Zealand: Subjects 2-80 years of age will be allowed to enroll in the post approval study.

b. Europe: Only subjects ≥7 years of age are allowed to enroll in the post-market study.

2. Subjects who are 2-21 years are determined by the investigator to have the appropriate, requisite support (family, caregiver or social network) to successfully participate in this study
3. Subject must have a minimum daily insulin requirement (Total Daily Dose) of equal to or greater than 8 units/day
4. Subjects who are determined by the investigator to be psychologically sound in order to successfully participate in this study.
5. Subject has been diagnosed with type 1 diabetes for at least three months

   Note: Determination of classification for diabetes will be based on American Diabetes Association Clinical Practice Guidelines accounting for several patient characteristics such as: age of onset, patient's weight or BMI, history of diabetic ketoacidosis, history of therapy management, if available in the medical records.

6. Subject must be on one of the following management therapies:
   - Multiple daily injections defined by use of rapid analogue with meals and approved long acting analogue (e.g. detemir or glargine) with or without CGM
   - Insulin pump therapy with or without CGM
7. Subject is willing to perform ≥ 4 finger stick blood glucose measurements daily
8. Subject is willing to perform required study procedures
9. Subject is willing to wear the system continuously throughout the study for at least 80% of the time
10. Subject is willing to upload data at least weekly from the study pump/meter, must have Internet access and a computer system that meets the requirements for uploading the study pump/meter for data collection
11. Subject must be willing to use the study glucose meter system (i.e. along with study meter strips).
12. If subject has celiac disease, it has been adequately treated as determined by the investigator
13. Subject with the diagnosis of 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, within 1 year of screening, will be included in the study with the consent of the Investigator

14. Subject is willing to take one of the following insulins and can financially afford to use either of the 2 insulin preparations throughout the course of the study (i.e. co-payments for insulin with insurance or able to pay full amount)
    a. Humalog® (insulin lispro injection)
    b. NovoLog® (insulin aspart)

8.4 Exclusion Criteria

1. Subject participated in any Closed Loop study in the past
2. Subject is unable to tolerate tape adhesive in the area of sensor placement
3. Subject has any unresolved adverse skin condition in the area of sensor placement (e.g., psoriasis, rash, *Staphylococcus* infection) or area of infusion set placement
4. Women of child-bearing potential who have a positive pregnancy test at screening or plan to become pregnant during the course of the study
5. Subject is being treated for hyperthyroidism at time of screening
6. Subject has an abnormality (out of reference range) in thyroid-stimulating hormone (TSH) at time of screening visit. TSH is not required for subjects 2-13 years of age.
7. Subject has taken any oral, injectable, or IV glucocorticoids within 8 weeks from time of screening visit, or plans to take any oral, injectable, or IV glucocorticoids during the course of the study.
8. 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
9. Subject is currently abusing illicit drugs or marijuana
10. Subject is currently abusing prescription drugs
11. Subject is currently abusing alcohol
12. Subject is using pramlintide (Symlin), SGLT2 inhibitors, GLP agonists, biguanides, DPP-4 inhibitors or sulfonylureas at time of screening
13. Subject is using hydroxyurea at the time of screening or plans to use it during the study
14. 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

15. Subject has a sickle cell disease, hemoglobinopathy; or has received red blood cell transfusion or erythropoietin within 3 months prior to time of screening
16. Subject plans to receive red blood cell transfusion or erythropoietin over the course of study participation
17. Subject diagnosed with current moderate to severe eating disorder such as anorexia or bulimia
18. Subject has been diagnosed with chronic kidney disease requiring dialysis or resulting in chronic anemia
19. Subjects who are currently being actively treated for cancer.
20. Subject who is designated as a research staff member for this study

9. Study Site Requirements

9.1 Study Site Activation

During the activation process (prior to subject enrollment), Medtronic will train investigational center staff using the sponsor training protocol. If new members join the study investigational center team, they will receive training on the applicable study requirements relevant to their role before contributing to the study.

Prior to performing study-related activities, all training requirements shall be fulfilled.

10. Study Procedures

10.1 Overview

Run-In Period Synopsis (Run-in Visits 1-3)

The purpose of the run-in period is to ensure that study subjects are introduced to study devices and to provide blinded CGM data. Subjects will be trained on CGM use and blinded CGM will be used to collect

data with each subject's existing diabetes therapy. There is a window of 60 days from the end of Visit 1 to the end of Visit 3 during which time subjects should complete run-in. Subjects will be started on the study pump at Visit 3.

- **Devices Worn:**
  - Medtronic CGM (blinded) only
  - Depending on age group, sensor is self-inserted by subject or inserted with assistance
  - Existing Therapy

Study Period Synopsis

Overview:

The study period is 6 months Subjects will be randomized at the start the study period into 2 arms:

- HCL Arm: Auto Mode feature on the study pump turned ON
- Control Arm: Continue with own therapy for 6 months
  - CSII Cohort: The CSII Cohort will use the MiniMed Pump without Real Time CGM during the 6 month study period. Blinded CGM (Guardian Link (3) Transmitter and Guardian Sensor (3)) will only be worn at baseline, 3 months, and 6 months (two weeks of sensors use)
  - MDI Cohort: The Multiple Daily Injection (MDI) Cohort will remain on MDI therapy with subjects using their own insulin for 6 months during the study period. Blinded CGM (Guardian Link (3) transmitter and Guardian Sensor (3)) will only be worn at baseline, 3 months, and 6 months (two weeks of sensors use).

    MDI subjects who are currently using CGM, i.e. Dexcom or Medtronic Guardian Connect

or who are currently using a SMBG alternative, i.e. Libre, will be allowed to enroll in the study and continue using their own device. There will be N=100

- SAP Cohort: The Sensor Augmented Pump (SAP) Cohort will use the MiniMed Pump (SAP without Low Management Suspend on Low, Low Management Suspend before low or Auto Mode) with Real Time CGM for the 6 month study period
-

Note: Subjects 2-6 years of age will automatically enter the HCL arm at the end of the run-in period

Study Period Device Procedures for HCL Arm

- **Devices Worn:**
  - MiniMed Pump
  - Depending on randomization and age group, sensor is self-inserted by subject or inserted with assistance
- **Calibration Requirements with Study Meter:**
  - Approximately 30 minutes to 2 hours after the Guardian Sensor (3) is initialized, the Study Pump will alert the user to enter meter BGs to perform initial calibration.
  - After the first calibration, the user must calibrate the Guardian Sensor (3) with the study meter within 6 hours of the first calibration.
  - The user must calibrate with the study meter when prompted by the study pump via the Smart Cal feature
  - The user must calibrate with the study meter every 12 hours after last calibration.
  - Recommend 3-4 calibrations per day with the study meter
  - All BGs used for Auto Mode in the MiniMed Pump system can also be used for sensor calibration. However, calibrating during rapid changes (2 or 3 arrows) may temporarily decrease sensor accuracy. Best practices should be followed for each BG measurement

(e.g. clean hands, accepting the calibration on the pump without delay)

- Other recommendations:
  - Always have clean dry fingers when you check your blood glucose
  - Only use your fingertips to obtain blood samples for calibration

- **Auto Mode Settings:**
  - The Auto Mode (Closed Loop) target for the closed loop algorithm is set at 120 mg/dL (6.7 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:
    - 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 Setup limit (i.e. the setting for a high glucose alert threshold based on sensor reading) is recommended to be set at 300 mg/dL (16.6 mmol/L)
    - Alert setting options may be set per investigator discretion
  - Low Setup limit (i.e. the setting for a low glucose alert threshold based on sensor reading) is recommended to be set at 70 mg/dL (4.0 mmol/L)
    - Alert setting options may be set per investigator discretion
    - For subjects 2-6 years of age, low limit should be set to 80mg/dL (4.4mmol/L) and no lower than 70mg/dL(4.0 mmol/L)
    - 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.

- **Manual Mode Settings:**
  - High Set up Limit recommend to be set at 300 mg/dL (16.6 mmol/L)
    - Alert Setting Options may be set per investigator discretion
  - Low Set up Limit recommend to be set at 70 mg/dL (4.0 mmol/L)
    - For subjects 2-6 years of age, low limit should be set 80 mg/dL (4.4 mmol/L) and no lower than 70 mg/dL(4.0 mmol/L)
    - Subjects will be instructed to follow up with an SMBG confirmatory measurement when receiving a low alert
  - Predictive alerts and rate of change alerts are optional
  - SmartGuard Manual Mode Low Management features may be used when Auto Mode is OFF
  - Consider setting the glucose target in the bolus wizard calculator to the same target as the closed loop algorithm, i.e. 120 mg/dL (6.7mmol/L) or higher, based on investigator discretion.
- **Monitoring Method:**
  - Study Meter

Continuation Period Synopsis

Overview:

The continuation period is 6 months in duration. Subjects will use MiniMed Pump System and continue from the end of the study period as follows:

Continuation Period Device Procedures

- **Devices Worn:**
  - MiniMed Pump with CGM
  - Sensor is self-inserted by subject or inserted with assistance
- **Calibration Requirements with Study Meter:**
  - Approximately 30 minutes to 2 hours after the Guardian Sensor (3) is initialized, the Study Pump will alert the user to enter meter BGs to perform initial calibration.
  - After the first calibration, the user must calibrate the Guardian Sensor (3) with the study meter within 6 hours of the first calibration.
  - The user must calibrate with the study meter when prompted by the study pump via the Smart Cal feature
  - The user must calibrate with the study meter every 12 hours after last calibration.
  - Recommend 3-4 calibrations per day with the study meter
  - All BGs used for Auto Mode in the MiniMed Pump system can also be used for sensor calibration. However, calibrating during rapid changes (2 or 3 arrows) may temporarily decrease sensor accuracy. Best practices should be followed for each BG measurement (e.g. clean hands, accepting the calibration on the pump without delay)
  - Other recommendations:

- Always have clean dry fingers when you check your blood glucose
- Only use your fingertips to obtain blood samples for calibration

- **Auto Mode Settings**
  - The Auto Mode (Closed Loop) target for the closed loop algorithm is set at 120 mg/dL (~6.7 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:
    - 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 Setup limit (i.e. the setting for a high glucose alert threshold based on sensor reading) is recommended to be set at 300 mg/dL (16.6 mmol/L)
    - Alert setting options may be set per investigator discretion
  - Low Setup limit (i.e. the setting for a low glucose alert threshold based on sensor reading) is recommended to be set at 70 mg/dL (4.0 mmol/L)
    - Alert setting options may be set per investigator discretion
    - For subjects 2-6 years of age, low limit should be set 80mg/dL (4.4 mmol/L) and no lower than 70 mg/dL (4.0 mmol/L)
    - 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.

- **Manual Mode Settings:**

- High Set up Limit recommend to be set at 300 mg/dL (16.6mmol/L)
  - Alert Setting Options may be set per investigator discretion
- Low Set up Limit recommend to be set at 70 mg/dL (4.0mmol/L)
  - For subjects 2-6 years of age, low limit should be set 80mg/dL (4.4 mmol/L) and no lower than 70 mg/dL(4.0mmol/L)
  - Subjects will be instructed to follow up with an SMBG confirmatory measurement when receiving a low alert
- Predictive alerts and rate of change alerts are optional
- SmartGuard Manual Mode Low Management features may be used when Auto Mode is OFF
- Consider setting the glucose target in the bolus wizard calculator to the same target as the closed loop algorithm, i.e. 120 mg/dL(6.8mmol/L) or higher, based on investigator discretion.

- **Monitoring Method:**

  Study Meter

10.2 Scheduled Follow-Up Visit Windows

Refer to the Appendices (Section 24) for the Cohort Visit Tables.

10.3 Schedule of Events

Each subject's participation will be comprised of the following scheduled visits listed below over the course of approximately 8 months during the run-in period and study period, and for 6 months during the continuation period.

- Telemedicine visits will be allowed to replace office visits if they do not involve collection of blood test samples or device related procedures that require staff assistance

Early Withdrawal:

Subjects who exit the study before the last scheduled study visit will complete all requirements that are listed for **Visit 13**, with the exception of c-peptide lab testing.

