Medtronic

Study Title	Use of the Guardian™ Connect System With Smart Connected Devices
NCT Number	NCT04809285
Document Description	Clinical Investigational Plan (Version C)
Document Date	08-JUN-2021

Medtronic Clinical Investigation Plan (CIP)	
Study Title	Use of the Guardian™ Connect system with Smart Connected Devices
CIP Identifier	331

Study Product Name & Study Product Model	**Investigational Devices**
	• Insulin capture devices and associated apps
	  ○ InPen™ Basal smart cap, also referred to as InCap (MMT-155)
	  ○ InPen™ Diabetes Management app, Version 6.0.0 by Companion Medical
	  ○ Adapter 1 FlexTouch (Levemir, Tresiba) (SPC-00789)
	  ○ Adapter 2 KwikPen (Basaglar) (SPC-00790)
	  ○ Adapter 3 SoloStar (Lantus) (SPC-00791)
	  ○ Adapter 4 SoloStar (Toujeo) (SPC-00792)
	  ○ Adapter 5 Max SoloStar (Toujeo Max) (SPC-00793)
	
	Investigational Devices for Subjects 2-13 Years of Age and 76-80 Years of Age
	• Guardian™ Connect app
	• Guardian™ Connect transmitter kit (MMT-7820)
	  ○ Guardian™ Connect transmitter
	  ○ One-press serter, referred to as the serter throughout the protocol
	  ○ Tester
	  ○ Charger
	
	FDA Approved Devices Used in an Investigational Manner
	• Guardian™ Connect app
	• Guardian™ Connect transmitter kit (MMT-7820)
	  ○ Guardian™ Connect transmitter
	  ○ One-press serter, referred to as the serter throughout the protocol
	  ○ Tester

	○ Charger **Non-Investigational Devices** • Guardian™ Sensor (3) (MMT-7020) • Insulin capture devices and associated apps (type, time, amount) ○ Companion Medical InPen for use with Humalog, NovoLog, Fiasp™* U100 (rapid-acting only) (MMT-105) ○ InPen™ Diabetes Management app, Version 5.4.4 by Companion Medical • Klue™ Health app by Klue, Inc. • FoodPrint™ food logging app by Nutrino™ • Apple Watch™* with Health™ app • Sleep tracking device such as Fitbit™* tracker • Sponsor-provided smartphone (Android or iPhone) with pre-loaded apps and cellular service • CareLink™ Personal software – referred to as CareLink Personal throughout this protocol • CareLink™ system – referred to as CareLink Professional throughout this protocol • CONTOUR™* NEXT ONE blood glucose meter – referred to as the study meter or BG meter throughout this protocol • CONTOUR™* DIABETES app • BodyGuardian® MINI cardiac remote monitor (BC2003)
Description of CIP	This study will collect sensor, insulin, sleep, activity and food/meal data for a minimum of 90 days of device wear (Phase 1) and up to a maximum of 9 months of device wear (Phase 2) with optional insulin injection video capture and/or menstrual cycle tracking and/or cardiac monitoring in subjects with insulin-requiring diabetes 2-80 years of age.
Sponsor	Medtronic MiniMed, Inc. (“Medtronic”) 18000 Devonshire St Northridge, CA 91325 866.948.6633
Document Version	Version C
Document Reference Number	D00323255
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1 Glossary

1.1 Glossary

Term	Definition
AE	Adverse Event
ASIC	Application-Specific Integrated Circuit
BG	Blood Glucose
BLE	Bluetooth Low Energy
BMI	Body Mass Index
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CIP	Clinical Investigation Plan
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DKA	Diabetic Ketoacidosis
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EIS	Electrochemical Impedance Spectroscopy
EMEA	Europe Middle East Africa
EMT	Emergency Medical Technician
EOS	End of Study
ER	Emergency Room
FDA	United States Food and Drug Administration
FST	Frequent Sample Testing
GCP	Good Clinical Practice
GST	Glucose Sensor Transmitter
HIPAA	Health Insurance Portability and Accountability Act of 1996
IB	Investigator's Brochure
ICF	Informed Consent Form
ICR	Insulin to Carb Ratio
ID	Identification
IFU	Instructions for Use
IRB	Institutional Review Board
IV	Intravenous
MC2	Medtronic Core Clinical Solutions
MDI	Multiple Daily Injections
NSR	Non-Significant Risk
OC-RDC	Oracle Clinical Remote Data Capture
PC	Personal Computer
PI	Principal Investigator

Term	Definition
QC	Quality Control
QOL	Quality of life
SADE	Serious adverse device effect
SAE	Serious Adverse Event
SG	Sensor Glucose
SID	Subject Identification
SMBG	Self-Monitoring of Blood Glucose
SOPs	Standard Operating Procedures
TDD	Total Daily Dose
TIR	Time in Range
TS	Technical Support
TLS	Transport Layer Security
UADE	Unanticipated Adverse Device Effect
USB	Universal Serial Bus

1.2 List of Trademarks

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2 Synopsis

Title	Use of the Guardian™ Connect system with Smart Connected Devices
Clinical Study Type	Feasibility/Data Collection
Sponsor	Medtronic MiniMed, Inc. ("Medtronic") 18000 Devonshire St Northridge, CA 91325 866.948.6633
Indication under investigation	Insulin-requiring type 1 and 2 diabetes who use multiple daily injections (MDI) insulin therapy

Devices	**Investigational Devices**
	• Insulin capture devices and associated apps
	  ○ InPen™ Basal smart cap, also referred to as InCap (MMT-155)
	  ○ InPen™ Diabetes Management app, Version 6.0.0 by Companion Medical
	  ○ Adapter 1 FlexTouch (Levemir, Tresiba) (SPC-00789)
	  ○ Adapter 2 KwikPen (Basaglar) (SPC-00790)
	  ○ Adapter 3 SoloStar (Lantus) (SPC-00791)
	  ○ Adapter 4 SoloStar (Toujeo) (SPC-00792)
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	Investigational Devices for Subjects 2-13 Years of Age and 76-80 Years of Age
	• Guardian™ Connect app
	• Guardian™ Connect transmitter kit (MMT-7820)
	  ○ Guardian Connect transmitter
	  ○ One-press serter, referred to as the serter throughout the protocol
	  ○ Tester
	  ○ Charger
	
	FDA Approved Devices Used in an Investigational Manner

	• Guardian™ Connect app
	• Guardian™ Connect transmitter kit (MMT-7820)
	  ○ Guardian™ Connect transmitter
	  ○ One-press serter, referred to as the serter throughout the protocol
	  ○ Tester
	  ○ Charger
	
	Non-Investigational Devices
	• Guardian™ Sensor (3) (MMT-7020)
	• Insulin capture devices and associated apps (type, time, amount)
	  ○ Companion Medical InPen for use with Humalog, NovoLog, Fiasp™ U100 (rapid-acting only) (MMT-105)
	  ○ InPen™ Diabetes Management App, Version 5.4.4 by Companion Medical
	• Klue™ Health app by Klue, Inc.
	• FoodPrint™ food logging app by Nutrino™
	• Apple Watch™ with Health app
	• Sleep tracking device such as Fitbit™ tracker
	• Sponsor-provided smartphone (Android or iPhone) with pre-loaded apps and cellular service
	• CareLink™ Personal software – referred to as CareLink Personal throughout this protocol
	• CareLink™ system – referred to as CareLink Professional throughout this protocol
	• CONTOUR™ NEXT ONE blood glucose meter – referred to as the study meter or BG meter throughout this protocol
	• CONTOUR™ DIABETES app
	• BodyGuardian® MINI cardiac remote monitor (BC2003)

Purpose	The purpose of this study is to collect sensor, insulin, sleep, activity and food/meal data for a minimum of 90 days of device wear (Phase 1) and up to a maximum of 9 months of device wear (Phase 2) with optional insulin injection video capture and/or menstrual cycle tracking and/or cardiac monitoring in subjects with insulin requiring diabetes 2-80 years of age.

Objective(s)	The primary objective of this feasibility study is to collect data to be used for development of Medtronic Diabetes and Cardiac Diagnostics devices and products.
Study Design	The study is a multi-center, prospective single-arm design without controls. All subjects will participate for a minimum of 90 days (Phase 1) and some subjects 18 years of age or older will participate for up to 9 months (Phase 2). All subjects will wear the Guardian Connect system (real-time continuous glucose monitoring (CGM)) continuously and use smart insulin pens or insulin pens with smart caps for multiple daily injections and continue their standard therapy throughout the duration of the study. Once trained, each subject 14 years of age or older or their parent or guardian (if applicable) may insert a sensor in the abdomen or arm. Subjects 2-13 years of age or their parent or guardian may insert a sensor in the abdomen or buttocks. Only subjects 13 years of age and older will wear an Apple Watch (waking hours), a Fitbit (sleeping hours) and have the Klue app. The subject's insulin delivery, sleep, physical activity (as applicable),food intake data, and medication (as applicable) will be collected through applications with meal logging and medication requiring manual entry. In addition, subjects may also participate in optional self-administered insulin injection video capture and upload using BOX and/or monthly menstrual cycle logging using Apple Health and/or cardiac monitoring using BodyGuardian MINI. Only subjects 13 years of age and older who choose to participate in optional video capturing of self-administered insulin injection will use the Klue app on the sponsor-provided smartphone to record insulin injection (capturing two videos per each injection location) any time during the study, and upload videos to BOX on the sponsor-provided smartphone. All other app data will be sent automatically to the cloud throughout study participation. Subjects will also be asked to enable location services on sponsor-provided smartphone throughout the study. Only subjects weighing more than 10 kg who choose to participate in optional cardiac monitoring using BodyGuardian MINI should wear the monitor for a minimum of 14 days. Electronic device data will be collected from the study devices using CareLink Personal software and the FoodPrint app and Nutrino cloud. Each site should create a new CareLink Professional account to review subjects' CGM data. CareLink software uses TLS technology, which encrypts all data it stores (21 CFR Part 11 compliant). Wearables will be reset to factory settings at subject's end of study visit. Sponsor-provided smartphone will be reset to factory settings prior to device return to sponsor. Throughout the study, both in Phase 1 and Phase 2, subjects will continually

	use the Guardian Connect system, track insulin delivery via the smart pen or pen caps, track sleep, track activity, and respond to prompts (as applicable). Subjects are instructed to use information from the Guardian Connect app in an adjunctive manner, per product labeling. The general study timeline of activities is as follows: **Phase 1** ▪ Day 1-30 For 7 consecutive days during Days 8-27 (to ensure there is sufficient time for site to review surveillance report prior to Visit 4), each subject should log food consumption (meals, drinks and snacks) concurrent with CGM, sleep and activity tracking, insulin delivery data collection, and medication. The subject will be asked to check a fasting SMBG using the study meter after a minimum of 8 hours of fasting for two mornings during the week they log their food. ▪ Day 31-90 Each subject should log food consumption for a minimum of 7 consecutive days per month. Day 100 will be the End of Study (EOS) unless the subject is participating in Phase 2. If EOS, devices should be returned, wearables reset to factory settings, and subject's participation in the study will be completed. **Phase 2** ▪ Day 91-280 Some subjects 18 years of age or older will continue to provide data for an additional 180 days based on adherence to study requirements demonstrated during Phase 1. Subjects will be asked to log food consumption (meals, drinks and snacks) for a minimum of 7 consecutive days per month concurrent with CGM, sleep and activity tracking, insulin delivery data collection, and medication. At End of Study (EOS, Day 280 (±7 Days)) devices should be returned, wearables reset to factory settings and subject's participation in the study will be completed.
Sample Size and Investigational Centers	Up to 500 subjects with insulin-requiring type 1 or type 2 diabetes age 2-80 who use multiple daily injections (MDI) insulin therapy will be enrolled in the study in order to have a minimum of 260 subjects complete 90 days of data collection with some adult subjects completing 280 days. Up to 30 investigational centers will be selected across the United States. Selection is based on each investigator's experience and qualifications, availability of sufficient resources to carry out the required study procedures, and the investigator's ability to recruit subjects into the study.
Duration	The study is anticipated to last approximately 24 months from first investigational center initiation to finalization of all data entry and monitoring procedures. Subject participation is expected to be

	approximately 100 days, and approximately 280 days for adult subjects who complete Phase 2.
Inclusion/ Exclusion Criteria	**Inclusion Criteria** 1. Individual is 2-80 years of age at time of consent. 2. A clinical diagnosis of type 1 or type 2 diabetes as determined by investigator for: o at least the last 6 months for subjects 2-6 years of age o at least the last 12 months for subjects 7-80 years of age 3. Subject is on multiple daily injection therapy (3 or more insulin injections per day one of which is a long acting insulin injection), is currently using or is willing and can afford to use insulin pen(s) and pen cartridge(s). 4. Subject is currently using or is willing to use the Guardian Connect system during the study. 5. Subject agrees to comply with the study protocol requirements. 6. For adult subjects: Subject is capable of providing legal consent without a legal authorized representative. **Exclusion Criteria** 1. Subject is using a syringe and unwilling or unable to use insulin pen(s). 2. Subject is using an insulin pump. 3. Subject is currently using a non-Medtronic standalone CGM system and unwilling to use only the Guardian Connect system during the study. 4. Subject is using hydroxyurea at time of screening or plans to use it during the study. 5. Subject will not tolerate tape adhesive in the area of device placement as assessed by a qualified provider. 6. Subject has any unresolved adverse skin condition in the area of device placement (e.g. psoriasis, rash, Staphylococcus infection). 7. Subject is actively participating in or plans to enroll in an investigational study (e.g. drug or device), other than this study, wherein they have received treatment from an investigational drug or device. 8. Subject has a positive urine pregnancy test at time of screening.

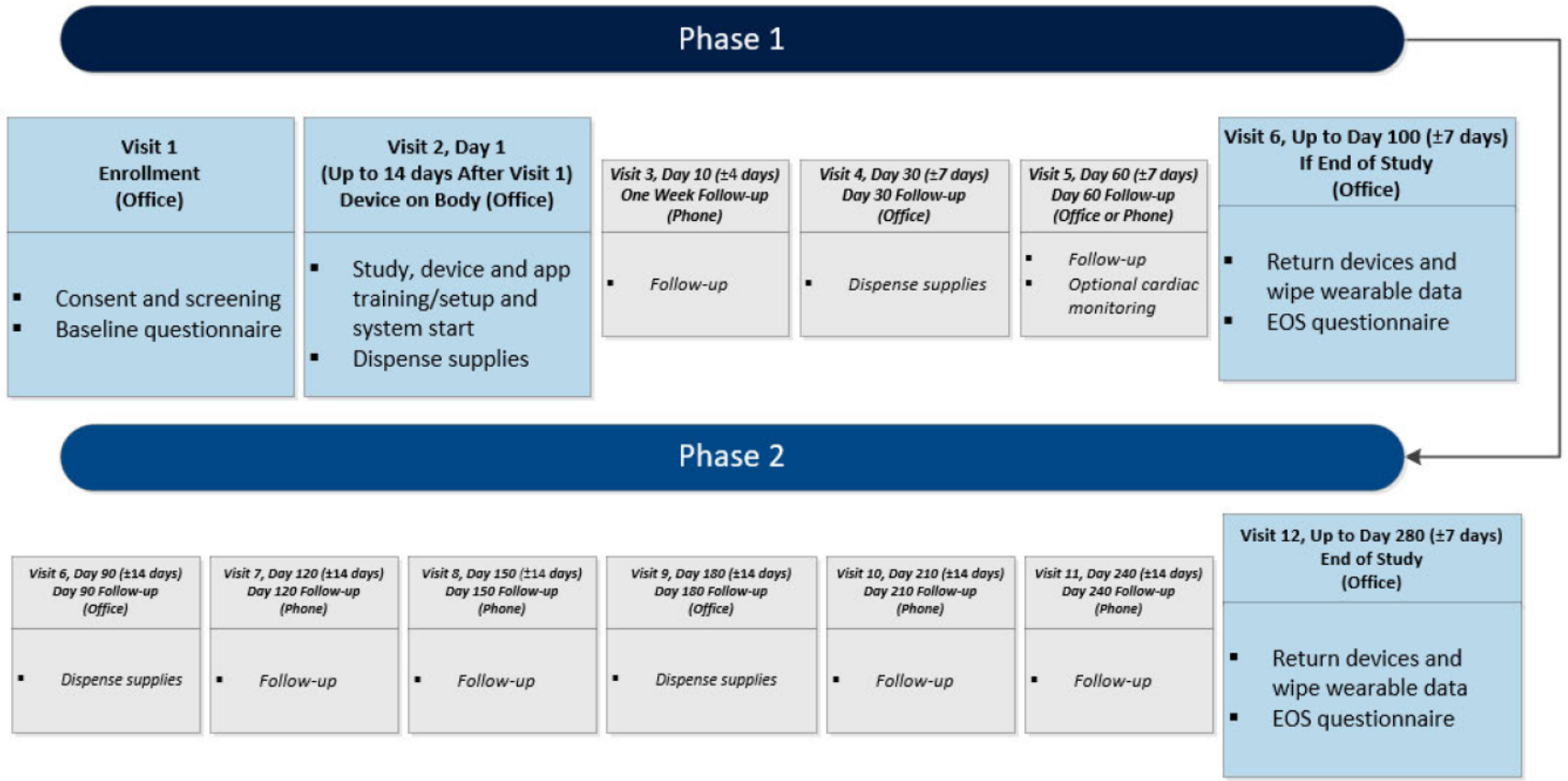
	9. Subject is female, sexually active without the use of contraception, able to become pregnant or plans to become pregnant during the course of the study. 10. Subject is unwilling to participate in study procedures. 11. Subject is directly involved in the study as research staff.
Study Visit Schedule	Subjects will participate in a minimum of 6 planned study visits, as presented in **Figure 1** for approximately 90 days of device wear and up to 12 planned study visits (up to 9 months of device wear) for some adult subjects participating in Phase 2. Telehealth (phone or video) visit may be performed for office visits in cases where an office visit is not possible (e.g. global pandemic). **Phase 1** ▪ Visit 1 Enrollment (Office): Consent and screening. o Administer baseline questionnaire ▪ Visit 2 Day 1 Device on Body (Office): (up to 14 days after Visit 1*): Study, device and app training. o Setup app settings, ensuring subjects accept app terms and conditions o Guardian Connect system start, including sensor insertion, and training o Provide app and wearables training o Dispense wearables o Dispense study supplies o Discuss and determine target date for completing one 7-day consecutive meal logging during Days 8-27, prior to Visit 4 *Note: If additional time is needed for training, Visit 2 may be split up into two visits at investigator's discretion. Site should complete an "Unscheduled Visit" eCRF to document additional visit. ▪ Visit 3 Day 10 Follow-up (Phone): Day 10 (±4 days) after Visit 2. o Remind subjects to have continuous sensor wear o Remind subject to complete 7-day consecutive meal logging on targeted dates prior to Visit 4 o Based on data surveillance reports as available (provided by sponsor), discuss subject compliance (e.g. meal logging, CGM use, sleep and insulin tracking etc.)

	▪ Visit 4 Day 30 Follow-up (Office): Day 30 (±7 days) after Visit 2. o Dispense study supplies o Based on data surveillance reports as available (provided by sponsor), discuss subject compliance (e.g. meal logging, CGM use, sleep and insulin tracking etc.) o Discuss and determine target date for completing one 7-day consecutive meal logging prior to Visit 5 ▪ Visit 5 Day 60 Follow-up (Office or Phone): Day 60 (±7 days) after Visit 2. o If subject is participating in cardiac monitoring: ▪ Train subject on cardiac monitor ▪ Dispense cardiac monitor and supplies o Based on data surveillance reports as available (provided by sponsor), discuss subject compliance (e.g. meal logging, CGM use, sleep and insulin tracking etc.) o Discuss and determine target date for completing one 7-day consecutive meal logging prior to Visit 6 o Determine if subject will participate in Phase 2 o If not participating in Phase 2, determine Day 90 when subject may stop data collection and schedule Visit 6 (EOS) ▪ Visit 6 (Office): Day 100 (±7 days) after Visit 2. o If EOS: ▪ Return study meter, transmitter, wearables and sponsor-provided smartphone ▪ Wipe data off (perform factory reset) wearables ▪ Administer EOS questionnaire *Note: EOS questionnaires will be administered to all subjects at the end of their participation in the study. This includes subjects who are terminated or who voluntarily discontinue participation in the study.* o If moving onto Phase 2, see below. **Phase 2:** Subjects participating in study for over 90 days (up to 9 months): ▪ Visit 6 Day 90 Follow-up (Office): Day 90 (±14 days) after Visit 2. o Dispense study supplies. o Based on data surveillance reports as available (provided by sponsor), discuss subject compliance (e.g. meal logging, CGM use, sleep and insulin tracking etc.)

	○ Discuss and determine target dates for completing one 7-day consecutive meal logging prior to Visit 7 ▪ Visit 7 Day 120 Follow-up (Phone): Day 120 (±14 days) after Visit 2. ○ Based on data surveillance reports as available (provided by sponsor), discuss subject compliance (e.g. meal logging, CGM use, sleep and insulin tracking etc.) ○ Discuss and determine target date for completing one 7-day consecutive meal logging prior to Visit 8 ▪ Visit 8 Day 150 Follow-up (Phone): Day 150 (±14 days) after Visit 2. ○ Based on data surveillance reports as available (provided by sponsor), discuss subject compliance (e.g. meal logging, CGM use, sleep and insulin tracking etc.) ○ Discuss and determine target date for completing one 7-day consecutive meal logging prior to Visit 9 ▪ Visit 9 Day 180 Follow-up (Office): Day 180 (±14 days) after Visit 2. ○ Dispense study supplies. ○ Based on data surveillance reports as available (provided by sponsor), discuss subject compliance (e.g. meal logging, CGM use, sleep and insulin tracking etc.) ○ Discuss and determine target dates for completing one 7-day consecutive meal logging prior to Visit 10 ▪ Visit 10 Day 210 Follow-up (Phone): Day 210 (±14 days) after Visit 2. ○ Based on data surveillance reports as available (provided by sponsor), discuss subject compliance (i.e. meal logging, CGM use, sleep and insulin tracking etc.) ○ Discuss and determine target date for completing one 7-day consecutive meal logging prior to Visit 11 ▪ Visit 11 Day 240 Follow-up (Phone): Day 240 (±14 days) after Visit 2. ○ Based on data surveillance reports as available (provided by sponsor), discuss subject compliance (e.g. meal logging, CGM use, sleep and insulin tracking etc.) ○ Discuss and determine target date for completing one 7-day consecutive meal logging prior to Visit 12 ○ Determine date for Day 280 when subject may stop data collection and schedule Visit 12 (EOS) ▪ Visit 12 End of study (EOS) (Office): Day 280 (±7 days) after Visit 2.