The schedule is planned as follows:

Screening and Run-In Period

All subjects will complete screening and the run-in period. This period must be completed in 60 days.

Visit 1: **Screening Visit –** Consent and Screening

- Patients may re-screened once with Sponsor approval

Visit 2: Begin Run-in Period

- Placement of blinded sensor to be worn for 2 Weeks (each sensor is worn for 7 days)
- Study training, including instruction on procedures for wearing blinded CGM (i.e., insertion of sensor)

Visit 3: Begin MiniMed Pump (Except MDI Control)

- Occurs after 2 week blinded sensor wear, either immediately at the end of sensor wear or suggested to be within 14 days.
- The run-in period may be repeated a second time with Sponsor approval

Randomization

At **Visit 3** all subjects (CSII, MDI, or SAP Cohort) will be randomized into one of 2 arms:

HCL Arm

- Note: Patients who are on SAP at baseline will start Medtronic CGM at this visit .

Control Arm

- Note: Patients in SAP will receive and be trained on Medtronic CGM if they are randomized to

the Control arm to ensure continuity with use of real time CGM.

In the US and Canada, when available, subjects will have the option to begin with MiniMed 770G system or exchange their MiniMed 670G for a MiniMed 770G system.

Note: Subjects 2-6 years of age will automatically enter the HCL arm at the end of the run-in period

To schedule Visit 4:

- For subjects who have been on insulin pump therapy prior to screening for at least 3 months, Visit 4 should occur 3-30 days after Visit 3
- For subjects without pump therapy experience, the following should occur:
    - If randomized to HCL Arm, Visit 4 should occur 14-30 days after Visit 3
    - If randomized to MDI Control Arm, Visit 4 should occur 1-7 days after Visit 3

The visit schedules for each of these Arms are as follows:

HCL Arm:

Visit 4: Start CGM - Day 0

- Start CGM with Guardian Sensor (3) (Note: SAP subjects will have already started CGM with Guardian Sensor (3) at Visit 3).

Visit 4A: Follow up Telephone visit - 2-3 days after Visit 4

Visit 5: Follow up Office Visit -7-21 days after Visit 4

- Auto Mode is enabled and activated. Investigator sets carbohydrate to insulin ratios and active insulin time, and basal rates for open loop periods

Visit 6A: Follow-up Telephone Visit (option of office visit) – 1 Day after Visit 5

Visit 6B: Follow-up Telephone Visit (option of office visit) - 2 Days after Visit 5

Visit 6C: Follow-up Telephone Visit - 5 Days (± 1 day) after Visit 5

Visit 7A: Follow up Office Visit - 14 Days (± 3 days) after Visit 5

Visit 7B: Follow-up Telephone Visit - 21 Days (± 3 days) after Visit 5

Visit 7C: Follow up Office Visit - 30 Days after Visit 5 (± 5 days)

Visit 7D: Follow-up Telephone Visit - 45 Days (± 7 days) after Visit 5

Visit 8: Follow up Office Visit - 90 Days after Randomization (± 10 days)

Visit 9: Follow up Office Visit - 180 Days after **Randomization** (± 10 days)

- End of Study Period and Start of Continuation period

Control Arm:

a. CSII Cohort

Visit 4: Day 0:

- Review pump settings

Visit 5: Follow up Office Visit 7-21 days after Visit 4

- Insulin Pump adjustments

Visit 6A: Follow up Telephone Visit - 1 Day after Visit 5

Visit 6B: Follow up Telephone Visit - 2 Days after Visit 5

Visit 6C: Follow up Telephone Visit - 14 Days (± 7 days) after Visit 5

Visit 6D: Follow up Office Visit - 30 Days after Visit 5 (± 7 days)

Visit 6E: Follow-up Telephone Visit - 45 Days (± 7 days) after Visit 5

Visit 7: Follow up Office Visit - 76 days after **Randomization** (-14 days)

- Blinded CGM Start
- 14 days of sensor wear before 90 Day study period visit. Transmitter is not connected to study pump

Visit 8A: Follow up Office Visit – 90 Days after **Randomization** (+14 days)

- Blinded CGM Return

Visit 8B: Follow up Office Visit - 166 days after **Randomization** (-14 days)

- Blinded CGM Start
- 14 days of sensor wear before 180 Day study period visit. Transmitter is not connected to study pump

Visit 9: Follow up Office Visit – 180 Days after **Randomization** (+14 days)

- Blinded CGM Return
- End of Study Period and Start of Continuation period.
- Start CGM with Guardian Sensor (3)

b. MDI Cohort

Visit 4: Day 0

Visit 5: Follow up Office Visit 7-21 days after Visit 4

Visit 6A: Follow up Telephone Visit - 1 Day after Visit 5

Visit 6B: Follow up Telephone Visit - 2 Days after Visit 5

Visit 6C: Follow up Telephone Visit - 14 Days (± 5 days) after Visit 5

Visit 6D: Follow up Office Visit - 25 Days after Visit 5 (± 5 days)

Visit 6E: Follow-up Telephone Visit - 35 Days (+1 day) after Visit 5

Visit 7: Follow up Office Visit - 76 days after **Randomization** (-2 days)

- Blinded CGM Start
- 14 days of sensor wear before 90 Day study period visit.

Visit 8A: Follow up Office Visit – 90 Days after **Randomization** (+14 days)

- Blinded CGM Return

Visit 8B: Follow up Office Visit - 166 days after **Randomization** (-14 days)

- Blinded CGM Start
- 14 days of sensor wear before 180 Day study period visit.

Visit 9: Follow up Office Visit – 180 Days after **Randomization** (+14 days)

- Blinded CGM Return
- End of Study Period and Start of Continuation period.
- Start study pump

c. SAP Cohort:

Visit 4: Day 0

Visit 4A: Follow up Telephone visit - 2-3 days after Visit 4

Visit 5: Follow-up Office Visit - 7-21 days after Visit 4

- Pump and Sensor adjustments

Visit 6A: Follow-up Telephone Visit (option of office visit) – 1 Day after Visit 5

Visit 6B: Follow-up Telephone Visit (option of office visit) - 2 Days after Visit 5

Visit 6C: Follow-up Telephone Visit 7 days after Visit 5 (±3 days)

Visit 7A: Follow-up Telephone Visit - 14 Days after Visit 5 (± 3 days)

Visit 7B: Follow-up Telephone Visit - 21 Days after Visit 5 (± 3 days)

Visit 7C: Follow-up Office Visit - 30 Days after Visit 5 (± 5 days)

Visit 7D: Follow-up Telephone Visit - 45 Days (± 7 days) after Visit 5

Visit 8: Follow-up Office Visit - 90 Days after **Randomization** (± 10 days)

Visit 9: Follow-up Office Visit - 180 Days after **Randomization** (± 10 days)

- End of Study Period and Start of Continuation period
- Auto Mode is enabled and activated.

Continuation Period:

HCL Arm:

Visit 10: Follow up Office Visit – 1 to 14 days after Visit 9

Visit 11: Follow up Office Visit – 15 to 30 days after Visit 9

Visit 12: Follow up Office Visit - 270 Days after **Randomization** (+/- 21 days)

Visit 13: Follow up Office Visit - 365 Days after **Randomization** (+/- 21 days)

- End of Continuation Period and End of Study

Control Arm

a. CSII Cohort:

Visit 10A: Follow up Telephone visit - 2-3 days after sensor start

Visit 10B: Follow up Office Visit 7-21 days after Visit 9

- Auto Mode is enabled and activated.

Visit 10C: Follow up Telephone Visit (option of office visit) – 1 Day after Visit 10B

Visit 10D: Follow up Telephone Visit (option of office visit) – 2 Days after Visit 10B

Visit 10E: Follow-up Telephone Visit – 5 Days (± 1 day) after Visit 10B

Visit 11A: Follow up Office Visit - 14 Days after Visit 10B (±3 days)

Visit 11B: Follow-up Telephone Visit - 21 Days (±3 days**)** after Visit 10B

Visit 11C: Follow up Office Visit - 30 Days after Visit 10B (±5 days)

Visit 11D: Follow-up Telephone Visit - 45 Days (±7 days**)** after Visit 10B

Visit 12: Follow up Office Visit - 270 Days after **Randomization** (+/- 21 days)

Visit 13: Follow up Office Visit - 365 Days after **Randomization** (+/- 21 days)

- End of Continuation Period and End of Study

b. MDI Cohort:

Visit 9A: Follow up Office Visit – 14-30 days after Visit 9

- Start CGM with Guardian Sensor (3)
- This visit should occur between 14 and 30 days after pump start.

Visit 10A: Follow up Telephone visit - 2-3 days after sensor start

Visit 10B: Follow up Office Visit 7-21 days after Visit 9A

- Patient has been wearing CGM for at least 4 days before enabling Auto Mode
- Auto Mode is enabled and activated.

Visit 10C: Follow up Telephone Visit (option of office visit) – 1 Day after Visit 10B

Visit 10D: Follow up Telephone Visit (option of office visit) – 2 Days after Visit 10B

Visit 10E: Follow-up Telephone Visit – 5 Days (± 1 day) after Visit 10B

Visit 11A: Follow up Office Visit - 14 Days after Visit 10B (±3 days)

Visit 11B: Follow-up Telephone Visit – 21 Days (± 3 day) after Visit 10B

Visit 11C: Follow up Office Visit - 30 Days after Visit 10B (±5 days)

Visit 11D: Follow-up Telephone Visit – 45 Days (± 7 day) after Visit 10B

Visit 12: Follow up Office Visit - 270 Days after **Randomization** (+/- 21 days)

Visit 13: Follow up Office Visit - 365 Days after **Randomization** (+/- 21 days)

- End of Continuation Period and End of Study

c. SAP Cohort:

Visit 10A: Follow up Telephone Visit (option of office visit) – 1 Day after Visit 9

Visit 10B: Follow up Telephone Visit (option of office visit) – 2 Days after Visit 9

Visit 10C: Follow-up Telephone Visit – 5 Days (± 1 day) after Visit 9

Visit 11A: Follow up Office Visit - 14 Days after Visit 9 (±3 days)

Visit 11B: Follow-up Telephone Visit – 21 Days (± 3 day) after Visit 9

Visit 11C: Follow up Office Visit - 30 Days after Visit 9 (±5 days)

Visit 11D: Follow-up Telephone Visit – 45 Days (± 5 day) after Visit 9

Visit 12: Follow up Office Visit - 270 Days after **Randomization** (+/- 21 days)

Visit 13: Follow up Office Visit - 365 Days after **Randomization** (+/- 21 days)

- End of Continuation Period and End of Study

10.4 Data Collection

For detailed data collection and study procedure requirements, see Appendices.

10.5 Subject Consent

Informed Consent/Assent will be obtained in accordance with the Code of Federal Regulations (CFR) Title 21, Part 50 (US only) or ISO14155:2011 (Europe, Australia and New Zealand only) or Tri-Council Policy Statement, Article 3.2 (Canada only), and applicable local regulations. The Investigator or designee must obtain written informed consent/assent before any clinical study related activity takes place. Prior to entry into the study, the California Experimental Subject's Bill of Rights (if applicable), the IRB/EC and Medtronic-approved Informed Consent Form (ICF)/Assent form, and the Health Insurance Portability and Accountability Act (HIPAA) Authorization Form (US only) will be given to each subject and legally authorized representative (if applicable). The Investigator or designee will fully inform the subject of all aspects of the clinical study that are relevant to the subject's decision to participate in the clinical study (e.g. purpose and duration of the study, requirements of the subject during the study, potential risks and possible benefits associated with participation in this study.

Subjects will be considered enrolled in the study upon signing the Informed Consent/Assent form(s).

All items addressed in the Informed Consent/Assent Form must be explained. The language used shall be as non-technical as possible and must be understandable to the subject or parent/guardian.

The subject or parent/guardian must have ample time and opportunity to read and understand the Informed Consent/Assent Forms, to inquire about details of the clinical study, and to decide whether or not to participate in the clinical study. All questions about the clinical study should be answered to the satisfaction of the subject.