	○ Administer EOS questionnaire *Note: EOS questionnaires will be administered to all subjects at the end of their participation in the study. This includes subjects who are terminated or who voluntarily discontinue participation in the study.* ○ Return study meter, transmitter, wearables and sponsor-provided smartphone ○ Wipe data off (perform factory reset) wearables

Figure 1. Study Visit Schedule for Phase 1 and Phase 2, 90 Days and 280 Days of Guardian Connect system Wear



Safety and Monitoring/Risk Analysis	Safety monitoring/risk analysis details are outlined in **Section 10**.
Device Deficiencies	Device deficiencies reported directly to the investigational center staff by a subject should either be reported to the Medtronic support line by the subject or investigational center staff. All applicable device deficiencies that are reported to the Medtronic support line will be documented. Depending on the study device or app, the subject and/or investigational center may be instructed by the support line to contact the respective device manufacturer. Device deficiencies for commercially released devices or apps should be captured according to local regulatory requirements and is the responsibility of the Investigator. For additional information, see **Section 11.8**.
Subject Stopping Rules	Refer to **Section 9.10** on "Subject Exit, Withdrawal or Discontinuation".
Study Stopping Rules for Entire Study	There are no predefined study stopping rules.

Statistical Analysis for Endpoints and Hypothesis	**<u>During Phase 1 and Phase 2</u>** **Primary Endpoint** Descriptive statistics will be performed; no statistically powered analyses or hypothesis testing will be performed. • Glycemic control: Percentage of Time in Range (SG <70 mg/dL, 70-180 mg/dL, and >180 mg/dL) **Other Descriptive Endpoints** • Summary of completed data collection/available data • Summary of study questionnaire results **Safety** Descriptive summary will be used to characterize safety events: • Serious adverse events (SAE) • Device related adverse events (AEs) • Procedure related AEs • Serious adverse device effect (SADE) • Unanticipated adverse device effect (UADE) • Severe hypoglycemia • Diabetic ketoacidosis (DKA) **Device Deficiencies** Descriptive summary will be used to characterize device deficiencies.
Final Report	A final report will be generated once all subjects have completed Phase 1 and Phase 2. Descriptive endpoints and safety data will be summarized and presented in the final report.

3 Introduction

3.1 Background

In patients with insulin dependent diabetes mellitus, glycemic control is influenced by numerous factors, such as insulin dosage, insulin absorption, timing, physiological/lifestyle factors such as exercise, food intake, sleep, hormones and illness. These factors may contribute to significant variability in insulin requirements, which makes self-management of diabetes challenging.

Today, there are 55 million patients globally taking insulin through injections as compared to the 1 million administering insulin via pump therapy. Some of these patients will move to insulin pump therapy over the course of their lifetime, but the majority will continue using injections. Their rationale to continue with insulin injections include the following reasons:

- There is higher patient out-of-pocket cost associated with pump therapy;
- The physical experience of wearing a pump device is not appealing; and
- There has been growth in new therapy options available to injection users, such as CGM, smart pens, and decision support apps.[1]

While CGM has greatly improved a patient's ability to get rapid and accurate glucose readings, patients are still required to make hundreds of decisions a day with little guidance on what to eat, what to dose, when to dose, and how to manage activities such as exercise. Without actionable therapy guidance, the following key needs remain unmet for these patients:

- Understanding how specific foods, physical activity, sleep patterns, and other routines affect their personal glucose levels;
- Recovering quickly from low and high glucose levels;
- Avoiding overnight lows;
- Optimizing physical exercise to stay in range; and
- Knowing exactly how much insulin to take, and when, at mealtime and throughout the day.[2]

Due to the lack of guidance on the key needs listed above, multiple daily injections (MDI) patients on the current state of the art therapies spend an average of 45-51% of their time within a healthy glycemic range, known as Time in Range (TIR)[3], which is well below the TIR outcomes for pump users[4, 5]. The overall goal of the Smart CGM system is to significantly improve TIR and quality of life (QOL) for injection-based insulin users by improving the user experience in three key areas:

(1) Personalizing dosing recommendations that are tailored to the patient's own physiology, lifestyle, and diabetes state;

(2) Providing holistic decision support to the user in point-of-care situations; and,

(3) Reducing the burden of logging information relevant to diabetes management.

The Smart CGM system will accomplish this by providing the patient with intelligent automation, detection, insights, and recommendations that will enable them to achieve significantly improved TIR and QOL as an MDI user.

3.2 Purpose

The purpose of this study is to collect sensor, insulin, sleep, activity and food/meal data for a minimum of 90 days of wear (Phase 1) and up to a maximum of 9 months of device wear (Phase 2) with optional insulin injection video capture and/or menstrual cycle tracking and/or cardiac monitoring in subjects with insulin requiring diabetes 2-80 years of age.

4 Objectives and/or Endpoints

4.1 Objectives

4.1.1 Primary Objective(s)

The primary objective of this feasibility study is to collect data to be used for development of Medtronic Diabetes and Cardiac Diagnostics devices and products.

4.2 Endpoints

Descriptive statistics will be performed; no statistically powered analyses or hypothesis testing will be performed.

- Glycemic control: Percentage of Time in Range (SG <70 mg/dL, 70-180 mg/dL, and >180 mg/dL)

4.2.1 Other Descriptive Endpoints

- Summary of completed data collection/available data
- Summary of study questionnaire results

4.3 Safety

Descriptive summary will be used to characterize safety events:

- Serious adverse events (SAE)
- Device related AEs
- Procedure related AEs
- Serious adverse device effect (SADE)
- Unanticipated adverse device effect (UADE)
- Severe hypoglycemia
- Diabetic ketoacidosis (DKA)

4.4 Device Deficiencies

Descriptive summary will be used to characterize device deficiencies.

5 Study Design

The study is a multi-center, prospective single-arm design without controls. All subjects will participate for a minimum of 90 days (Phase 1) and some subjects 18 years of age or older will participate for up to 9 months (Phase 2). All subjects will wear the Guardian Connect system (real-time CGM) continuously and use smart insulin pens or insulin pens with smart caps for multiple daily injections and continue their standard therapy throughout the duration of the study.

Once trained, each subject 14 years of age or older or their parent or guardian (if applicable) may insert a sensor in the abdomen or arm. Subjects 2-13 years of age or their parent or guardian may insert a sensor in the abdomen or buttocks.

Only subjects 13 years of age and older will wear an Apple Watch (waking hours), a Fitbit (sleeping hours) and have the Klue app.

The subject's insulin delivery, sleep, physical activity (as applicable), food intake data, and medication (as applicable) will be collected through applications with meal logging and medication requiring manual entry. In addition, subjects may also participate in optional self-administered insulin injection video capture and upload using a secure cloud-based site and/or monthly menstrual cycle logging using Apple Health and/or cardiac monitoring using BodyGuardian MINI.

Only subjects 13 years of age and older who choose to participate in optional video capturing of self-administered insulin injection will use the Klue app on the sponsor-provided smartphone to record insulin injections (capturing two videos per each injection location) any time during the study, and upload videos to a secure cloud-based site on the sponsor-provided smartphone. All other app data will be sent automatically to the cloud throughout study participation. Subjects will also be asked to enable location services on the sponsor-provided smartphone throughout the study.

Only subjects weighing more than 10 kg who choose to participate in optional cardiac monitoring using

the BodyGuardian MINI monitor, should wear the monitor for a minimum of 14 days.

Electronic device data will be collected from the study devices using CareLink Personal and the FoodPrint mobile app and Nutrino cloud. Each site should create a new CareLink Professional account to review subjects' CGM data. CareLink software uses TLS technology, which encrypts all data it stores (21 CFR Part 11 compliant). Wearables will be reset to factory settings at subject's end of study visit. Sponsor-provided smartphone and watch will be reset to factory settings after subject exits study and prior to device return to sponsor.

Throughout the study, both in Phase 1 and Phase 2, subjects will continually use the Guardian Connect system, track insulin delivery via the smart pen or pen caps, track sleep, track activity, and respond to prompts (as applicable). Subjects are instructed to use information from the Guardian Connect app in an adjunctive manner, per product labeling. The general study timeline of activities is as follows:

Phase 1

- Day 1-30

For 7 consecutive days during Days 8-27 (to ensure there is sufficient time for site to review surveillance report prior to Visit 4), each subject should log food consumption (meals, drinks and snacks) concurrent with CGM, sleep and activity tracking, and insulin delivery data collection. The subject is required to check a fasting SMBG using the study meter after a minimum of 8 hours of fasting for two mornings during the week they log their food.

- Day 31-90

Each subject should log food consumption for a minimum of 7 consecutive days per month.

Day 100 will be the EOS unless the subject is participating in Phase 2. If EOS, devices should be returned, wearables reset to factory settings, and subject's participation in the study will be completed.

Phase 2

- Day 91-280

Some subjects 18 years of age or older will continue to provide data for an additional 180 days based on adherence to study requirements demonstrated during Phase 1. Subject will be asked to log food consumption (meals, drinks and snacks) for a minimum of 7 consecutive days per month concurrent with CGM, sleep and activity tracking, and insulin delivery data collection. At End of Study (EOS, Day 280 (±7 days)) devices should be returned, wearables reset to factory settings, and subject's participation in the study will be completed.

5.1 Duration

The study is anticipated to last approximately 24 months from first investigational center initiation to finalization of all data entry and monitoring procedures. Subject participation is expected to be

approximately 100 days and approximately 280 days for some adult subjects participating in Phase 2.

5.2 Rationale

This study is intended to allow collection of sensor, insulin, activity and food/meal data for use in the development of Medtronic Diabetes and Cardiac devices and products.

6 Product Description

6.1 Intended Population

A diverse population of type 1 or type 2 insulin-requiring subjects who use multiple-daily injections (MDI) insulin therapy will be studied. The study population will have a large range of duration of diabetes and glycemic control.

6.2 Investigational Devices

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

6.2.1 Insulin capture devices and associated apps

6.2.1.1 InPen Basal smart cap

The InPen Basal smart cap , also referred to as InCap, is a reusable electronic pen injector cap for single-patient use by people with diabetes. The Cap is compatible with Levemir®, Tresiba®, Lantus®, Basaglar®, and Toujeo® prefilled pens. In this study, the smart cap should be used under the supervision of an adult caregiver or by a patient age 7 and older for the tracking of long-acting insulin doses.

6.2.1.2 InPen Diabetes Management App, Version 6.0.0

The InPen app uses data from a user's InPen smart insulin pen system or InPen Basal smart cap to keep track of the user's data and helps the user make decisions. It automatically records insulin doses, tracks active insulin, recommends mealtime and correction doses, shares therapy data with the user's doctor or caregiver. The information collected by the InPen Diabetes Management app is stored on the Companion Medical data cloud and will be sent to the Nutrino data servers.

6.2.1.3 Adapters

The InPen Basal smart cap requires one of five adapters to fit the subject's long-acting insulin pen. The adapter is an accessory which makes the smart cap compatible with Levemir®, Tresiba®, Basaglar®, Lantus®, Toujeo®, and Toujeo® Max prefilled pens.

6.3 Investigational Devices for Subjects 2-13 Years of Age and 76-80 Years of Age

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

6.3.1 Guardian Connect App

The Guardian Connect app is a mobile application downloaded onto a sponsor-provided smartphone or tablet device. This device serves as a CGM system only with no insulin delivery capabilities. The Guardian Connect system receives data from the Glucose Sensor Transmitter (GST) via Bluetooth Low Energy radio signal. Refer to the device IFU for further information on such use for onboarding in aircraft. The sensor data is displayed numerically and graphically. Additionally, the Guardian Connect app sends blood glucose data to the transmitter to calibrate the sensor. Blood glucose values are entered manually by the user into the Guardian Connect app.

In this study, the Guardian Connect app will be pre-loaded onto a sponsor-provided smartphone. Additionally, data will be sent to the Nutrino data servers.

6.3.2 Guardian Connect Transmitter Kit

6.3.2.1 Guardian Connect Transmitter

The Guardian Connect transmitter is a device that reads the electronic signal generated by the sensor. In addition, the transmitter contains a custom ASIC, which enables EIS. The EIS measurements are used as diagnostics for the sensor, which are incorporated into the sensor calibration logic algorithm. Calibrations must be entered manually into the Guardian app to be relayed to the transmitter. The transmitter transmits the calculated glucose data to the Guardian app via 2.4GHz RF technology (BLE).

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

6.3.2.2 One-press Serter

The One-press serter (**Figure 2**), referred to as the serter throughout the protocol, is an insertion device that is used to ensure correct placement of the sensors into the user's subcutaneous tissue. Insertion is triggered when the two spring loaded buttons on the sides of the serter are pressed simultaneously. All other functionality and requirements are the same. The serter is intended as a single patient, non-sterile multi-use device.

Figure 2.One-press serter

6.3.2.3 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. The tester is also used for device cleaning.

6.3.2.4 Charger

The charger is used to recharge the transmitter after each use. The charger is also used when pairing the transmitter with the smartphone during setup.

6.4 Non-Investigational Devices

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

6.4.1 Guardian Sensor (3)

The Guardian Sensor (3) is a sensor that contains one microelectrode with a thin coating of glucose

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

6.4.2 Insulin capture devices and associated apps (type, time, date, amount)

6.4.2.1 Companion Medical InPen for use with Humalog, NovoLog, Fiasp U100 (rapid-acting only)

Companion Medical InPen smart insulin pen system that combines a reusable, Bluetooth® insulin pen and an intuitive mobile app that helps users take insulin doses. In this study, the InPen pen and InPen Diabetes Management app should be used under the supervision of an adult caregiver or by a subject age 7 and older for the self-injection of a desired dose of insulin.

6.4.2.2 InPen Diabetes Management App, Version 5.4.4

The InPen app uses data from a user's InPen to keep track of the user's data and helps the user make decisions. It automatically records insulin doses, tracks active insulin, recommends mealtime and correction doses, shares therapy data with the user's doctor or caregiver. The information collected by the InPen Diabetes Management app is stored on the Companion Medical data cloud and will be sent to the Nutrino data servers.

6.4.3 Klue Health App by Klue, Inc.

Klue Health app is a smartwatch app that tracks food and drink intake. It can tell from how the arm wearing the smartwatch moves when you are taking a bite or a sip. Klue will helps track food and hydration and, once it has learned the user's behavior patterns, it can coach the user to eat mindfully and check blood sugar at key times. The information collected by Klue is stored on the Klue data cloud and will be sent to the Nutrino data servers. In this study, only subjects 13 years of age or older may use the Klue app.

6.4.4 FoodPrint Food Logging App by Nutrino

The FoodPrint food logging app by Nutrino is a meal logging app. It lets the user take pictures of a meal

which are synced with the food diary. FoodPrint can also be used to log workouts, sleep, medications, blood glucose, and insulin. In this study, data from this and all of the other apps used in this study will be sent to the Nutrino data servers.

6.4.5 Apple Watch with HealthKit

Apple Watch with HealthKit is a commercially available accelerometer that continuously monitors energy expenditure, sleep, and other physiological data for basic and applied medical research. Data collected by the Apple Watch will be sent to the Nutrino data servers. In this study, data collected includes but is not limited to blood glucose, menstrual cycle, heart rate and physical activity. Additionally, only subjects 13 years of age or older will wear an Apple Watch during waking hours.

6.4.6 Fitbit tracker

Fitbit tracker is a commercially available accelerometer that continuously monitors energy expenditure, sleep, and other physiological data for basic and applied medical research. The information collected by Fitbit is stored on the Fitbit data cloud and will be sent to the Nutrino data servers. In this study, only subjects 13 years of age or older will wear a Fitbit tracker during sleeping hours.

6.4.7 Sponsor-provided Smartphone (Android or iPhone) with pre-loaded apps and cellular service

In this study, apps and cellular service will be pre-loaded onto a sponsor-provided smartphone prior to subject's use. The smartphones will be distributed with investigational labeling due to the fact that the Guardian Connect app is considered investigational for subjects 2-13 years of age and subjects 76-80 years of age. Subjects 14-75 years of age will also be issued smartphones with investigational labeling but will use the Guardian Connect app within labeled indications for use.

6.4.8 CareLink system – commercially-approved software referred to as CareLink Professional throughout this protocol

CareLink Professional is a web-based system diabetes therapy management software. Clinical study sites can create accounts to manage data gathered from a subject's device. Data from insulin pumps, continuous glucose monitors, and blood glucose meters can be uploaded to the software. This data can be stored, and then used to generate reports. CareLink Professional can also interface with the subject's CareLink Personal software, allowing access to device data stored in the software. Therapy reports can be generated from the device data.

CareLink Professional is password protected and uses standard Transport Layer Security (TLS), which ensures a secure link between the computer and the server. The TLS transmission protocol invokes encryption on both ends of the transmissions and is the standard for all security-based systems. The encryption remains in effect whether the data is moving to and from the client and server. 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.

In this study, sites can review the subject's CGM data using Carelink Professional but will not upload the subject's CGM device.

6.4.9 CareLink Personal Software – commercially-approved software – referred to as CareLink Personal throughout this protocol

CareLink Personal is a web-based system. It uploads data from the insulin pump, continuous glucose monitors, and supported blood glucose (BG) meters. Uploaded data stored on CareLink Personal is used to generate reports, which users can access using a standard web browser. Care partners can be invited to see device data. CareLink Personal uses the same Transport Layer Security (TLS) technology that CareLink system does.

In this study, CareLink Personal will be used to collect CGM data from the Guardian Connect system automatically.

6.4.10 CONTOUR NEXT ONE blood glucose meter – referred to as the study meter or BG meter throughout this protocol

The CONTOUR NEXT ONE meter and app system consists of a Bluetooth-enabled BG meter that sends BG meter readings to the CONTOUR DIABETES app on the users smartphone. CONTOUR NEXT test strips, control solution, lancets and a lancet device are also a part of the system. The meter measures glucose in fresh capillary whole blood drawn from the fingertips.

In this study, if a subject is dispensed the CONTOUR NEXT ONE blood glucose meter, subjects will check their blood glucose with this meter and use the readings to calibrate the Guardian Connect system. Data (blood glucose readings) from this meter will be automatically synced and logged in the app, which is also compatible with the Apple Health app.

6.4.11 CONTOUR DIABETES App

The CONTOUR DIABETES app syncs with the CONTOUR NEXT ONE blood glucose meter to collect blood glucose readings. In this study, data (blood glucose readings) will stored on the Ascensia CONTOUR data cloud and will be sent to the Nutrino data servers.

6.4.12 BodyGuardian MINI

The BodyGuardian MINI is an ambulatory, wearable, portable, externally applied ECG recorder. It monitors patient ECG and generates event markers using arrhythmia detection algorithms and stores all data on its internal memory.

6.5 Anticipated Device Changes

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

6.6 Product Accountability

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

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

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices. The accountability logs may be maintained at each study site. Additional details regarding device accountability and device disposition requirements are provided in **Table 1**.

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

6.6.1 Receipt and Inventory of Investigational Devices by Investigational Center

Upon receipt of the study devices, the investigational center staff will take inventory of the shipment, making sure that information on the packing slips/invoices matches exactly the contents of the containers, as applicable, including:

  - Ship to Address
  - Reference Number
  - Device Type
  - Quantity
  - Quantity per package
  - Lot number (where applicable)
  - Serial number (where applicable)
- Ensure that devices and supplies received have not reached or exceeded their expiration date

- Sign and date the packing slips/invoices, noting any discrepancies, and file in appropriate study binder
- Notify the study monitor of any discrepancies
- Storage of Study Devices at Investigational Center

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

6.6.2 Dispensing of Study Devices

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

- Date dispensed
- Subject ID
- Lot number(s)
- Serial Number
- Device Type
- Amount dispensed

6.6.3 Return or Disposal of Study Devices

After use by the subject, the investigational center is expected to accept and retain all devices as described in **Table 1** and store them in a secure environment. If containers/units/devices are missing, the reasons should be documented in the applicable source document. If discrepancies between the amounts used by subjects and the amounts expected to be returned exist, the reasons should be documented in the applicable source document.

Requirements for return of devices by subjects to the investigational center and return of device by the investigational center to the sponsor are listed in **Table 1.** The devices that are being returned to the investigational center may be returned to the sponsor as subjects complete the study, at the end of study (EOS) or upon sponsor request.

Other consumable devices (i.e., alcohol wipes, study meter and accessories shipped in kits, supplies or materials) may be returned to the sponsor, they may be retained by investigational centers for educational purposes only, or they may be disposed of properly by the investigational center staff.

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

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

The investigator or authorized member of the research team is to record dispensement and return of study devices from subject on the Subject Device Identification eCRF.

Table 1. Product Return Requirements

Device	Subject Return Device to Investigational Center	Site Return Device to Sponsor at Conclusion of Study
Guardian Sensor (3) (MMT-7020)	Yes (unused only)	No
Guardian Connect transmitter (MMT-7820)	Yes	Yes (used and unused)
Companion Medical InPen for use with Humalog, NovoLog, Fiasp U100 (rapid-acting only) (MMT-105)	Yes	Yes (unused only)
Companion Medical InPen Basal smart cap (MMT-155)	Yes	Yes (unused only)
Adapters: • Adapter 1 FlexTouch (Levemir, Tresiba) (SPC-00789) • Adapter 2 KwikPen (Basaglar) (SPC-00790) • Adapter 3 SoloStar (Lantus) (SPC-00791) • Adapter 4 SoloStar (Toujeo) (SPC-00792) • Adapter 5 Max SoloStar (Toujeo Max) (SPC-00793)	Yes	Yes (unused only)
Apple Watch with HealthKit	Yes	Yes (used and unused)
Fitbit tracker	Yes	Yes (used and unused)
Sponsor-provided smartphone (Android or iPhone) with pre-loaded apps and cellular service	Yes	Yes (used and unused)
CONTOUR NEXT ONE blood glucose meter (9763)	Yes	Yes (unused only)
BodyGuardian MINI (BC2003)	Yes	Yes (used and unused)

7 Selection of Subjects

7.1 Study Population

Up to 500 subjects with insulin-requiring type 1 or type 2 diabetes age 2-80 who use multiple-daily injections (MDI) insulin therapy will be enrolled in the study in order to have minimum of 260 subjects complete approximately 100 days of study participation with some adult subjects completing approximately 280 days in Phase 2.