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

When the subject decides to participate in the clinical study, the California Experimental Subject's Bill of Rights (if applicable), the HIPAA Form (US only) and the Informed Consent/Assent Form must be signed and personally dated by the patient or legally authorized representative. In the Europe, Canada, Australia and New Zealand the investigator or authorized designee must also countersign the Informed Consent/Assent Form. The consenting process must be documented in each subject's source files.

After all persons have signed and dated the Informed Consent/Assent Form, the investigator must provide the subject with a fully signed and dated copy.

Medtronic will inform the investigators whenever information becomes available that may be relevant to the

subject's confirmed participation in the clinical study. The investigator or his/her authorized designee should inform the subject or parent/guardian in a timely manner.

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

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

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

Subjects will be informed that qualified personnel from the investigational center, the sponsor (Medtronic), agencies such as the FDA/Health Canada/local regulatory authority in Europe, Australia, and New Zealand and/or the IRB/EC may have access to clinic records that reveal their identity.

The investigational center must report the following violations to their IRB/EC:

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

10.6 Randomization and Treatment Assignment

At the end of the run-in period, subjects are randomized to either the HCL or the Control arm. Depending on the type of therapy subjects are using at the start of the study the randomization will be to participate in the Hybrid Closed Loop arm or use their own therapy for the duration of the study period. Randomization is generated via the RDC study database.

Note: Subjects 2-6 years of age will automatically enter the HCL arm at the end of the run-in period.

10.7 Assessment of Safety

10.7.1 Adverse Event

The Medtronic Clinical Research Department, in conjunction with the Regulatory Affairs Department, will monitor and manage adverse event reporting for the study and determine whether the event requires reporting to regulatory agencies. The sponsor will ensure timely Adverse Event reporting to meet regulatory requirements.

Throughout the course of the study, investigational centers will make all efforts to remain alert to possible reportable adverse events or untoward findings. The study personnel will elicit reports of adverse events 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, resolution and description that includes the details of the event.

10.7.2 Causality Assessment

An adverse event 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. It should also be noted that should the control arm utilize a non-Medtronic device, these would not be considered device related.

Causality assessment is the determination of the relationship between an adverse event and the device being studied. It is expected that the investigational center will review all elements surrounding the adverse event 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 adverse event 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**

10.7.3 Anticipated or Unanticipated

If the adverse event 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/IB or user guide.

- **Unanticipated:** the event has not been previously identified in the CIP; labeling; report of priors/IB, Investigator brochure, or user guide

10.8 Recording Data

In the Oracle Clinical Remote Data Capture (OC-RDC) database, the investigational centers will be identified numerically, i.e. from 001 to 070 (depending on center number). At the Screening visit, investigational center staff will assign each subject a sequential ID number that corresponds to a pre-defined casebook in the OC-RDC database.

Each case book will contain all relevant Case Report Forms for each subject. Each subject will be assigned a unique identifier All study documents, electronic Case Report Forms (eCRFs) and correspondence will use this identifier sequence in lieu of a subject's name or initials.

10.9 Deviation Handling

A deviation is any instance(s) of failure to follow, intentionally or unintentionally, the requirements of the protocol. It is expected that the investigator will conduct this clinical trial in compliance with the protocol 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:

- Observation in the monitoring report
- Deviation to document the event
- Corrective action plan
- Investigational center disqualification
- Notification to the regulatory authorities / IRB/EC depending on the severity of the deviation and reporting requirements

The investigator is responsible for protecting the safety and welfare of the clinical research subjects.

Reporting of Deviations

USA (to Sponsor and IRB): Any deviation from the CIP shall be recorded in eCRF together with an explanation for the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an

emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. *(21 CFR 812.150(a)(4))*

Europe (Sponsor, Ethics Committee and Regulatory Authority): Any deviation from the CIP shall be recorded in eCRF together with an explanation for the deviation. Deviations shall be reported to the sponsor who is responsible for analyzing them and assessing their significance.

Note: When relevant, ECs, regulatory authorities or the appropriate regulatory bodies should be informed. (ISO 14155:2011)

Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred.

No waivers for deviations from CIP will be allowed.

Canada, Australia and New Zealand (Sponsor and Ethics Committee): Any deviation from the CIP shall be recorded in eCRF together with an explanation for the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred.

10.10 Subject Exit, Withdrawal or Discontinuation

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

If a subject chooses to end his or her study participation or if a subject is removed from the study at the Investigator's discretion, the reason for termination must be documented both in source documents and on the appropriate eCRF. All study devices and supplies must be returned and the return documented both in source documents and on the appropriate eCRF.

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

- In the opinion of the Investigator, the subject's health or safety would be compromised by continuing in the study
- In the opinion of the Investigator, it is in the subject's best interest to discontinue participation in the study
- During the course of the study, subject begins participation in another investigational study (drug or device).

- During the study it becomes known that subjects are using own SMBG or system that replaces SMBG
- During the course of the study, subject begins abusing illicit drugs or marijuana.
- During the course of the study subject begins abusing prescription drugs.
- During the course of the study subject begins abusing alcohol.
- During the course of the study subject begins using pramlintide (Symlin), DPP-4 inhibitors, liraglutide (Victoza or other GLP-1 agonists), metformin, canagliflozin (Invokana or other SGLT2 inhibitors).
- During the course of the study, subject begins using hydroxyurea.
- During the course of the study, subject receives red blood cell transfusion or erythropoietin.
- During the course of the study, the subject demonstrates that he/she is not able to comprehend instructions for study procedures, as evaluated by the appropriate research staff.
- During the study, subject repeatedly activates SmartGuard when instructed otherwise (e.g. Auto Mode is turned on in SAP Cohort)
- During the course of the study, subject is taking oral, injectable, or IV glucocorticoids for 3 or more weeks (e.g. oral prednisone daily or weekly glucocorticoid administration)
- During the study, (female) subject becomes pregnant.
- During the study, the subject experiences two severe hypoglycemic episodes
- The first episode of Severe Hypoglycemia may lead to withdrawal, if it is secondary to subject non-compliance or other individual safety concerns:
    - Subject is not using the bolus wizard
    - Subject is not checking blood glucose using finger sticks
    - Subject is non-compliant with sensor wear
    - Subject is not following protocol procedures
- During the study, the subject experiences one episode of DKA
- During the study subject has a cardiovascular event or any vascular event such as stroke.

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

For Europe only: If patient withdrawal is due to problems related to the device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside the clinical investigation.

Lost to Follow-up:

Lost to Follow-up refers to a subject who was actively participating in the study, but is no longer keeping study visit appointments and/or fails to respond to communications from the investigative site. A subject is only considered to be lost to follow-up in the event the investigational center is unable to determine the status of the subject. It is recommended that the Investigative site:

- Document at least 2 separate attempts to contact subject by phone
- If no response to phone contact, send the subject a registered letter with return receipt
- Requesting the subject contact the investigational center
- If there is no response, the subject should be considered lost to follow-up and investigative site would withdraw the subject

If the subject contacts the investigational center and wishes to withdraw, the subject would no longer be lost to follow-up but instead would be documented as subject withdrawing consent to continue in the study.

10.11 Investigational Center Disqualification

Medtronic and/or the IRB/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 regard to quality and 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 devices.

A written statement fully documenting the reasons for such a termination will be provided to Medtronic, the Institutional Review Board (IRB) or Ethics Committee (EC) and other regulatory authorities, as required.

11. Stopping Rules

11.1 Subject Stopping Rules

1. One episode of DKA or 2 episodes of severe hypoglycemia will result in withdrawal of subject from study, regardless of which arm or period they are in.
2. The first episode of Severe Hypoglycemia may lead to withdrawal, if it is secondary to subject non-compliance or other individual safety concerns:
    - Subject is not using the bolus wizard
    - Subject is not checking blood glucose using finger sticks
    - Subject is non-compliant with sensor wear
    - Subject is not following protocol procedures

11.2 Stopping Rules for Entire Study

The study will be stopped if DMC determines that there are significant safety issues. (See DMC section.)

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

12. Safety Success Criteria

In order to achieve safety success, the following study success criteria must be met for the HCL Arm by the end of the study:

Table 14. Safety Success Criteria

Adverse Event	Reference	Reference Rate > 25 years old	Reference Rate 15-25 years old	Reference Rate <15 years old	Study Success Criteria
DKA events per 100 patient years	STAR 3 Bergenstal et. al	SAP arm: 0.68 Control arm: 0	SAP arm: 2.7 Control arm: 3.6	SAP arm: 2.2 Control arm: 0	≤ 4 events per 100 patient years with HCL arm
	530 G Adult inhome study CEP 266 (MDT on file)	1.27	3.4	N/A	
	530 G Pediatric inhome study CEP 287 (MDT on file)	N/A	N/A	0	
	Type 1 exchange Weinstock et. al	4.8	N/A	N/A	
	Type 1 exchange Cengiz et. al	N/A	9.9	9.9	
Severe hypoglycemia per 100 patient years	STAR 3 Bergenstal et. al	SAP arm: 16.5 Control arm: 20.9	SAP arm: 5.4 Control arm: 3.9	SAP arm: 10.2 Control arm: 3.6	≤ 8 events per 100 patient years with HCL arm

Adverse Event	Reference	Reference Rate > 25 years old	Reference Rate 15-25 years old	Reference Rate <15 years old	Study Success Criteria
	530 G Adult inhome study CEP 266 (MDT on file)	0.85	0	N/A	
	530 G Pediatric inhome study CEP 287 (MDT on file)	N/A	N/A	1.42	
	Type 1 exchange Weinstock et. al	11.8	N/A	N/A	
	Type 1 exchange Cengiz et. al	N/A	6.2	6.2	

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

Severe hypoglycemia and DKA event rates were taken from the following

1. Richard Bergenstal et.al: Effectiveness of Sensor-Augmented Insulin-Pump Therapy in Type 1Diabetes.New England Journal of Medicine, 2010; 363:311-20
2. Weinstock et. al: Severe hypoglycemia and diabetic ketoacidosis in adults with type 1 diabetes: results from the T1D Exchange clinic registry. J Clin Endocrinol Metab. 2013 Aug;98(8):3411-9.
3. Cengiz et. al: Severe hypoglycemia and diabetic ketoacidosis among youth with type 1 diabetes in the T1D Exchange clinic registry. Pediatr Diabetes. 2013 Sep;14(6):447-54.
4. MDT on file: Statistical Analysis Plan (SAP) for CEP304, 056-F286

13. Medical Oversight

In order to conduct the study, staffing with the appropriate training is required:

13.1 Medical Staff

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

13.2 Qualification

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

13.3 Experience

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

14. Safety Monitoring/Risk Analysis

14.1 Glucose Monitoring Risk

- Subjects will be instructed to use clean fingers when performing finger stick glucose testing. Subjects will be instructed to test 4-6 times a day and also before driving (as applicable). Subjects will have training on diabetes self-management principles.

14.2 Hypoglycemic/Hyperglycemic Risk

- Intervention and treatment for hypoglycemia and hyperglycemia is addressed in Section 16.

14.3 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 re-calibrate the CGM. This can result in an incorrect bias. In order to mitigate this risk, every new sensor will have an initial calibration.

14.4 Reuse Risk

- All study devices (including the Serter) will be single patient use.

14.5 Sterilization Risk

The following devices will be supplied sterilized:

- Infusion sets
- Insulin reservoirs
- Glucose sensors

14.6 Misuse Risk

- Comprehensive training will take place for clinical staff regarding the operation of the HCL, all of its

functional components and all other study devices to be used during the study at the investigational center initiation visit.

14.7 Risk of Blood Sample Collection, Contamination From Sampling Techniques

- Detailed mitigations to blood sampling risk are provided in Section 15.

14.8 A1C Risk

- A Central laboratory will be used for A1C testing and a laboratory manual will be provided separately. A1C is a primary endpoint. For subjects 2-6 years of age, Point of Care testing is an acceptable alternative.