7.2 Subject Enrollment

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

A subject will be assigned a unique study subject identification (ID) via the eCRF, which is a 9-digit code (331XXXXXX). The first three numbers refer to the clinical investigation plan (CIP) number (331), the next three numbers refer to the investigational center number, and the last three numbers refer to the subject number, assigned during Visit 1 (e.g., 331002001 is subject 001 from site 002).

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

7.3 Inclusion Criteria

1. Individual is 2-80 years of age at time of consent.
2. A clinical diagnosis of type 1 or type 2 diabetes as determined by investigator for:
    - at least the last 6 months for subjects 2-6 years of age
    - at least the last 12 months for subjects 7-80 years of age
3. Subject is on multiple daily injection therapy (3 or more insulin injections per day one of which is a long acting insulin injection), is currently using or is willing and can afford to use insulin pen(s) and pen cartridge(s).
4. Subject is currently using or is willing to use the Guardian Connect system during the study.
5. Subject agrees to comply with the study protocol requirements.
6. For adult subjects: Subject is capable of providing legal consent without a legal authorized representative.

7.4 Exclusion Criteria

1. Subject is using a syringe and unwilling or unable to use insulin pen(s).
2. Subject is using an insulin pump.

3. Subject is currently using a non-Medtronic standalone CGM system and unwilling to use only the Guardian Connect system during the study.
4. Subject is using hydroxyurea at time of screening or plans to use it during the study.
5. Subject will not tolerate tape adhesive in the area of device placement as assessed by a qualified provider.
6. Subject has any unresolved adverse skin condition in the area of device placement (e.g. psoriasis, rash, Staphylococcus infection).
7. Subject is actively participating in or plans to enroll in an investigational study (e.g. drug or device), other than this study, wherein they have received treatment from an investigational drug or device.
8. Subject has a positive urine pregnancy test at time of screening.
9. Subject is female, sexually active without the use of contraception, able to become pregnant or plans to become pregnant during the course of the study.
10. Subject is unwilling to participate in study procedure.
11. Subject is directly involved in the study as research staff.

8 Study Site Requirements

8.1 Study Site Activation

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

Prior to performing study related activities, all regulatory requirements shall be fulfilled, including, but not limited to the following:

- IRB approval (and voting list, as required by local law) of the current version of the CIP and IC
- Fully executed CTA
- Financial disclosure (if applicable)
- CV of investigators
- Documentation of delegated tasks
- Documentation of study training

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

Medtronic will provide each study site with documentation of study site/investigator readiness; this letter must be received prior to performing delegated study activities.

9 Study Procedures

9.1 Schedule of Events

9.1.1 Study Visit Schedule & Scheduled Follow-up Visit Windows

Subjects will participate in a minimum of 6 planned study visits, as presented in **Figure 3** for approximately 90 days of device wear and up to 12 planned study visits (up to 9 months of sensor wear) for some adult subjects participating in Phase 2. Telehealth (phone or video) visit may be performed for office visits in cases where an office visit is not possible (e.g. global pandemic).

Phase 1

- Visit 1 Enrollment (Office): Consent and screening.
  - Administer baseline questionnaire

- Visit 2 Day 1 Device on Body (Office): (up to 14 days after Visit 1*): Study, device and app training.
  - Setup app settings, ensuring subjects accept app terms and conditions, and provide training
  - Guardian Connect system start, including sensor insertion
  - Dispense wearables
  - Dispense study supplies
  - Discuss and determine target date for completing one 7-day consecutive meal logging during Day 8-27, prior to Visit 4

*Note: If additional time is needed for training, Visit 2 may be split up into two visits at investigator's discretion. Site should complete an "Unscheduled Visit" eCRF to document additional visit.

- Visit 3 Day 10 Follow-up (Phone): Day 10 (±4 days) after Visit 2.
  - Remind subject to have continuous sensor wear
  - Remind subject to complete 7-day consecutive meal logging on targeted dates prior to Visit 4
  - Based on data surveillance reports as available (provided by sponsor), discuss subject compliance (e.g. meal logging, CGM use, sleep and insulin tracking etc.)

- Visit 4 Day 30 Follow-up (Office): Day 30 (±7 days) after Visit 2.
  - Dispense study supplies

- Based on data surveillance reports as available (provided by sponsor), discuss subject compliance (e.g. meal logging, CGM use, sleep and insulin tracking etc.)
- Discuss and determine target date for completing one 7-day consecutive meal logging prior to Visit 5

- Visit 5 Day 60 Follow-up (Office or Phone): Day 60 (±7 days) after Visit 2.
  - If subject is participating in cardiac monitoring:
    - Train subject on cardiac monitor
    - Dispense cardiac monitor and supplies
  - Based on data surveillance reports as available (provided by sponsor), discuss subject compliance (e.g. meal logging, CGM use, sleep and insulin tracking etc.)
  - Discuss and determine target date for completing one 7-day consecutive meal logging prior to Visit 6
  - Determine if subject will participate in Phase 2
  - If not participating in Phase 2, determine Day 90 when subject may stop data collection and schedule Visit 6 (EOS)

- Visit 6 (Office): Day 100 (±7 days) after Visit 2.
  - If EOS:
    - Return study meter, transmitter, wearables, sponsor-provided smartphone and cardiac monitor (if applicable)
    - Wipe data off (perform factory reset) wearables
    - Administer EOS questionnaire

      Note: EOS questionnaires will be administered to all subjects at the end of their participation in the study. This includes subjects who are terminated or who voluntarily discontinue participation in the study.

  - If moving onto Phase 2, see below.

Phase 2: Subjects participating in study for over 90 days (up to 9 months):

- Visit 6 Day 90 Follow-up (Office): Day 90 (±14 days) after Visit 2.
  - Dispense study supplies.
  - Based on data surveillance reports as available (provided by sponsor), discuss subject compliance (e.g. meal logging, CGM use, sleep and insulin tracking etc.)
  - Discuss and determine target dates for completing one 7-day consecutive meal logging prior to Visit 7

- Visit 7 Day 120 Follow-up (Phone): Day 120 (±14 days) after Visit 2.
  - Based on data surveillance reports as available (provided by sponsor), discuss subject compliance (e.g. meal logging, CGM use, sleep and insulin tracking etc.)
  - Discuss and determine target date for completing one 7-day consecutive meal logging

prior to Visit 8

- Visit 8 Day 150 Follow-up (Phone): Day 150 (±14 days) after Visit 2.
  - Based on data surveillance reports as available (provided by sponsor), discuss subject compliance (e.g. meal logging, CGM use, sleep and insulin tracking etc.)
  - Discuss and determine target date for completing one 7-day consecutive meal logging prior to Visit 9

- Visit 9 Day 180 Follow-up (Office): Day 180 (±14 days) after Visit 2.
  - Dispense study supplies.
  - Based on data surveillance reports as available (provided by sponsor), discuss subject compliance (e.g. meal logging, CGM use, sleep and insulin tracking etc.)
  - Discuss and determine target dates for completing one 7-day consecutive meal logging prior to Visit 10

- Visit 10 Day 210 Follow-up (Phone): Day 210 (±14 days) after Visit 2.
  - Based on data surveillance reports as available (provided by sponsor), discuss subject compliance (e.g. meal logging, CGM use, sleep and insulin tracking etc.)
  - Discuss and determine target date for completing one 7-day consecutive meal logging prior to Visit 11

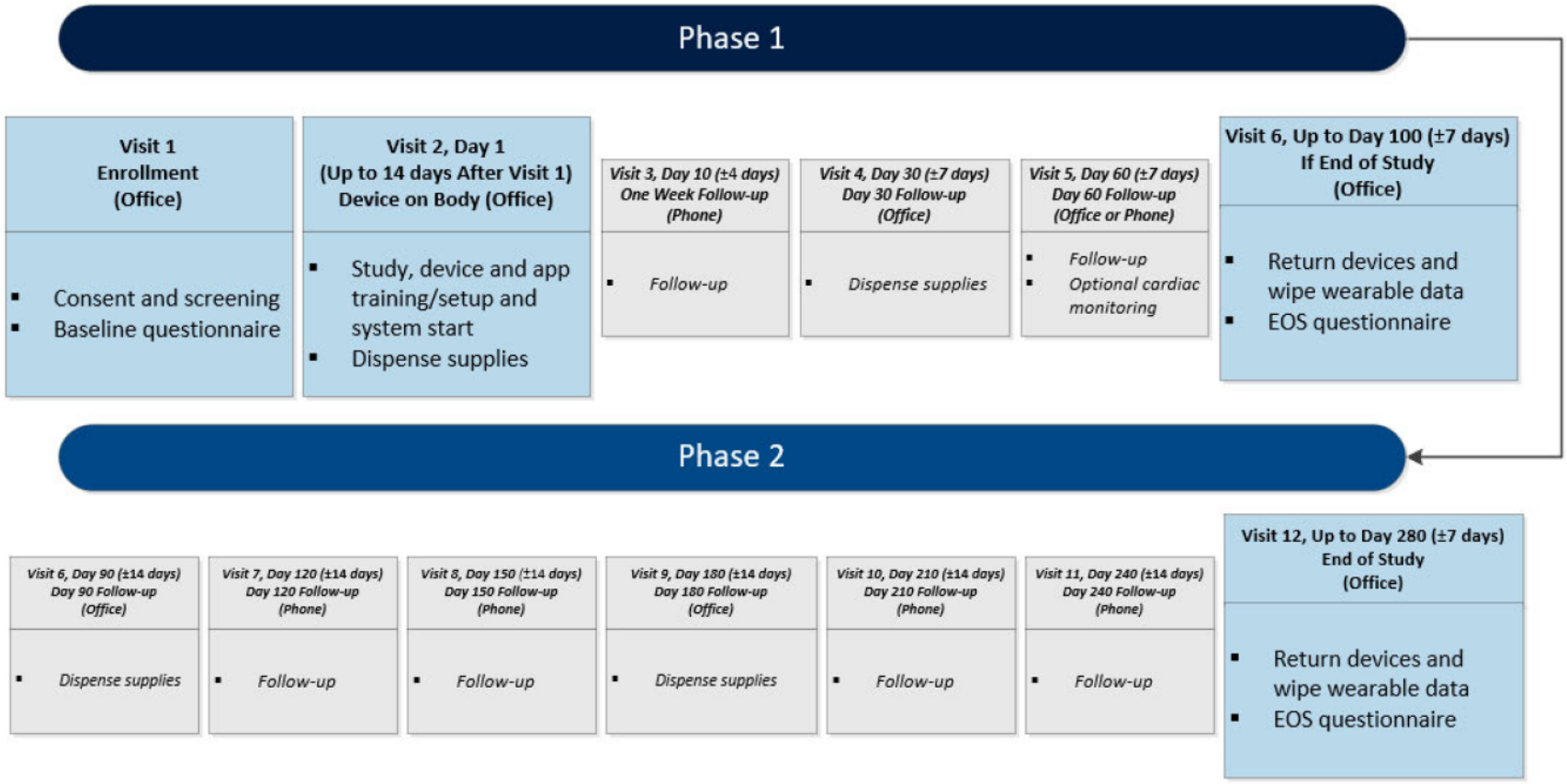
- Visit 11 Day 240 Follow-up (Phone): Day 240 (±14 days) after Visit 2.
  - Based on data surveillance reports as available (provided by sponsor), discuss subject compliance (e.g. meal logging, CGM use, sleep and insulin tracking etc.)
  - Discuss and determine target date for completing one 7-day consecutive meal logging prior to Visit 12
  - Determine date for Day 280 when subject may stop data collection and schedule Visit 12 (EOS)

- Visit 12 End of study (EOS) (Office): Day 280 (±7 days) after Visit 2.
  - Administer EOS questionnaire

    Note: EOS questionnaires will be administered to all subjects at the end of their participation in the study. This includes subjects who are terminated or who voluntarily discontinue participation in the study.