15. Glucose and Glycemia Measurements

15.1 Glucose and Glycemia Measurements

During the course of the study, the subjects' blood glucose, SG levels, A1C, and blood ketone, will be assessed using the following methods in this section (Section 15).

15.2 Daily Blood Glucose

Values will be assessed during the study by all subjects using the Study Meter. The control solution test will be done following the manufacturer's IFU during Home use. Subjects will be trained on the use of the Study Meter per the manufacturer's instructions for use.

15.3 Blood Ketone Values

Blood ketones will be determined by all subjects using the Ketone Meter during home use The control solution test will be done following the manufacturer's IFU during Home use. Study staff will be trained on the use of

the Ketone Meter per the manufacturer's IFU. All ketone measurements will be recorded on the appropriate eCRF upon entry into the Log Book section of CareLink Personal for Clinical Research/CareLink Clinical Software.

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

15.4 Sensor Glucose Values

Assessed using the following methods:

SG data collected by subject's Study Pump and calibrated by subject's Study Meter

15.5 A1C

Collected at baseline, will be used as demographic information. Also collected at various points throughout and at end of study.

16. Risks and Benefits

16.1 Potential Risks

Potential Risk with Infusion Sets	Mitigation
Potential side effects related to infusion sets may include: • Localized infection • Skin irritation/redness • Bruising • Discomfort/pain • Bleeding • Irritation	Prevention and mitigation risks of infusion sets include: • Investigational center staff and subjects will be instructed to 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 subjects will be instructed to remove current infusion set and replace with new infusion set and give

• Rash • Hyperglycemia secondary to infusion set occlusion or site failure • Hyperglycemia secondary to site falling off	correction insulin if needed with syringe. Investigational center staff and subjects will be instructed to follow the provided user guides for insulin pump management. • Subjects will be trained prior to study device use and diabetes management principles and told to call with problems.
Potential Risk with Insulin Administration and Pump Use	**Mitigation**
Potential risks associated with the use of an insulin infusion pump 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 (DKA) • Severe hypoglycemia with or without associated seizure, coma or death • Kinked cannula leading to hyperglycemia • Infusion set disconnection from pump leading to hyperglycemia • Dislodged cannula leading to hyperglycemia • A pump error indicating hardware failure may lead to under delivery • Battery failure – no insulin	Prevention and mitigation risks of infusion sets include: • Investigational center staff and subjects will be instructed to follow the provided user guides for insulin pump management. • Subjects will be trained prior to study device use and diabetes management principles and told to call with problems. • Subjects will be required to check SMBG 4-6 times a day and also before driving (as applicable). • Subjects will be told to have glucose on hand for hypoglycemia • Subject will be told they may need to change their infusion set if they suspect catheter occlusion or administer insulin with syringe with persistent hyperglycemia especially if ketones develop.

delivered • Remove a reservoir, without suspending and reconnecting after a while resulting in a Hypoglycemia • Insulin deterioration leading to hyperglycemia • Incomplete priming; Fails to priming 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 /MiniLink malfunction • Inaccurate insulin delivery due to sudden altitude changes. • Hypoglycemia or hyperglycemia from manual bolus • Hypoglycemia or hyperglycemia from computer hacking	
Risks associated with hyperglycemia include • DKA • Symptomatic ketosis • Cardiovascular event • Dehydration	Prevention and mitigation risks include: • Investigational center staff and subjects will be instructed to follow the provided user guides for insulin pump management. • Subjects will be trained prior to study device use and diabetes management principles.

• Potassium and sodium imbalance • Shock • Altered mental status • Coma • Acidosis	
<u>Risks associated with hypoglycemia include:</u> • Seizure • Coma • Altered mental status • Loss of consciousness • Cardiovascular event • Death • Risk of rebound hyperglycemia with ketosis	Prevention and mitigation risks include: • Investigational center staff and subjects will be instructed to follow the provided user guides for insulin pump management. • Subjects will be trained prior to study device use device and diabetes management principles.
Potential Risk with Sensor	**Mitigation**
Potential risks with Sensor include: • Skin irritation or reaction to adhesives • Bruising • Discomfort • Redness • Bleeding • Pain • Rash • Infection • Irritation from tapes used with glucose-sensing products • Raised bump • Appearance of a small "freckle-like" dot where needle was inserted	Prevention and mitigation risks of Sensor include: • Investigational center staff and subjects will be instructed to 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. • Patients are instructed to use fingerstick glucose reading for diabetes management and diabetes management decisions and told to call with problems.

• 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 • Incorrect SG reading results in incorrect diabetes management • Subject over-treating secondary to alarms which can result in hyperglycemia or hypoglycemia	
Potential Risk with Serter	**Mitigation**
Potential risks with Serter use include: • Skin infection around the area where the Serter is used. • Improper insertion may result in device performance issue	Prevention and mitigation risks of Serter include: • Investigational center staff and subjects will be instructed to follow the provided user guides for insertions and care of Serters. The investigational centers and subjects will receive training on proper use of the Serter and skin preparation prior to insertion.
Potential Risk with Finger Stick	**Mitigation**
Potential risks with frequent finger	Prevention and mitigation risks of finger stick testing include:

stick testing 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 drawing blood include discomfort and bruising • Syncopal episode can occur secondary to needle insertion	• Investigational center staff and subjects will be instructed to follow the provided user guides for use of meter with fingerstick testing. The investigational centers and subjects will receive training on proper use of the meter and fingerstick testing.
Potential Risk with HCL	**Mitigation**

Risks for HCL include:
• Hypoglycemia
• Severe hypoglycemia
• Hyperglycemia
• DKA
• 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 hypo and hyperglycemia
  ○ Patient entering false BG values for calibration leading to hypo or hyperglycemia
• Sensor failure resulting from patient failure to calibrate leading to hypo or
	Mitigations specific to the HCL System:
	• Investigational center staff and subjects will be instructed to follow the provided user guides for insulin pump management.
	• Subjects will be trained prior to study device use and diabetes management principles and told to call with problems.
	• Subjects will be required to check SMBG 4-6 times a day and also before driving (as applicable).
	• Subjects will be told to have glucose on hand for hypoglycemia
	• Subjects will be asked to avoid 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.
	• Subjects will be instructed to exit AutoMode

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 hyper or hypoglycemia • Voluntary insulin delivery (with the pump or with a syringe) immediately prior to entering HCL may result in severe hypoglycemia despite shutting down insulin delivery by the algorithm • Patient takes insulin via injection while in Closed Loop • Hypoglycemia or hyperglycemia related to entering or exciting closed loop • Insulin over-delivery due to Acetaminophen	

Risks associated with hyperglycemia include • DKA • Symptomatic ketosis • Cardiovascular event • Dehydration • Potassium and sodium imbalance • Shock • Altered mental status • Coma • Acidosis	Prevention and mitigation hyperglycemic risks include: • Investigational center staff and subjects will be instructed to follow the provided user guides for insulin pump management. • Subjects and/or parent guardian will be trained on study device and diabetes management principles. • Subjects will be trained prior to study device use and diabetes management principles. • Subjects will be required to check SMBG 4 -6 times a day and also before driving (as applicable).
Risks associated with Hypoglycemia include: • Seizure • Coma • Altered mental status • Loss of consciousness • Cardiovascular event • Death • Rebound hyperglycemia with ketosis	Prevention and mitigation of hypoglycemia risks include: • Investigational center staff and subjects will be instructed to follow the provided user guides for insulin pump management. • Subjects will be trained prior to study device use and diabetes management principles. • Subjects will be required to check SMBG 4 -6 times a day and also before driving (as applicable). • Subjects will be told to have glucose on hand for hypoglycemia

16.2 Risk Minimization

Refer to Section 16.1, Potential Risks.

16.3 Potential Benefits

Subjects are not expected to benefit from participation in this study; however, they may gain increased awareness of emerging technologies for diabetes management as a result of their participation.

In Australia, inclusion of the 2-6 years of age group will expand our knowledge and provide specific data in this region.

16.4 Risk-Benefit Rationale

See sections 14, 16.1, 16.2 and 16.3. In Australia, the Investigator Brochure (IB) will be provided to sites.

16.5 Payments for Participants

Subjects will be compensated financially for their participation, as permitted by local law.

17. Adverse Event Assessments

17.1 Definitions/Classifications

Medtronic uses the definitions provided in ISO 14155:2011 and 21 CFR 812 for adverse event definitions. Where the definition indicates “device”, it refers to any device used in the study. This might be the device under investigation, or any market released component of the system. Medtronic will apply causality definitions (Section 10.7.2) across all events, not only serious adverse events and definitions have been adapted accordingly.

17.1.1 Adverse Event (AE) (ISO14155-2011, 3.2)

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.

17.1.2 Adverse Device Effect (ADE) (ISO 14155-2011, 3.1)

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, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

Note 2: This definition includes any event that is a result of a use error or intentional misuse of the investigational medical device.

17.1.3 Serious Adverse Event (SAE) (ISO 14155-2011, 3.37)

Adverse event that:

- Led to a death
- Led to a serious deterioration in the health of the subject, that either resulted in
- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- in-patient or prolonged hospitalization, or
- medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note 1: A planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health, is not considered to be a serious adverse event.

For the purpose of this study, Inpatient Hospitalization is defined as: 24 hour acute admission to the hospital 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)

17.1.4 Serious Adverse Device Effect (SADE) (ISO 14155-2011, 3.36)

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

17.1.5 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.

17.1.6 Unanticipated Serious Adverse Device Effect (USADE) (ISO 14155-2011, 3.42)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Note 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report

17.1.7 Significant Safety Issue (SSI) (Australia, NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016)

A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.

17.1.8 Urgent Safety Measure (USM) (Australia, NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016)

A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.

Note 1: This type of significant safety issue can be instigated by either the investigator or sponsor and can be implemented before seeking approval from Human Research Ethics Committee (HRECs) or institutions

17.2 Reporting of Adverse Events

The investigator or designee will record ALL adverse events 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/Medtronic 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 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
- Not related to procedure or device: cold, flu, appendicitis

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 adverse events 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 adverse events have occurred and require reporting.

Narratives gathered from completed questionnaires will not provide the basis of an adverse event 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.

Sponsor Notification:

Investigator centers should target reporting within 24 hours of investigator or study coordinator awareness for all Severe Hypoglycemia; DKA; Serious Adverse Events; and Serious Adverse Device Effects to Medtronic. The AE eCRF will be completed with all known details within 24 hours of investigational center awareness – 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.

Expedited reporting by sponsor to the regulatory authorities

- Device related Severe Hypoglycemia events
    - The sponsor should report device related severe hypoglycemic events for those subjects > 6 years of age to FDA following notification by investigator prior to enrollment of subjects 2-6 years of age and through study completion.
    - Once enrollment commences for 2-6 year old subjects, the sponsor should report device related severe hypoglycemic events to the FDA within 7 days from sponsor notification by investigator
- Unanticipated, Device related Severe Hyperglycemia events which meet SAE criteria (SADE)
- Sponsor will assess and if event is unanticipated, complete expedited reporting
- Sponsor will follow reporting requirements according to their regulatory authority requirements.

Expedited Safety Reporting of UADE

UADE: For device studies, investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB/EC as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (21 CFR 812.150(a)(1)).

For Canada: Investigators are required, per the TPD Investigator Agreement, to report any incident that is

related to a failure of the device or deterioration in its effectiveness, or any inadequacy in its labeling or directions for use leading to death or serious deterioration in a subject's health within 72 hours after the occurrence (Canada Medical Device Regulations, SOR/98-282; 77, 59.)

For Europe, Australia and New Zealand: It is the responsibility of the investigator to follow their IRB/EC reporting requirements.

For Australia: It is the responsibility of the investigator are to report USDAE to their HREC and institution without undue delay and no later than 72 hours of the Principal Investigator becoming aware of the event.

(NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.g)

For US, Canada, Europe, Australia and New Zealand:

The Sponsor will complete safety and vigilance reporting and notify the investigator and IRB/EC of any event that results in a safety report to the regulatory authorities. Documentation of IRB/EC notification of any safety event must be kept at the investigational center and a copy sent to the Sponsor.