  - Return study meter, transmitter, wearables and sponsor-provided smartphone
  - Wipe data off (perform factory reset) wearables

Figure 3. Study Visit Schedule for Phase 1 and Phase 2, 90 Days and 280 Days of Guardian Connect system Wear



9.2 Scheduled Follow-up Visit Windows for Phase 1 and Phase 2, Subjects Participating in Study for Over 90 Days and Up to 9 Months, Visit Activities

	Phase 1						Phase 2						
	Visit 1 (Office)	Visit 2 (Office)	Visit 3 (Phone)	Visit 4 (Office)	Visit 5 (Office or Phone)	Visit 6, EOS (Office)	Visit 6 (Office)	Visit 7 (Phone)	Visit 8 (Phone)	Visit 9 (Office)	Visit 10 (Phone)	Visit 11 (Phone)	Visit 12, EOS (Office)
Visit Window	Enrollment	Up to 14 Days After Visit 1	Day 10 (±4 Days) After Visit 2	Day 30 (±7 Days) After Visit 2	Day 60, Day 60 (±7 Days) After Visit 2	Day 100 (±7 Days) After Visit 2	Day 90, (±14 Days) After Visit 2	Day 120 (±14 Days) After Visit 2	Day 150 (±14 Days) After Visit 2	Day 180 (±14 Days) After Visit 2	Day 210 (±14 Days) After Visit 2	Day 240 (±14 Days) After Visit 2	Up to Day 280 (±7 Days) After Visit 2
Visit Activities and Data Collection													
Obtain California Experimental Subject's Bill of Rights (if applicable), ICF and assent form (if applicable), and HIPAA form	x												
Assess subject eligibility to participate in the study.	x												
Measure subject height and weight Note: BMI will be calculated automatically in the study database, based on height and weight measurements entered.	x			x		x	x			x			x
Obtain demographic and other baseline characteristics including (as applicable): • Age • Gender • Race • Ethnicity • Diabetes classification (e.g., type 1, type 2) and date of diabetes diagnosis • Diabetes Therapy (e.g. insulin and/or oral medication, dosing regimen, CGM use) • Insulin Carb Ratio (ICR), Insulin Sensitivity Factor (ISF) and Total	x												

	Phase 1						Phase 2						
	Visit 1 (Office)	Visit 2 (Office)	Visit 3 (Phone)	Visit 4 (Office)	Visit 5 (Office or Phone)	Visit 6, EOS (Office)	Visit 6 (Office)	Visit 7 (Phone)	Visit 8 (Phone)	Visit 9 (Office)	Visit 10 (Phone)	Visit 11 (Phone)	Visit 12, EOS (Office)
Visit Window	Enrollment	Up to 14 Days After Visit 1	Day 10 (±4 Days) After Visit 2	Day 30 (±7 Days) After Visit 2	Day 60, Day 60 (±7 Days) After Visit 2	Day 100 (±7 Days) After Visit 2	Day 90, (±14 Days) After Visit 2	Day 120 (±14 Days) After Visit 2	Day 150 (±14 Days) After Visit 2	Day 180 (±14 Days) After Visit 2	Day 210 (±14 Days) After Visit 2	Day 240 (±14 Days) After Visit 2	Up to Day 280 (±7 Days) After Visit 2
Daily Dose (TDD) • Insulin dosage calculation method (i.e. calculator or intuitively) • If applicable, starting Glycemic control levels (i.e. percentage of time hypoglycemic/hyperglycemic/in-range, average glucose)													
Perform urine test for pregnancy, female subjects of child-bearing age or capability (required screening lab test)	x												
Collect concomitant medications	x*	x*	x*	x*	x*	x*	x*	x*	x*	x*	x*	x*	x*
Administer baseline questionnaire.	x												
Set up all apps, ensuring subject accepts Terms of Use and End User License Agreements, and prepare all study devices following the instructions including the following: • A subject e-mail address will be needed for apps setup • Guardian Connect system which includes creating subject's CareLink Personal account • Fully charge the transmitter(s), smartphone, wearables (if applicable) prior to distribution to subject		x											
Link subject's CareLink Personal to your CareLink System/Professional		x											

	Phase 1						Phase 2						
	Visit 1 (Office)	Visit 2 (Office)	Visit 3 (Phone)	Visit 4 (Office)	Visit 5 (Office or Phone)	Visit 6, EOS (Office)	Visit 6 (Office)	Visit 7 (Phone)	Visit 8 (Phone)	Visit 9 (Office)	Visit 10 (Phone)	Visit 11 (Phone)	Visit 12, EOS (Office)
Visit Window	Enrollment	Up to 14 Days After Visit 1	Day 10 (±4 Days) After Visit 2	Day 30 (±7 Days) After Visit 2	Day 60, Day 60 (±7 Days) After Visit 2	Day 100 (±7 Days) After Visit 2	Day 90, (±14 Days) After Visit 2	Day 120 (±14 Days) After Visit 2	Day 150 (±14 Days) After Visit 2	Day 180 (±14 Days) After Visit 2	Day 210 (±14 Days) After Visit 2	Day 240 (±14 Days) After Visit 2	Up to Day 280 (±7 Days) After Visit 2
Perform Quality Control (QC) testing of the study meter user guide. Shake control solution bottle well prior to use. QC should be performed: • Prior to dispensing a study meter • Any time additional study meter strips are given to the subject		x											
Dispense transmitter, charger, serter, and tester		x											
Dispense the study sensors		x		x			x			x			
Dispense other off-the-shelf adhesive(s) and adhesive promotors		x		x			x			x			
Dispense study meter		x											
Dispense study meter supplies (e.g. strips, lancet device, and lancets)		x		x			x			x			
Dispense insulin capture devices		x											
Dispense smartphone and accessories		x											
Dispense Apple Watch and accessories		x (if applicable)											
Dispense Fitbit tracker and accessories		x (if applicable)											
Dispense other study materials (e.g. device user guides, subject training materials, etc.)		x											
Dispense other study supplies as needed (e.g. alcohol swabs, adhesive remover, etc.)		x		x			x			x			

	Phase 1						Phase 2						
	Visit 1 (Office)	Visit 2 (Office)	Visit 3 (Phone)	Visit 4 (Office)	Visit 5 (Office or Phone)	Visit 6, EOS (Office)	Visit 6 (Office)	Visit 7 (Phone)	Visit 8 (Phone)	Visit 9 (Office)	Visit 10 (Phone)	Visit 11 (Phone)	Visit 12, EOS (Office)
Visit Window	Enrollment	Up to 14 Days After Visit 1	Day 10 (±4 Days) After Visit 2	Day 30 (±7 Days) After Visit 2	Day 60, Day 60 (±7 Days) After Visit 2	Day 100 (±7 Days) After Visit 2	Day 90, (±14 Days) After Visit 2	Day 120 (±14 Days) After Visit 2	Day 150 (±14 Days) After Visit 2	Day 180 (±14 Days) After Visit 2	Day 210 (±14 Days) After Visit 2	Day 240 (±14 Days) After Visit 2	Up to Day 280 (±7 Days) After Visit 2
Investigational center staff will record and track all study devices outlined in device accountability section (see **Section 6.5, Table 1**).		X				x	x						
Train subject or subject's parent/guardian on study devices, smartphone, wearables, study procedures, and apps (including Guardian Connect system and sensor insertion). All such training will be documented in the subject source files. Please refer to user guides for specific instructions for each device being used. • For pediatric subjects, the subject's parent/guardian can assist in sensor insertion(s). • Subject will be instructed to wash hands thoroughly with soap and water prior to sensor insertion. • Subject will be instructed to clean the insertion site with alcohol and let the insertion site air dry prior to sensor insertion. • Instruct subject to perform a fasting SMBG (minimum of 8 hours of fasting) using the study meter for two mornings during the first 7 consecutive days. Subject will also perform SMBGs as required to calibrate sensor and/or manage their daily routine (minimum of 2 SMBGs).		X											

	Phase 1						Phase 2						
	Visit 1 (Office)	Visit 2 (Office)	Visit 3 (Phone)	Visit 4 (Office)	Visit 5 (Office or Phone)	Visit 6, EOS (Office)	Visit 6 (Office)	Visit 7 (Phone)	Visit 8 (Phone)	Visit 9 (Office)	Visit 10 (Phone)	Visit 11 (Phone)	Visit 12, EOS (Office)
Visit Window	Enrollment	Up to 14 Days After Visit 1	Day 10 (±4 Days) After Visit 2	Day 30 (±7 Days) After Visit 2	Day 60, Day 60 (±7 Days) After Visit 2	Day 100 (±7 Days) After Visit 2	Day 90, (±14 Days) After Visit 2	Day 120 (±14 Days) After Visit 2	Day 150 (±14 Days) After Visit 2	Day 180 (±14 Days) After Visit 2	Day 210 (±14 Days) After Visit 2	Day 240 (±14 Days) After Visit 2	Up to Day 280 (±7 Days) After Visit 2
• Instruct subject how to log meals and medication* in the FoodPrint app. If meal occurs when an SG value is not being displayed (e.g., during sensor warm up), subject should still log the meal.													
Instruct subjects that additional off-the shelf adhesives or adhesives promotors may be used if needed per subject's routine care.		x		x			x			x			
Train subject on use of study meter: • Subject will be instructed to wash his/her hands thoroughly with warm, soapy water; rinse; and dry before testing BG. • Consider best practice to use "second drop" technique, express first drop and wipe away, express second drop for meter BG testing. • Subject will be instructed to use only the study meter during the course of the study to perform study defined SMBG measurement		x											
Instruct subject to follow their routine diabetes care. Qualified investigational center staff should follow routine diabetes management throughout the study.		X	x	x	x		x	x	x	x	x	x	

	Phase 1						Phase 2						
	Visit 1 (Office)	Visit 2 (Office)	Visit 3 (Phone)	Visit 4 (Office)	Visit 5 (Office or Phone)	Visit 6, EOS (Office)	Visit 6 (Office)	Visit 7 (Phone)	Visit 8 (Phone)	Visit 9 (Office)	Visit 10 (Phone)	Visit 11 (Phone)	Visit 12, EOS (Office)
Visit Window	Enrollment	Up to 14 Days After Visit 1	Day 10 (±4 Days) After Visit 2	Day 30 (±7 Days) After Visit 2	Day 60, Day 60 (±7 Days) After Visit 2	Day 100 (±7 Days) After Visit 2	Day 90, (±14 Days) After Visit 2	Day 120 (±14 Days) After Visit 2	Day 150 (±14 Days) After Visit 2	Day 180 (±14 Days) After Visit 2	Day 210 (±14 Days) After Visit 2	Day 240 (±14 Days) After Visit 2	Up to Day 280 (±7 Days) After Visit 2
Instruct subjects to perform insulin injection video capture and upload into a secure cloud-based site		x (if applicable)											
Instruct subjects to log monthly menstrual cycle logging using Apple Health.		X (if applicable)	x (if applicable)	x (if applicable)	x (if applicable)		x (if applicable)	x (if applicable)	x (if applicable)	x (if applicable)	x (if applicable)	x (if applicable)	
Collect subject's blood pressure and ask them about underlying heart conditions and kidney dysfunction.					x (if applicable)								
Dispense cardiac monitor and supplies. Train subjects on the use of cardiac monitor.					x (if applicable)								
Instruct subject to contact the investigational center staff in the event they experience problems with their study devices (refer to **Section 11.8**).		x											
Assess subjects for the occurrence of any adverse events or device deficiencies (see **Section 11**) at each visit and document on the appropriate source and record event(s) on the appropriate eCRF.		x	x	x	x	x	x	x	x	x	x	x	x
Based on data surveillance reports as available (uploaded to BOX by sponsor), discuss subject compliance (e.g. meal logging, CGM use, sleep and insulin tracking etc.)			x	x	x		x	x	x	x	x	x	
Schedule next visit/phone call date and time.	X	x	x	x	x		x	x	x	x	x	x	

	Phase 1						Phase 2						
	Visit 1 (Office)	Visit 2 (Office)	Visit 3 (Phone)	Visit 4 (Office)	Visit 5 (Office or Phone)	Visit 6, EOS (Office)	Visit 6 (Office)	Visit 7 (Phone)	Visit 8 (Phone)	Visit 9 (Office)	Visit 10 (Phone)	Visit 11 (Phone)	Visit 12, EOS (Office)
Visit Window	Enrollment	Up to 14 Days After Visit 1	Day 10 (±4 Days) After Visit 2	Day 30 (±7 Days) After Visit 2	Day 60, Day 60 (±7 Days) After Visit 2	Day 100 (±7 Days) After Visit 2	Day 90, (±14 Days) After Visit 2	Day 120 (±14 Days) After Visit 2	Day 150 (±14 Days) After Visit 2	Day 180 (±14 Days) After Visit 2	Day 210 (±14 Days) After Visit 2	Day 240 (±14 Days) After Visit 2	Up to Day 280 (±7 Days) After Visit 2
Discuss and schedule with subject the targeted 7-consecutive days of meal logging to occur before next.		x		x	x		x	x	x	x	x		
Determine if subject will participate in Phase 2					x								
Return cardiac monitor and supplies						x (if applicable)							
Return study devices), unused supplies, and study guides from subject (Refer to **Table 1**)						x							x
Administer EOS questionnaire						x							x
An Exit eCRF will be completed at this visit. The investigational center staff will complete the Exit eCRF even if the study devices are not worn for the required time or if the subject self-removed one or more study devices at home.						x							x
Enter data into eCRFs as appropriate.	X	x	x	x	x	x	x	x	x	x	x	x	x
General Reminders													
Inform subject that observation or assistance by sponsor may occur at any time during the study	x												
Remind subject to bring insulin pen to Visit 2	x												
Remind subjects to bring in the study meter and control solution for quality control testing to each visit		x	x		x		x	x	x		x	x	

	Phase 1						Phase 2						
	Visit 1 (Office)	Visit 2 (Office)	Visit 3 (Phone)	Visit 4 (Office)	Visit 5 (Office or Phone)	Visit 6, EOS (Office)	Visit 6 (Office)	Visit 7 (Phone)	Visit 8 (Phone)	Visit 9 (Office)	Visit 10 (Phone)	Visit 11 (Phone)	Visit 12, EOS (Office)
Visit Window	Enrollment	Up to 14 Days After Visit 1	Day 10 (±4 Days) After Visit 2	Day 30 (±7 Days) After Visit 2	Day 60, Day 60 (±7 Days) After Visit 2	Day 100 (±7 Days) After Visit 2	Day 90, (±14 Days) After Visit 2	Day 120 (±14 Days) After Visit 2	Day 150 (±14 Days) After Visit 2	Day 180 (±14 Days) After Visit 2	Day 210 (±14 Days) After Visit 2	Day 240 (±14 Days) After Visit 2	Up to Day 280 (±7 Days) After Visit 2
Remind subject to keep applicable devices charged			x	x	x		x	x	x	x	x	x	
Remind subject to check on the adequacy of their supplies			x	x	x		x	x	x	x	x	x	
Remind subject to contact the investigational center staff or Medtronic support line in the event they experience problems with their study devices (refer to **Section 11.8**).		x	x	x	x		x	x	x	x	x	x	
Provide subjects with the opportunity to bring up study-related questions and concerns (e.g. sensor related issues).	x	x	x	x	x	x	x	x	x	x	x	x	x

*All concomitant medications collected except vitamins and supplements.

9.3 Unscheduled Visit

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

Examples of reasons for an unscheduled visit and completion of the appropriate eCRF include, but are not limited to:

- Replacement of a study sensor(s) within 24 hours of the initial sensor insertion if there is need of replacement.
- Subject requests investigational center staff to examine sensor insertion site(s)
- Subject has an AE and/or device deficiency that requires a visit prior to next scheduled visit
- For subject re-training (e.g. subject expected activities and/or app use)

9.4 Subject Consent

Informed Consent and Assent will be obtained in accordance with the Code of Federal Regulations (CFR) Title 21, Part 50. Prior to entry into the study, the California Experimental Subject's Bill of Rights (if applicable), the Institutional Review Board (IRB) and Medtronic approved ICF and assent form and an Authorization Form required by the Health Insurance Portability and Accountability Act (HIPAA) will be presented to each subject to review and sign as applicable. The subject and their parent or guardian will be offered the opportunity to review these documents away from the investigational center.

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

The subject must have ample time and opportunity to read and understand the ICF, to inquire about details of the study, and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the subject.

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

Subjects will complete California Experimental Subject's Bill of Rights (if applicable), the HIPAA Form, and the ICF and assent form. The consenting process must be documented in the subject's source documents. The subject and their parent or guardian will receive copies of the documents. A subject's participation in study procedures cannot begin before the consent process has been properly executed.

When the subject decides to participate in the study, the ICF must be signed and personally dated by the subject and investigator or authorized designee, as required by the ICF.

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

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

If the ICF and assent form are amended during the course of the study, the IRB will determine:

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

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

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

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

9.5 Medical Oversight

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

9.5.1 Medical Staff

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

9.5.2 Qualification

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

9.5.3 Experience

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

9.6 Glucose and Glycemia Measurements

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

9.6.1 Daily Blood Glucose

Values will be assessed during the study by all subjects using the study meter. The control solution test will be performed following the manufacturer's user guide. Subjects will be trained on the use of the study meter per the manufacturer's instructions.

9.6.2 Sensor Glucose Values

Sensor Glucose (SG) data will be collected by subject's Guardian Connect system.

9.7 Recording Data

Data, excluding uploads, will be captured on eCRFs using Oracle Clinical Remote Data Capture (OC-RDC) module. Original eCRFs will not be considered as source data and supporting documentation will be required.

Electronic device data will be collected from the Guardian Connect transmitter, wearables, smartphone apps, smart pen cap/smart pen, cardiac monitor, and study meter. Electronic data collected will be collected by smartphone apps and stored on their respective data cloud. Data from all apps used in this study will be sent to the Nutrino data servers, where it will be processed. Klue video capture data files will be sent to the sponsor electronically using the internet and a secure cloud-based site. The CareLink software system uses TLS technology, which encrypts all data it stores (21 CFR Part 11 compliant). Electronic device data will be collected from the transmitters utilizing the respective software.

The Investigator will ensure that all eCRFs are completed promptly, completely, and accurately. Medtronic will provide detailed instructions to assist with eCRF completion. In the event of data discrepancies, investigational centers will be asked to resolve queries electronically in the OC-RDC system; otherwise, irresolvable data-related issues will be routed to the sponsor for review and final

disposition. An audit trail is maintained in OC-RDC to capture any corrections or changes of the eCRFs. System backups for data stored in the Oracle Clinical system will be consistent with Medtronic Standard Operating Procedures (SOPs).

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

9.8 Deviation Handling

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

- Investigational center disqualification
- Notification to the regulatory authorities/IRB depending on the severity of the deviation and reporting requirements

The investigator should not implement any deviation from, or changes to, the CIP without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB, except where necessary to eliminate an immediate hazard(s) to trial subjects or when the change does not affect the scientific soundness of the plan or the rights, safety, and welfare of the subjects.

9.8.1 Documenting Requirements for Study Deviations

9.8.1.1 Unplanned CIP Deviations

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

Deviations from the CIP, regardless of the reason should be documented as soon as possible, after the deviation occurs or is identified. This documentation should include deviation date, description of the deviation, the reason for deviation, and the corrective action. Refer to **Table 3** for reporting timelines for emergency deviations.

CIP deviations should be reported as follows:

a) To the IRB for notification/acknowledgement;
b) To the sponsor and, if required;
c) To the applicable regulatory agency (reported by sponsor)

9.9 Reporting Requirements for Study Deviations

All study deviations must be reported on the eCRF regardless of whether medically justifiable, an inadvertent occurrence, or taken to protect the subject in an emergency. The date and reason for each deviation will be documented (21 CFR 812.140 Records).

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

- Failure to obtain informed consent and assent, i.e., there is no documentation of consenting
- Informed consent and assent obtained after initiation of study procedures
- Continuation of a subject who did not meet all inclusion/exclusion criteria
- Performing study procedure not approved by the IRB
- Failure to inform IRB and sponsor of reportable AEs (see **Section 11**)
- Investigational study device dispensed without obtaining informed consent and assent

Reporting of all other study deviations should comply with:

- IRB policies and/or
- local laws and/or
- regulatory agency requirements

They must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation. Refer to Investigator Reports, **Table 3**, for specific deviation reporting requirements and timeframes for reporting to Medtronic, IRB, and regulatory agency (if applicable).

9.9.1 Analyzing Deviations

Medtronic is responsible for reviewing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, conduct additional training, terminate the investigation). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and investigational center, and in some cases, necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study.