Reporting of Glycemic Events

1. **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)**

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

3. Diabetic Ketoacidosis/DKA diagnostic criteria: blood glucose greater than (>) 250 mg/dL (or greater than (>) 13.9 mmol/L), arterial pH less than (<) 7.3, bicarbonate less than (<) 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

Reporting of Use Errors

The CEC will review adverse events (AE, including: Serious Adverse Event, Serious Adverse Device Effect, Unanticipated Adverse Device Effect, Severe Hypoglycemia, Diabetic Ketoacidosis, Severe Hyperglycemia) to assess the aspect of critical task, user error, potential harm and severity of harm. Once the adjudication is completed, the internal Medtronic team (e.g. clinical, regulatory, human factors, training and etc.) will assess the risk mitigation control and its evidence of effectiveness for each AE. A use error analysis will be provided to FDA every 6 months (Table 15).

Table 15. Use Error Report

Adverse Event #	Critical Task	Use Error	Potential Harm	Severity of Harm	Risk Mitigation Control (Labeling or Training	Evidence for the Effectiveness of Risk Control Mitigation

18. Data Review Committees

18.1 Clinical Events Committee

A clinical events committee (CEC) consisting of external physicians with an expertise in Endocrinology and

the management of diabetes including Insulin Pumps and CGM will be convened. The CEC will review all 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

18.2 Data Monitoring Committee

A Data Monitoring Committee (DMC) consisting of external physicians with an expertise in Endocrinology and the management of insulin requiring diabetes including CGM, along with an external statistician will be convened to review study progress and safety. The Board will convene approximately every 90 days, until at least 2000 Auto Mode patient days in both the 2-6 year and 7-13 year age groups in the CEP302 and/or CEP304 study have been reviewed and approved by the DMC. After review of the patient day report(s), the

meeting cadence will transition to 180 days. The Board will also meet when ad hoc review is required.

In addition, the DMC will review interim analysis data, performed by an independent statistician, per Cohort at the following points in time:

- After 80 subjects from Group 1 (baseline A1c > 8%) have completed the first 6 months of the study period
- After 80 subjects from Group 2 (baseline A1c ≤ 8%) have completed the first 6 months of the study period

The DMC will perform 4 main functions:

First: DMC will review data related to staged enrollment of subjects 2-6years of age (Ad Hoc Review)

- Subjects 2-6 years of age will be allowed to enroll in the post approval study, once DMC has reviewed data from 10 subjects age 2-4 years who have completed participation in the study period of the CEP302 study and has given approval to enroll
- Should an Unanticipated Severe Hyperglycemia event which meets SAE criteria or a device related Severe Hypoglycemia event occur, subjects 2-6 of age will not be allowed to enroll, unless FDA provides approval to include this age group.

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

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

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

Applicable information for device related adverse events may include:

- Whether or not the event was unanticipated
- Review of sensor data from CareLink report (when applicable)
- Review of pump data from CareLink report (when applicable)
- Misuse of the device by the user

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

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

Fourth: During Interim analysis, independent statistician will perform sample size re-estimation and report it to DMC. DMC will then provide a recommendation:

- Whether or not N of enrollment per Group should be increased
- Whether or not the entire study will need to be stopped for futility

General guidance for DMC's recommendations to sponsor should be based on the following:

In general, a DMC recommendation regarding study stoppage or resumption of enrollment should be made to the sponsor within 1 week of the DMC meeting where the determination is made. However, if more data is needed, the DMC may meet again to re-assess their decision within 2 weeks or when required data becomes available.

Review of events may require the following information. Final disposition may be delayed based on obtaining this information:

- Monitoring by sponsor at site
- Device return and failure analysis
- CareLink upload and review of CareLink reports
- Subject clarification to site regarding details about the event
- Source documents that support event: Paramedic records; ER records; Lab records; Hospital admission and discharge summary

The following factors should be carefully considered in the DMC's recommendation to sponsor:

1. Was the severe hypoglycemia or DKA related to the HCL algorithm, or was it related to a known insulin pump risk? For example, a question that may be considered in DKA would be whether the event was related to an infusion set issue or caused by the HCL algorithm.
2. Another important consideration would be if the severe hypoglycemia, severe hyperglycemia or DKA event was related to a device malfunction versus patient non-compliance. For example, if a software anomaly leading to an under-delivery of insulin is discovered versus the subject repeatedly ignoring alarms prompting the subject to take action.

3. Severe hypoglycemia, severe hyperglycemia or DKA caused directly by an infusion set issue when the study pump is functioning as intended would likely result in acceptance to proceed with the study versus severe hypoglycemia or DKA that are directly caused by the HCL algorithm or a device malfunction might stop study enrollment or entire study altogether.
4. It should be noted that the final determination of causality related to HCL System that is made by the DMC may include additional factors which the members consider to be clinically relevant and important.
5. The DMC may take into account the thresholds listed below for the number of subjects experiencing hypoglycemia requiring assistance from another person or DKA to identify when the number of subjects experiencing these events exceeds the number that would be anticipated for the study population over the duration of this study. These thresholds should be interpreted with caution due to potential differences in study populations and study design.
    a. Rates taken from Type 1 exchange (Cengiz et. Al, and Weinstock et. Al), are higher than the clinical studies STAR 3, 530G adult in-home study (CEP266) and 530G Pediatric in-home study(CEP287).
    b. Reasons for lower rates of severe hypoglycemia and DKA in the clinical studies mentioned could be related to several factors including but not limited to the exclusion of those with DKA or severe hypoglycemia, additional attention secondary to mandatory study visits, selection bias of motivated patients willing to perform study procedures and access to free study devices during the course of the study.
    c. The CL outcome study (CEP304) will include several aspects noted above including the provision of free study devices during the course of the study. Therefore, the DMC should consider stopping study if rates of severe hypoglycemia and DKA are significantly worse (e.g. higher) in HCL arm than rates provided by clinical trials mentioned in Table 16.
    d. Age consideration may also be factored in by the DMC. For example, severe hypoglycemia rates in those >25 years may be higher than those 25 years and below.
    e. Should DKA and/or severe hypoglycemia occur early in the study, the DMC should consider that the higher event rate may not necessarily represent a significant safety concern.

Table 16. Hyperglycemia/Hypoglycemia / DKA Threshold

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

Adverse Event	Reference	Reference Rate > 25 years old	Reference Rate 15-25 years old	Reference Rate <15 years old
	(MDT on file)			
	530 G Pediatric inhome study CEP 287 (MDT on file)	N/A	N/A	1.42
	Type 1 exchange Weinstock et. al	11.8	N/A	N/A
	Type 1 exchange Cengiz et. al	N/A	6.2	6.2

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

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

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

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

3. Cengiz et. al: Severe hypoglycemia and diabetic ketoacidosis among youth with type 1 diabetes in the T1D Exchange clinic registry. Pediatr Diabetes. 2013 Sep;14(6):447-54.

4. MDT on file: Statistical Analysis Plan (SAP) for CEP304, 056-F286

19. Statistical Design and Methods

19.1 Statistical Methods and Data Analysis

19.1.1 General Aspects of Analysis

All endpoints are hierarchically ordered and will be evaluated in the fixed sequence from primary endpoints to secondary endpoints. Unless the primary endpoints hypotheses are rejected, secondary endpoints will not be tested.

Effectiveness endpoints will be evaluated during the 6 month study period by individual Cohort (CSII, MDI or SAP), stratified by A1C;

- Group 1: Baseline A1C > 8%
- Group 2: Baseline A1C ≤ 8%

The comparison of HCL **arm** vs. Control **arm** will be performed. For SG-based comparison between HCL vs Control analyses, two weeks of CGM data collected at 3 month visit and 6 month visits will be used.

19.1.2 Endpoints and Hypotheses

Primary Safety Endpoints

The primary safety endpoint is the event rate of severe hypoglycemia and DKA from both Groups (1 & 2) during the first 6 months of study phase and second 6 months of continuation phase. The descriptive summary statistics will be presented by number of event and event rate (100 patient years) for severe hypoglycemia and DKA **separately**.

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

Co-Primary Effectiveness Endpoints

The primary effectiveness endpoints consist of one-primary endpoint for each group.

Group 1 – Baseline A1C > 8%: Change in A1C (ΔA1C)

The primary effectiveness endpoints for the baseline A1C > 8% group is change in A1C from baseline to end of six-month treatment period, defined as A1C measured at the six-month treatment visit minus A1C measured at the randomization visit. The goal is to show superiority of the HCL Arm compared to the Control Arm in reducing A1C from baseline to end of six-month treatment period.

The hypothesis is mathematically expressed as:

$H0: \mu(HCL) \geq \mu(Control)$

$Ha: \mu(HCL) < \mu(Control)$

where μ(HCL) is the mean of change in A1C (%) with the HCL Arm, μ(Control) is the mean of change in A1C (%) with the Control Arm.

Group2 – Baseline A1C ≤ 8%: Time in Hypoglycemic Range

The primary effectiveness endpoint for the baseline A1C ≤ 8% group is the time with SG below 70 mg/dL (3.9mmol/L) during the six-month study period, defined as percentage of SG below 70 mg/dL (3.9mmol/L) out of total number of available SG readings. The goal is to show superiority of the HCL Arm compared to the Control Arm in reducing daily time in hypoglycemic range. The hypothesis is mathematically expressed as:

H0: μ(HCL) ≥ μ(Control)

Ha: μ(HCL) < μ(Control)

where μ(HCL) is the subject mean of time with SG below 70 mg/dL (3.9 mmol/L) in the HCL Arm, μ(Control) is the subject mean of time with SG below 70 mg/dL (3.9 mmol/L) in Control Arm.

Key Secondary Effectiveness Endpoints

Group 1 – Baseline A1C > 8%: Time in Hypoglycemic Range

The key secondary effectiveness endpoint for the baseline A1C > 8% group is the time with SG below 70 mg/dL (3.9mmol/L) during the six-month study period, defined as percentage of SG below 70 mg/dL (3.9mmol/L) out of total number of available SG readings. The goal is to show non-inferiority (with a non-inferiority margin of 2%) of the HCL Arm compared to the Control Arm. The hypothesis of non-inferiority is mathematically expressed as:

H0: μ(HCL) ≥ μ(Control) + 2%

Ha: μ(HCL) < μ(Control) + 2%

where μ(HCL) is the subject mean of time with SG below 70 mg/dL (3.9mmol/L) in the HCL Arm, μ(Control) is the subject mean of time with SG below 70 mg/dL (3.9mmol/L) in the Control Arm.

Group2 – Baseline A1C ≤ 8%: Change in A1C (ΔA1C)

The key secondary effectiveness endpoint for the baseline A1C ≤ 8% group is change in A1C from baseline to end of six-month treatment period, defined as A1C measured at the six-month treatment visit minus A1C measured at the randomization visit. The goal is to show non-inferiority (with a non-inferiority margin of 0.4%) of the HCL Arm compared to the Control Arm in reducing A1C from baseline to end of six-month treatment period. The hypothesis of non-inferiority is mathematically expressed as:

H0: μ(HCL) ≥ μ(Control) + 0.4%

Ha: μ(HCL) < μ(Control) + 0.4%

where μ(HCL) is the mean of change in A1C (%) with the HCL Arm, μ(Control) is the mean of change in A1C (%) with the Control Arm.

Rest of Secondary Effectiveness Endpoints

Group1+Group 2: Time in Hypoglycemic Range during Night

The secondary effectiveness endpoint is the time with SG below 70 mg/dL (3.9mmol/L) during Night. The goal is to show superiority of the HCL Arm compared to the Control Arm reducing time in hypoglycemic range during night . The hypothesis is mathematically expressed as:

$H0: \mu(HCL) \geq \mu(Control)$

$Ha: \mu(HCL) < \mu(Control)$

where μ(HCL) is the subject mean of time with SG below 70 mg/dL (3.9mmol/L) in the HCL Arm during night, μ(Control) is the subject mean of time with SG below 70 mg/dL (3.9mmol/L) in the Control Arm during the night.

Group1+Group 2: Time in Hypoglycemic Range during Day and Night

The endpoint of time in hypoglycemic range below 70 mg/dL (3.9mmol/L) will be evaluated for superiority in the combined Groups during day and night. The goal is to show superiority of the HCL Arm compared to the Control Arm in reducing time in hypoglycemic range. The hypothesis is mathematically expressed as:

$H0: \mu(HCL) \geq \mu(Control)$

$Ha: \mu(HCL) < \mu(Control)$

where μ(HCL) is the subject mean of time with SG below 70 mg/dL (3.9 mmol/L) in the HCL Arm, μ(Control) is the subject mean of time with SG below 70 mg/dL (3.9 mmol/L) in the Control Arm.

Group1+Group 2: Time in Target Range 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) during Night

The endpoint of time in target range measures the time with SG in target range 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) during Night. The goal is to show superiority of the HCL Arm compared to the Control Arm in improving the time in target range. The hypothesis is mathematically expressed as:

$H0: \mu(HCL) \leq \mu(Control)$

$Ha: \mu(HCL) > \mu(Control)$

where μ(HCL) is the subject mean of time with SG between 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) range in the HCL Arm during Night, μ(Control) is the subject mean daily time with SG between 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) range in the Control Arm.

Group1+Group 2: Time in Target Range 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) during Day and

Night

The endpoint of time in target range measures the time with SG in target range 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) during Day and Night. The goal is to show superiority of the HCL Arm compared to the Combined Control Arm in improving the time in target range. The hypothesis is mathematically expressed as:

H0: $\mu(HCL) \leq \mu(Controls)$

Ha: $\mu(HCL) > \mu(Controls)$

where $\mu(HCL)$ is the subject mean of time with SG between 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) range in the HCL Arm during Day and Night, $\mu(Control)$ is the subject mean daily time with SG between 70mg/dL (3.9mmol/L) – 180 mg/dL (10.0mmol/L) range in the Control Arm.

Group1+Group 2: Change in A1C

The endpoint of change in A1C will be evaluated for superiority in the combined groups. The goal is to show superiority of the HCL Arm compared to the Control Arm in reducing A1C from baseline to end of six-month treatment period. The hypothesis is mathematically expressed as:

H0: $\mu(HCL) \geq \mu(Control)$

Ha: $\mu(HCL) < \mu(Control)$

where $\mu(HCL)$ is the mean of change in A1C (%) with the HCL Arm, $\mu(Control)$ is the mean of change in A1C (%) with the Control Arm.

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19.1.4 Randomization

For each Cohort (CSII, MDI or SAP) subjects will be randomized to HCL and Control Arm with a 1:1 ratio for greater than 6 years of age. 2-6 years of age subjects will automatically enter the HCL arm at the end of the run-in period.

The randomization will be stratified by the diabetes management therapies at time of enrollment and baseline A1c categories:

Diabetes Management Therapies(Cohort):

- CSII: Insulin pump therapy without CGM
- MDI
- SAP: Insulin pump therapy with CGM

Baseline A1C categories(Group):

- Baseline A1C ≤ 8%
- Baseline A1C >8%

Randomization will be based on a total of four strata per Cohort. In each stratum, block randomization will be used to divide potential patients into 2m blocks of size of 2n (block size can be different for each stratum). Please note that MDI group will be further stratified to equal number of subjects without CGM and with CGM. The clinical team and investigators are blind to the block size. Equal amount of subjects will be enrolled for Baseline A1C ≤ 8% group and Baseline A1C > 8% group.

19.1.5 Study Populations

Intention to Treat (ITT) Population

The primary study population is the Intention to Treat (ITT) population, which consists of all randomized subjects.

Per Protocol (PP) Population

The Per Protocol (PP) population will include all randomized subjects who complete the trial without any major deviations, have worn the sensor for both Arms (Control and HCL) and have used Automode (HCL only) for ≥ 80% of the time. In addition, those subjects who take steroids after randomization will be excluded from PP population. Primary effectiveness endpoints and key secondary endpoints will be evaluated for PP Population.

Safety Population

The Safety Population will be all enrolled subjects.

19.1.6 Analysis of Endpoints

Primary Effectiveness Endpoints:

Test will be tested against the 0.025 (one-sided) significance level and both have to be met to claim success for the associated Cohort.

Group1 – Baseline A1C > 8%: Change in A1C (ΔA1C)

The initial univariate analysis for this endpoint will be an analysis of covariance at six months. If the computed F-statistic has a one-sided P<0.025 (can be computed from the two-sided F-statistic by taking the square root and comparing to a one-sided t-statistic), the null hypothesis will be rejected in favor of the alternative, Other supporting analysis including multivariable modeling may also be done to support this finding.

Group2 – Baseline A1C ≤ 8%: Time in Hypoglycemic Range

The initial univariate analysis for this endpoint will be an analysis of covariance F-test at six months. If the computed F-statistic has a one-sided P<0.025 (can be computed from the two-sided F-statistic by taking the square root and comparing to a one-sided t-statistic), the null hypothesis will be rejected in favor of the

alternative. Other supporting analysis including multivariable modeling may also be done to support this finding.

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19.1.11 Coding of Adverse Events

Adverse events will be coded based on the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus.

[redacted]

20. Ethics

Risk Determination

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

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

Therefore, for subjects 2-13 years of age, submission of an Investigational Device Exemption (IDE) application

to the United States Food and Drug Administration is required

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

Institutional Review Board (IRB) / Ethics Committee (EC)

This protocol, any subsequent amendments to this protocol, the Informed Consent/Assent form, subject material and any form of subject recruitment information (e.g. advertisements) relating to this study will be approved by the responsible EC/IRB in accordance with 21 CFR Part 56 in the US, ISO 14155:2011, Declaration of Helsinki and local ethic requirements, as applicable. The study will not start until IRB/EC approval has been granted, the Sponsor has cleared the investigational center to begin the study, and the investigational clinical staff has been appropriately trained to conduct the study. Copies of all relevant correspondence between the investigational center and the IRB/EC will be retained at investigational center and the Sponsor files.

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

Regulatory Submission

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 Clinical Investigation Plan 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.

Regulatory Compliance

In Canada, Europe, Australia and New Zealand this clinical study will be conducted in compliance with the Declaration of Helsinki 2013, the international standard ISO 14155:2011 ('Clinical Investigation of medical devices for human subjects'), as well as laws and regulations of the country/ies in which the clinical study is conducted (including data protection laws). Europe is also compliant with FDA regulations 21 CRF Part 11 and 21 CRF Part 54, and EU MDR.

In Canada, SOR/98-282 will also be followed.

In the US, this clinical study will be conducted in compliance with the Declaration of Helsinki 2013, the Clinical Investigation Agreement, the Clinical Investigation Plan, FDA regulations CFR, Title 21, Part 54 (Financial Disclosure by Clinical Investigators), CFR, Title 21, Part 11 (Electronic Records; Electronic Signatures), 21 CFR

Part 812 (Investigational Device Exemptions), 21 CFR Part 56 (Institutional Review Boards) , 21 CFR Part 50 (Informed consents) and all other applicable federal and local regulatory requirements.

All principles of the Declaration of Helsinki have been implemented in this clinical study by means of the informed consent process, IRB/EC approval, study training, clinical trial registration, preclinical testing, risk benefit assessment, publication policy, etc.

Ethical Considerations

The sponsor will avoid improper influence on, or inducement of the subject, monitor, and investigator(s) or other parties participating in, or contributing to, the clinical study by implementing the informed consent process, Clinical Investigation Agreements and IRB/EC approval. Pediatric patients (2-21 years) will be involved in this study and will be provided with assent as applicable.

20.1 Statement(s) of Compliance

The investigator or person designated by the investigator will document and explain any deviation from the approved protocol that occurs during the course of the clinical trial. The date and reason for each deviation will be documented. (21 CFR 812.140 Records for US/ ISO14155:2011 9.6g for Europe, Australia and New Zealand)

The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/EC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)).

The investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/EC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

- To the IRB/EC for review and approval/favorable opinion
- To the sponsor for agreement and, if required
- To the regulatory authority or authorities

Except in an emergency, prior approval by the sponsor, regulatory authorities and IRB/EC is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects. (21 CFR 812.35(a)) for US / ISO14155:2011 4.5.4 b))
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In any emergency situation the investigator shall exercise his/her judgment to safeguard the subject's interest. The investigator shall report a deviation as soon as possible to Medtronic and the reviewing IRB/EC, according to IRB/EC reporting guidelines, as applicable. Medtronic will inform the regulatory authorities, if required.

Emergency deviations must be reported to the sponsor and IRB/EC within 5 days. In Australia, clinical trials with unapproved medical devices require reporting of serious breaches by investigator and sponsor.

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, i.e., there is no documentation of informed consent
- Informed consent obtained after initiation of study procedures
- Enrollment of a subject who did not meet all inclusion/exclusion criteria
- Performing study procedure not approved by the IRB/EC
- Failure to report serious adverse event to the IRB/EC and sponsor
- Investigational study device dispensed without obtaining informed consent

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, additional training, terminate the study, etc.). Repetitive or serious investigator compliance issues may result in the need to initiate a corrective action plan, and in some cases freeze enrolment or ultimately terminate the investigator's participation in the clinical study (see section 10.9).

The investigator will propose any appropriate modification(s) of the Clinical Investigation Plan or investigational device/product or investigational device/product use. Medtronic will review this proposal and decide whether the modification(s) will be implemented.

Medtronic will submit any significant amendment to the Clinical Investigation Plan, including a justification for this amendment, to the appropriate regulatory authorities and to the investigators to obtain approval from their IRB/EC. The investigator will only implement the amendment after approval of the IRB/EC, regulatory authority and sponsor. Administrative amendments to the Clinical Investigation Plan will be submitted to the IRB/EC for notification. Furthermore investigators shall sign any approved amendment for agreement:

21. Device Deficiencies and Troubleshooting

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

device deficiencies that are reported to the TS will be documented by the TS staff.

Medtronic will review all device deficiencies and determine whether the deficiency requires reporting to regulatory agencies; vigilance reporting includes all devices that are CE marked in Europe. The sponsor will ensure timely Device Deficiency reporting to meet regulatory requirements.

Note: For commercially available devices, device deficiency reporting will be documented per study and relevant regulatory requirements

Depending on the country, 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 and for the possibility of an AE. If an AE is detected the investigational center staff will also complete an AE eCRF.

In the US, 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 Europe Canada, Australia and New Zeland all device deficiencies reported directly to the investigational center staff by a subject and should be documented on a Device Deficiency eCRF.

A device deficiency is any communication that alleges 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. (**Adapted from ISO14155:2011 3.15**)

In the US, Canada, Europe, Australia and New Zealand: While 24-Hour TS may direct the return/replacement of study devices, all such transactions will be managed by investigational centers directly. Subjects are asked to call the 24-Hour TS for help with the troubleshooting of devices.

It is the responsibility of the Investigator to follow the center's IRB/EC and local regulatory authority reporting requirements.

For Europe Canada, Australia and New Zealand:

Device deficiencies that did not lead to an Adverse Event, but could have led to an SADE require immediate reporting to the sponsor via completion of the applicable CRF. In addition, follow the IRB/EC and regulatory authority reporting requirements per ISO14155:2011 if any of the following apply:

a) if either suitable action had not been taken,

b) if intervention had not been made, or

c) if circumstances had been less fortunate

In Australia: All device deficiencies for investigational devices with potential SADE need to be reported by investigator without unjustified delay (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.b).

22. Study Administration

22.1 Monitoring

Monitoring will be conducted to ensure the protection and safety of human subjects, the quality and integrity of the clinical data, and compliance with the protocol. The Monitoring Plan will give details on how and when data review will be conducted by clinical monitors. It will be updated and revised as needed due to changes in documents or processes.

Employees of the Sponsor, or its designees, who have received appropriate training, will serve as the Study Monitor(s). Monitoring visits will be conducted based on Medtronic's Standard Operating Procedures and the needs of the study. Quality documents will be followed for the conduct of all activities related to monitoring for this study.

Site Qualification and Initiation Visits will be completed prior to enrollment of the first subject. On Site study monitoring activities will include an inspection of completed study documents, source document verification and reporting, verification of database accuracy and completeness. All subjects enrolled in the trial will be monitored and the eCRF data verified against the subjects' source documents. Following each monitoring visit, a report will be prepared and submitted to the Sponsor. From initiation of study to close out visit, the Study Monitor(s) will assume primary responsibility for communications between the Study Investigators and the Sponsor.

The Principal Investigator is responsible for ensuring that investigational center staff is appropriately trained to manage the protocol. Initial and ongoing investigational center training will be provided during the Site Initiation Visit, subsequent monitoring visits, and regular investigational center contact. All investigational center staff must complete and sign the Study Training Record(s) and maintain the record(s) in the investigational center regulatory binder. Prior to enrollment of the first subject, Investigators and study coordinators who will be participating in enrollment, eCRF completion, device insertion/application, device training, and consenting subjects must complete the Sponsor-required training. Investigators and staff who are actively engaged in the study after the start of subject enrollment must complete all required training before their involvement starts.

All monitoring visits and visits from the Sponsor to the investigational center will be recorded using the Monitoring Visit Log. The log will be kept in the investigational center regulatory binder and the original will be collected and submitted to the sponsor.

22.2 Data Management

All data required for analysis will be captured on eCRFs using OC-RDC module. Original eCRFs will not be

considered as source data and supporting documentation will be required. However, in cases where center-administered, web-based subject questionnaires are considered source data, said source data is electronic and associated systems must comply with CRF 21 Part 11 requirements. Electronic device data will be collected from the MiniMed Pump System using Medtronic CareLink Personal for Clinical Research/CareLink Clinical Software. The system uses TLS technology, which encrypts all data it stores (21 CFR Part 11 compliant). Certain data points stored in the uploaded information may also be captured on the appropriate eCRF.

The Investigator will ensure that all eCRFs are completed promptly, completely, and accurately. Information on case report forms must conform to the information in the source documents. 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 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. If a person is only authorized to complete CRFs or to make changes to an already signed CRF, the investigator shall re-sign this CRF. System backups for data stored in the OC-RDC system will be consistent with Medtronic standard procedures.

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

22.3 Data Preparation

Prior to data extraction, all collected data will undergo a final verification by Data Management. Documentation of this verification will be maintained in the sponsor study files. Upon the completion of the verification, data will be extracted and transferred to the appropriate personnel for analysis.

22.4 Study Binders

Investigator Binders will be provided by the Sponsor to be maintained by the designated investigational center staff. Each binder will have tabs to facilitate filing of study documents. Examples include:

- Medtronic Contact Information
- CV's & Medical Licenses
- Agreement(s)
- Delegation of Authority Log

- Training Records
- Randomization Documentation (if applicable)
- Laboratory Documentation
- Subject Identification Log
- Screening Log
- Case Report Forms (CRFs) & Instructions
- Sponsor/Monitor Visit Log
- Investigator Brochure (IB)
- Protocol and Amendments
- Device Instructions for Use (IFU)
- IRB/EC Documentation & Approvals
- IRB/EC Approved Consent Documents
- IRB/EC approved Investigator's Brochure/ Report of Priors
- Regulatory Authority approval or notification
- Financial Disclosures
- Insurance certificates, where applicable
- Reports
- Essential Correspondence
- Product Accountability
- Regulations and Guidance Documents
- Site Study Materials
- Subject Study Materials
- Note to File
- Miscellaneous
- Relevant communication

There will be an individual file for each subject which will include, but will not be limited to:

- Source Documents
- Signed and dated Informed Consents/Assents
- Adverse Event Notifications, if any
- Questionnaires
- Study Logs, if any

For Europe, Australia and New Zealand: The investigator will clearly mark the clinical records to indicate that the subject is enrolled in this clinical study.Where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigational site team with a statement that it is a true reproduction of the original source document.

22.5 Direct Access to Source Data/Documents

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

These audits are done in addition to the regular monitoring visits.

Regulatory bodies may also perform inspections at participating investigation sites. Any regulatory authority inspection announcements shall be forwarded immediately to the sponsor contact person.

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

22.6 Confidentiality

The investigator will ensure that the subject's anonymity is maintained. Subjects will not be identified in any publicly released reports of this study. All records will be kept confidential to the extent provided by federal, state and local law. The study monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records. The investigator will inform the subjects that the above-named representatives will review their

study-related records without violating the confidentiality of the subjects. All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified only by the subject identification 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.

22.7 Liability

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.

22.8 CIP Amendments

When an amendment is required, the CIP will be forwarded to FDA and applicable regulatory authorities outside the United States for approval. Upon receipt of regulatory authority approval, the document will be version controlled using the next version number in succession, e.g. A to B. After the document is released by Medtronic's document control system, it will be submitted to all applicable regulatory agencies, IRBs and Ethics Committees for review and approval. Individual investigational centers may not enroll subjects under the amended investigational plan until Regulatory/IRB/Ethics approvals have been obtained including, if applicable, a revised Informed Consent.

22.9 Record Retention

The Sponsor and Investigator will retain all records and documents pertaining to this study. They will be available for inspection by the appropriate regulatory agencies. In addition, the Investigator will retain the source documents from which the information entered on the eCRF was derived. These records are to be retained in a secure storage facility maintained by the investigational center until 2 years (or longer if local laws require) after approval of the above-listed study devices or termination of the study, whichever is longer. The Investigator should not dispose of these records without the approval of the Sponsor. The investigator should take measures to prevent accidental or early destruction of the clinical study related materials.

22.10 Publication and Use of Information

The contents of this protocol, the manuals pertaining to this study and the results of the investigation are confidential and may not be published or disclosed without the written consent of Medtronic Diabetes. 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 of the clinical study will be submitted for publication and handled according to Standard Operating Procedures.

22.11 Suspension or Early Termination

This study will be conducted at up to 70 investigational centers where all study-related activities will take place; at each center, the study will be led by a principal investigator. Per 21 CFR 812.3(i), *Investigator* means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

It is expected that the investigator(s) are familiar with the regulations governing the conduct of clinical research on human subjects. Guidance for Industry Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects provides clarification for investigators and sponsors.

FDA's expectations concerning the investigator's responsibility

(1) to supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other third parties and

(2) to protect the rights, safety, and welfare of study subjects

The investigator's responsibilities include:

- Ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of medical devices, the investigational plan, and applicable regulations set forth in 21 CFR Part 812 and all other applicable regulations, and any conditions of approval imposed by an IRB/EC or regulatory requirements.
- Medtronic contracts with participating institutions/investigators through a Clinical Trial Agreement that defines the scope and responsibilities and associated compensation related to carrying out the obligations under a clinical study sponsored by Medtronic.
- 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 protocol so that study subjects are not exposed to unreasonable risks

- Controlling devices under investigation (21 CFR 812.100 for US / ISO14155:2011 6.9 for Europe, Australia & New Zealand and in accordance with Canadian regulations where applicable).
- Investigator is responsible for providing adequate supervision of those to whom tasks have been delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of a clinical study.
- Ensuring that informed consent is obtained from each subject in accordance with 21CFR Part 50 for the US, Tri-Council Policy Statement, Article 3.2 for Canada and ISO14155:2011 for Europe, Australia & New Zealand and that the study is not commenced until regulatory authority and IRB/EC approvals have been obtained.
- Supervising the use of investigational device. In US, an investigator shall permit an investigational device to be used only with subjects under the investigator's supervision. In US, an investigator shall not supply an investigational device to any person not authorized under 21 CFR Part 812 to receive it. In Europe and Australia, the investigational devices shall only be used in the clinical investigation and according to the protocol (ISO14155:2011 6.9).
- 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.
- Continuously monitoring, assessing and documenting risks
- An investigator shall maintain at a minimum the following accurate, complete and current records relating to the investigator's participation in an investigation (21 CFR 812.140 140 for US, ISO14155:2011 7.4 for Europe, Australia and New Zealand):
- Correspondence with another investigator, an IRB/EC, the sponsor, a monitor or FDA/ local regulatory authority in Europe, Australia and New Zealand.
- Records of receipt, use or disposition of study devices
- Records of each subject's case history and exposure to the study devices
- Documents showing the dates of and reasons for each deviation from the protocol
- Any other records the FDA/ local regulatory authority in Europe, Australia & New Zealand requires to be maintained by regulations or by specific requirement for a category of investigations or a particular

investigation

- Investigators are required to permit FDA/ local regulatory authority to inspect and copy any records pertaining to the investigation including, in certain situations, those which identify subjects.(21 CFR 812.145 in US / ISO14155:2011 6.7)
- An investigator shall prepare and submit the following complete, accurate, and timely reports

Table 17. Investigator records and reporting responsibilities applicable to the United States

Report	Submit To	Description/Constraints
Withdrawal of IRB approval (either suspension or termination)	Sponsor	An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation. *(21 CFR 812.150(a)(2)).*
Progress report	Sponsor and IRB	The investigator must submit this report to the sponsor and IRB at regular intervals, but in no event less than yearly. *(21 CFR 812.150 (3))*.
Study deviations	Sponsor and IRB	Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. *(21 CFR 812.150(a)(4))*
Failure to obtain IC prior to investigational device use	Sponsor and IRBs	If an investigator uses a device without obtaining informed consent, the investigator shall report such use within 5 working days after device use. *(21 CFR 812.150(a)(5))*
Final investigator report	Sponsor, IRB s and Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation. *(21 CFR 812.150(a)(6))*
Other	IRB and FDA	An investigator shall, upon request by a reviewing IRB, FDA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation. *(21 CFR 812.150(a)(7))*

Table 18. Investigator Reports Applicable to Europe

Report	Submit To	Description/Constraints
Withdrawal of MEC approval	Sponsor	The investigator must report a withdrawal of approval by the reviewing MEC of the investigator's part of the investigation within 5 working days of the date of withdrawal. *(Medtronic Requirement)*
Progress Report	Sponsor and Ethics Committee	Provide if required by local law or EC. (ISO 14155:2011)
Study Deviations	Sponsor and Ethics Committee and Regulatory Authority	Any deviation from the CIP shall be recorded together with an explanation for the deviation. Deviations shall be reported to the sponsor who is responsible for analyzing them and assessing their significance. Note: When relevant, ECs, regulatory authorities or the appropriate regulatory bodies should be informed. (ISO 14155:2011) Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred.
Final investigator report	Ethics Committee and Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation.

Table 19. Investigator Reports Applicable to Canada

Report	Submit To	Description/Constraints
Withdrawal of Ethics Committee approval	Sponsor	The investigator must report a withdrawal of approval by the reviewing Ethics Committee of the investigator's part of the investigation within 5 working days of the date of withdrawal. *(Medtronic Requirement)*

Report	Submit To	Description/Constraints
Progress Report	Sponsor and Ethics Committee	Provide if required by local law or EC.
Study Deviations	Sponsor and Ethics Committee	Any deviation from the CIP shall be recorded together with an explanation for the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. (*Medtronic Requirement)*
Final investigator report	Ethics Committee and Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation. *(Medtronic Requirement)*

Table 20 Investigator Reports Applicable to Australia

Report	Submit To	Description/Constraints
Withdrawal of Ethics Committee approval	Sponsor	The investigator must report a withdrawal of approval by the reviewing Ethics Committee of the investigator's part of the investigation within 5 working days of the date of withdrawal.
Progress Report	Sponsor and Ethics Committee	Provide if required by local law or EC.
Study Deviations	Sponsor and Ethics Committee	Any deviation from the CIP shall be recorded together with an explanation for the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred.
Final Investigator Report	Ethics Committee and Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation.
Serious Breaches by	Sponsor,	Investigator shall report any suspected breaches to the

Report	Submit To	Description/Constraints
Investigator or Sponsor (Pre-market requirement)	Institution's Research Governance Office, Ethics Committee, or Principal Investigator as applicable	sponsor and confirmed serious breaches to their institution (research governance office) within 72 hours of becoming aware or notified of the same; provide any follow-up information as required and work with the institution or sponsor, as appropriate, to implement any corrective and preventative actions by sponsor shall report serious breaches to the reviewing HREC and PI within 7 calendar days of confirming a serious breach has occurred and provide follow-up reports when required Australia - Serious Breach: A breach of Good Clinical Practice or the protocol that is likely to affect to a significant degree: a) The safety or rights of a trial participant,or b) The reliability and robustness of the data generated in the clinical trial.
Significant Safety Issues (Pre-market requirement)	Sponsor, HREC and institution	Urgent Safety Measure (USMs): Within 24 hours (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.c) All other significant safety issues: without undue delay and no later than 72 hours of the principal investigator becoming aware of the event (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.g)

Table 21 Investigator Reports Applicable to New Zealand

Report	Submit To	Description/Constraints
Withdrawal of Ethics Committee approval	Sponsor	The investigator must report a withdrawal of approval by the reviewing Ethics Committee of the investigator's part of the investigation within 5 working days of the date of withdrawal. *(Medtronic Requirement)*
Progress Report	Sponsor and Ethics Committee	Provide if required by local law or EC.

Report	Submit To	Description/Constraints
Study Deviations	Sponsor and Ethics Committee	Any deviation from the CIP shall be recorded together with an explanation for the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred.
Final investigator report	Ethics Committee and Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation.

- To the sponsor and IRB/EC (per their requirements):
    - Any *unanticipated adverse device effect* occurring during an investigation. (Due no later than 24 hours after the investigator first learns of the effect)
- It is prohibited to promote and commercialize a device that has not been first cleared or approved for marketing by the FDA (per IDE regulations) or local regulatory authority in Europe,Canada, Australia or New Zealand.
- The principal investigator(s) are required to assess whether or not to continue the clinical study at the respective investigation site.
- The principal investigator(s), his/her delegate(s) and the study coordinator(s) shall be accessible to Medtronic personnel. This accessibility is of particular importance for reviewing data in the Case Report Form (CRF). Direct access to patient medical files for source data verification will need to be granted and prepared prior to any monitoring visits
- Sponsor will inform the clinical investigators of termination or suspension and the reasons and inform the regulatory authorities, where required.

The investigator's signature on the Investigator Statement confirms that the investigator is familiar with the protocol in its entirety and agrees to conduct this study in accordance with the provisions of the protocol 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, investigational protocol, or other regulatory requirements, the Sponsor shall promptly secure compliance or discontinue that Investigator's participation in the study.

22.12 Study Closure Procedures

Upon completion of the study, when all subjects have completed their visit schedules (all eCRFs have been entered and all related queries have been resolved), all study devices, unused study materials and equipment will be collected and returned to Medtronic and/or its designees. Medtronic and/or its designees will notify the investigational center of its intention to close out the study and a close-out visit will be conducted. The Monitor will ensure that the Investigator's regulatory files are up-to-date and complete and that any outstanding issues from previous visits have been resolved. Other issues that will be reviewed at this visit include discussing retention of study files, possibility of investigational center audits, and notifying the IRB/EC of study closure.

23. References

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

American Diabetes Association Workgroup on Hypoglycemia. Defining and Reporting Hypoglycemia in Diabetes, Diabetes Care. 2005. 28: 1245-9.

Diabetes Research in Children Network (DirecNet) Study Group; Type 1 Diabetes TrialNet Study Group, Buckingham BA, Beck RW, Ruedy KJ, Cheng P, Kollman C, Weinzimer SA, DiMeglio LA, Bremer AA, Slover R, Cantwell M. The effects of inpatient hybrid closed-loop therapy initiated within 1 week of type 1 diabetes diagnosis. Diabetes Technol Ther. 2013. May;15(5):401-8.

Medtronic, HCL Outcomes Study Clinical Study Training Protocol.Weinzimer et. al: Fully Automated Closed Loop Delivery versus Semi-Automated Hybrid Control in Pediatric Patients with Type 1 diabetes using the Artificial Pancreas. Diabetes Care, 2008, 31:934-939.

24. Appendices

24.1 Appendix A: CEP304 Cohort Visit Table- HCL Arm

Refer to excel sheet labeled as “CEP304_ Cohort Visit Table_HCL Arm”.

24.2 Appendix B: CEP304 Cohort Visit Table- CSII Arm

Refer to excel sheet labeled as “CEP304_ Cohort Visit Table_CSII Arm”.

24.3 Appendix C: CEP304 Cohort Visit Table- MDI Arm

Refer to excel sheet labeled as “CEP304_ Cohort Visit Table_MDI Arm”.

24.4 Appendix D: CEP304 Cohort Visit Table- SAP Arm

Refer to excel sheet labeled as “CEP304_ Cohort Visit Table_SAP Arm”.

25. Version History

Version	Summary of Changes	Author(s)/Title
A	• Not applicable, New Document	[redacted]
B	• Corrected visit schedule • Revised Statistical Section • Updated Visit Tables • Revised Subject Stopping Rules • Revised Safety Section according to new Meddev regulations • Deleted redundancies • Revised Visit Schedule • Revised DMC Section • Revised Study and Continuation Period Summaries • Updated Inclusion Criteria • Revised Safety Success Criteria table	[redacted]
C	• Corrected Visit Schedule Tables • Updated device classifications • Revised inclusion/exclusion criteria • Revised device accountability tables • Revised Risk/Mitigations tables	[redacted]
D	• Updated references of EMEA to Europe • Added reference to StartRight program for HCL subjects	[redacted]

Version	Summary of Changes	Author(s)/Title
	• Updated device classifications and device numbers • Updated and corrected Visit Schedule Tables and transferred visit tables into Appendix. • Updated study procedures (includes run-in period window and additional study visits for each group after Auto Mode is turned on) • Revised inclusion/exclusion criteria • Updated subject withdrawal or discontinuation criterias • Updated subject stopping rules • Revised device accountability tables • Updated Adverse Events Assessment section • Removed statement about regulatory submission in Israel • Modified pediatric distribution for enrollment in CSII cohort. • Transferred to updated version of Medtronic corporate branded form CIP template (Version 3.0) • Moved CIP version history table to end of document • Updated Packaging section– removed investigational labeling statement for US and added statement that copies of labeling for study devices will be provided under separate cover • Updated device descriptions for infusion sets, reservoirs and infusion set serter devices • Provided information about subjects who are Freestyle Libre users at time of screening	

Version	Summary of Changes	Author(s)/Title
	• Provided information about telemedicine visits • Updated Product Training Requirements section to expand to be more generic on who supports the sites • Added Liability section to align with CIP required elements • Updated IRB/Ethics requirements • Updated Device Deficiencies and Troubleshooting section	
E	• See "CEP304 Summary of Protocol Changes, Version D to E"	[redacted]
F	• Updated study devices status for Canada • Statement updated to reflect investigational devices in US for subjects 2-6 years age group • Updated protocol to reflect CE marked devices • Updated Run-in and Study period - additional clarification to the blinded CGM section • Permitted MDI subjects with concurrent CGM to enroll • Updated sample size number during study period for Cohort 2: MDI subjects • Added sensor insertions should proceed with approved User Guide • Inclusion criteria #6 updated • Removed exclusion criteria #1 • Added Early withdrawal procedures • Added rescreening • Added exploratory analysis	[redacted]

Version	Summary of Changes	Author(s)/Title
	• Updated safety sections • Added Severe Hyperglycemia adverse event reference rates from the CEP302 Clinical study • Updated Visit Schedule Tables • Made changes to Exploratory analysis section regarding alert performance • Added statement regarding SMBG confirmation upon low alert • Added statement regarding investigational labeling requirement to visit table attachments in each cohort • Re-arranged devices according to age group in synopsis and Table 7.2 • For details on protocol changes, see "CEP304 Description of Protocol Changes, Version E to F"	
G	• Updated part numbers to reflect correct numbers. • Deleted references to the 670G system to allow for inclusion of the 770G system. • Added 770G system and devices to reflect 770G system approval and use in the US and other geographies. • Updated study duration to 6.5 years, enrollment completion to 54 months, Table 5 and Table 6 to account for a slow-down in pediatric enrollment. Deleted Chart 1 and Chart 2. • Updated the minimum requirement per cohort • Updated minimum eligible subjects table to facilitate recruiting. • Updated the Inclusion criteria remove TSH	[redacted]

Version	Summary of Changes	Author(s)/Title
	requirement for subjects 2-13 years of age. • Changed randomization for 2-6 year olds so that all enrolled subjects will participate in the study group only • Updated telemedicine requirements • Updated Medtronic CareLink Clinical Therapy Management Software name to reflect the correct product name. • Updated the treatment cohort statement to allow for transition to the 770G system in US and Canada. • Added the Contour Next Link 2.4 Blood Glucose Meter to the list of investigational devices for US subjects 2-6 years. • Updated product status headings and bullets for clarity. • Deleted note on StartRight program. • Updated visit scheduling to avoid visit window overlap. • Added explanation of remote monitoring for pediatric patients. • Updated Table 7 to reflect correct numbers for parts distributed in Canada. Added footnotes for clarity. • Added Table 8 to reflect addition of 770G to the study. • Updated Table 9 to incorporate 770G pump and related devices. Split Guardian Sensor (3) into 2 rows to account for difference in disbursement to subject. • Updated Table 10 to remove part numbers for	

Version	Summary of Changes	Author(s)/Title
	Canada and update device disposition. • Updated Table 11 to incorporate 770G pump and related devices. Split Guardian Sensor (3) into 2 rows, correct part numbers and update disbursement to subject. • Added Table 12 and 13 to reflect Australian and New Zealand requirements. • Added Reporting of Use Errors section per FDA guidance. • Updated document to align new EUMDR guidelines which includes name of the local sponsor contact, specific language related to public databases (e.g., clinicaltrials.gov), product accountability, deviations, Europe record retention requirement, regulatory compliance statement, glossary, and investigator statement. • Updated Investigator Statement name to reflect the correct name of form. • Updated trademark notation to conform with updated trademarking by Ascensia. Contour Next Link is no longer owned by Bayer. • Updated Clinical Study Type for clarity. • Updated Schedule of Events introduction • Updated Early Withdrawal description for clarity. • Corrected MDI Cohort Visit 7 description. • Updated document to reflect new CIP • template requirements, including Study Site Requirement section, section heading titles, Lost to Follow-up definition, Risk Minimization section, updated document footer, study binder tab list, and Aspects of Analysis section header.	

Version	Summary of Changes	Author(s)/Title
	• Updated Causality Assessment description for clarity. • Updated AE Assessment section headings for clarity. • Updated AE, SAE, and ADE definitions for clarity. • Updated Sponsor Notification for clarity. • Updated Introduction to include recent study results. • Updated Blue Adapter CareLink Clinical Application and Guardian Link (3) descriptions for clarity. • Updated glossary to reflect new abbreviations. • Update 24-Hour HelpLine to 24-Hour Technical Support. • Updated Device Deficiencies and Troubleshooting section for clarity. • Added new reference to References section. • Updated Appendix section to reflect the correct file names. • Updated the Cohort Appendices to remove the TSH, A1C, and c-peptide requirement for subjects 2-13 years of age. • Corrected small typographical errors throughout the document. • Updated date and version number to reflect new version of CEP. • Updated Version History. • For detailed information, see "CEP304 Summary of Protocol Changes, Version F to G."	

Version	Summary of Changes	Author(s)/Title
H	• Added copyright statement to Glossary. • Updated sponsor contacts to correct titles. • Removed sponsor contact name/title for Canada. • Updated Section 1 heading to conform to template. • Updated Primary Objective section to include additional detail. • Added Data Collection section to conform to template. • Updated Sample Size Considerations to include updated subject availability statement. • Added number of subjects currently enrolled to synopsis and study design sections to address FDA request • Corrected small typographical errors throughout the document. • Updated date, version number and document footer to reflect new version of CEP. • Updated Version History. • Updated page headers, and section titles to conform to corporate template updates. • For detailed information, see “CEP304 Summary of Protocol Changes, Version G to H”.	[redacted]