9.10 Subject Exit, Withdrawal or Discontinuation

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

If a subject chooses to end his or her study participation or if the subject is removed from the study at the Investigator's discretion or for failure to meet the study requirements, the reason for withdrawal

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

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).
- The subject is found to no longer meet all inclusion criteria, or is found to meet one or more exclusion criteria
- The subject fails to comply with one or more study requirements
- During the study, (female) subject becomes pregnant.

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

10 Risks and Benefits

10.1 Potential Risks

The potential risks and mitigations associated with the investigational devices used during this study are listed in **Table 2**. Risks associated with the commercially available devices used in the study are listed in the associated device labeling and are no different than a subject would experience with normal device use outside of the study.

Table 2. Risk Prevention and Mitigation

Risk with Sensors	Prevention and Mitigation
Risks with Sensors may include: ▪ Skin irritation or reaction to adhesives ▪ Bruising ▪ Discomfort ▪ Redness ▪ Bleeding ▪ Excessive bleeding due to anticoagulants ▪ Pain ▪ Rash ▪ Infection ▪ Irritation from tapes used with glucose-sensing products ▪ Raised bump ▪ Appearance of a small "freckle-like" dot where needle was inserted ▪ Allergic reaction ▪ Syncopal episode secondary to needle insertion ▪ Soreness or tenderness ▪ Swelling at insertion site ▪ Sensor fracture, breakage or damage ▪ Minimal blood splatter associated with sensor needle removal ▪ Residual redness associated with adhesive and/or tapes ▪ Scarring ▪ Scab ▪ Blister ▪ Itchiness ▪ Inflammation ▪ Anxiety ▪ Incorrect sensor glucose reading results in incorrect diabetes management ▪ Subject over-treating secondary to alarms which can result in hyperglycemia or hypoglycemia	Prevention and mitigation include: ▪ Follow the provided user guides for insertions and care of sensors. ▪ If a sensor site becomes infected or inflamed, the sensor will be removed and another placed in a new location ▪ Base diabetes management on fingerstick readings and not on sensor glucose values. ▪ Instruct to check their meter glucose if their high or low symptoms do not match their sensor alerts or sensor glucose readings in order to make diabetes treatment decisions. ▪ Instruct to check their meter glucose if there are any concerns that the sensor glucose value is not accurate. ▪ Instruct if there are no sensor values, no treatment decisions will be made until a BG is confirmed.

▪ Anxiety associated with insertion	
Risks with Guardian Connect Transmitter	**Prevention and Mitigation**
Risks with Transmitter may include: ▪ Skin irritation or reaction to adhesives ▪ Bruising ▪ Discomfort ▪ Redness ▪ Pain ▪ Rash ▪ Infection ▪ Irritation from tapes used with glucose-sensing products ▪ Raised bump ▪ Allergic reaction ▪ Soreness or tenderness ▪ Residual redness associated with adhesive and/or tapes ▪ Scarring ▪ Scab ▪ Blister ▪ Itchiness ▪ Inflammation	Prevention and mitigation include: ▪ Follow the provided user guides ▪ Train on the proper use of the transmitters.
Risks with InPen Basal Smart Cap	**Prevention and Mitigation**
Risks with smart cap may include: ▪ Hypoglycemia ▪ Moderate Hyperglycemia	Prevention and mitigation include: ▪ Follow the provided user guides ▪ Train on the proper use of the insulin pen smart cap.
Risk with BodyGuardian MINI and Electrodes	**Prevention and Mitigation**
▪ Skin irritation or reaction to adhesives ▪ Bruising ▪ Discomfort ▪ Redness ▪ Pain ▪ Rash ▪ Raised bump ▪ Allergic reaction ▪ Soreness or tenderness ▪ Residual redness associated with adhesive and/or tapes ▪ Scab ▪ Blister ▪ Itchiness ▪ Inflammation	Prevention and mitigation include: ▪ Follow the provided user guides ▪ Train on the proper use of the monitor.

10.2 Risk Minimization

Refer to "Prevention and Mitigation" column in **Table 2**.

10.3 Potential Benefits

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

10.4 Risk-Benefit Rationale

The data collected has the potential to facilitate the development and availability of improved Medtronic devices that may provide significant benefits to patients in the future. In light of this, we believe that the overall future potential benefits to the general population of patients with diabetes outweigh any risk to subjects who choose to participate in the investigation.

10.5 Risk Determination

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

- The devices are not intended as an implant and do not present potential for serious risk to subject health, safety, or welfare.
- The devices are not to be used for supporting or sustaining human life and do not present potential for serious risk to subject health, safety, or welfare.
- The devices are not for a use of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise preventing impairment of human health and do not present potential for serious risk to subject health, safety, or welfare.
- Review of the device risk analysis did not identify potential for serious risk to subject health, safety, or welfare.

The NSR determination is also based on the commensurate safety experience of continuous glucose monitoring in commercial use. Furthermore, subjects should be instructed to make all treatment decisions based on a fingerstick glucose measurement and not on sensor glucose information provided by CGM system.

11 Adverse Events and Device Deficiencies

Throughout the course of the study, investigational centers will make all efforts to remain alert to possible reportable adverse events (AEs) or untoward findings. The study personnel will elicit reports of AEs from the subject at each visit (including phone calls) starting at the time of signing the informed

consent documenting the medical diagnosis, date of event start and end, causality (relationship to device or procedure), treatment, outcome, and description that includes the details of the event.

11.1 Definitions and Classification of Adverse Events

Medtronic uses the definitions provided in ISO 14155:2020 and 21 CFR 812 for AE definitions. Where the definition indicates "device", it refers to any device used in the study. This might be the device under investigation, or any market released component of the system.

Severe Hypoglycemia is an event requiring assistance of another person due to altered consciousness to actively administer carbohydrate, glucagon, or other resuscitative actions[6]. This means that the subject was impaired cognitively to the point that he/she was unable to treat himself or herself, was unable to verbalize his or her needs, and was incoherent, disoriented and/or combative.

These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Diabetic Ketoacidosis/DKA diagnostic criteria: blood glucose greater than (>) 250 mg/dL or greater than (>) 13.9 mmol/L, arterial pH less than (<) 7.3, bicarbonate less than (<) 15 mEq/L, moderate ketonuria or ketonemia and requiring treatment within a health care facility[7].

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

- Arterial blood pH less than (<) 7.30 or serum bicarbonate less than (<) 15 mEq/L
- Blood glucose greater than (>) 250 mg/dL or greater than (>) 13.9 mmol/L
- Serum ketones or large/moderate urine ketones
- Symptoms such as polyuria, polydipsia, nausea, or vomiting
- Treatment provided in a health care facility

Adverse Event (AE) (ISO 14155-2020)

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

Note 1: 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 the use of

investigational medical devices or comparators.

Adverse Device Effect (ADE) (ISO 14155-2020)

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

Note 1 to entry: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

Note 2 to entry: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Note 3 to entry: This includes 'comparator' if the comparator is a medical device.

Serious Adverse Event (SAE) (ISO 14155-2020)

Adverse event that led to any of the following

a) death,

b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:

   1. a life- threatening illness or injury, or
   2. a permanent impairment of a body structure or a body function including chronic diseases, or
   3. in-patient* or prolonged hospitalization, or
   4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function

c) fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment

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

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

For the purpose of this study, 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[8].

Serious Adverse Device Effect (SADE) (ISO 14155-2020)

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

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

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

11.2 Reporting of Adverse Events

The Investigator or designee will record AEs that are device related and procedure related, SAEs, SADEs, Severe Hypoglycemia, and DKA while the subject is enrolled in the clinical study. Each AE needs to be assessed for its device or procedure relatedness. A device related AE is associated with the use of the study device (e.g. infection of sensor site or infusion set occlusion resulting in DKA). A procedure related AE is associated with testing related to the study procedures specified in the CIP.

Examples of device or procedure related AEs include:

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

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

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

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

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

11.3 Notification of Adverse Events

Sponsor Notification:

The investigational center staff must report all reportable AEs to Medtronic in a timely manner. All Severe Hypoglycemia, DKA, SAE, and SADEs should be reported as soon as possible (desired within 24 hours of investigator or study coordinator awareness) to Medtronic. For the previously mentioned events, the AE eCRF will be completed with all known details as soon as possible, this will serve as notification to Medtronic. If the study database cannot be accessed due to technical problems, contact the sponsor via email at dl.diabetesclinicalresearchsafety@medtronic.com and provide the known details of the event. Once the access issue has been corrected, the event should be entered onto an AE eCRF.

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

11.4 Expedited Safety Reporting Requirements

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

The sponsor will notify the investigator and IRB of any event that results in a safety report per regulations to the FDA. Documentation of IRB notification of any safety event must be kept at the investigational center and a copy sent to the sponsor.

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

11.5 Causality Assessment

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

Causality assessment is the determination of the relationship between an AE and the device being

studied. It is expected that the investigational center will review all elements surrounding the AE to properly assess the causality of the event to the study device or to a study procedure.

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

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

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

beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
  - the investigational device or procedures are applied to;
  - the investigational device or procedures have an effect on;
- the event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

11.6 Anticipated or Unanticipated

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

- **Anticipated:** the event is identified in the CIP, labeling, report of priors/IB, or user guide.
- **Unanticipated:** the event has not been previously identified in the CIP, labeling, report of priors/IB, or user guide.

11.7 AEs Related to Glucose Sensor Insertion Sites

It is expected that subjects will experience mild irritation, redness, bleeding or bruising associated with the insertion and or wear of the glucose sensor and devices. An AE eCRF will be completed only if the following criteria are met:

- Redness/Irritation (i.e., abrasion, scab, blisters, bumps, itchy bumps, raised ridge or other) which required medical or emergency medical treatment
- Bruising greater than or equal to 6 cm or required emergency medical treatment

11.8 Device Deficiencies and Troubleshooting

The Medtronic support line will be consulted for device troubleshooting if assistance is needed by subject to operate study devices and apps. When subjects call the support line, they are instructed to notify the support line operator that they are currently participating in a clinical research study.

Depending on the study device or app, the subject and/or investigational center may be instructed by the support line to contact the respective device manufacturer for device troubleshooting and device complaints. Device deficiencies for commercially released devices or apps should be captured according to local regulatory requirements and is the responsibility of the Investigator.

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

Device deficiencies reported directly to the investigational center staff by a subject should either be reported to the Medtronic support line by the subject or investigational center staff. All applicable device deficiencies that are reported to the Medtronic support line will be documented. A device deficiency is any 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. This definition includes device deficiencies related to the investigational medical device or comparator. (SO14155:2020)

To return a study device as part of a device deficiency, the subject is to contact the investigational center staff, and the investigational center should then follow the study procedures for returning products with device deficiencies.

It is the responsibility of the Investigator to follow their IRB reporting requirements.

12 Data Review Committees

12.1 Clinical Events Committee

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

- Serious Adverse Event
- Serious Adverse Device Effect
- Unanticipated Adverse Device Effect
- Severe Hypoglycemia

- Diabetic Ketoacidosis

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

If the CEC disagrees with the investigator's classification of the event, the rationale will be provided to the investigator. If the investigator agrees with the CEC's adjudication, the CRF documenting the AE will be updated accordingly.

If the investigator does not agree with the CEC's adjudication classification, both determinations will be provided within the final report; however, the CEC's adjudication will be used for data analysis. The disagreement will also be included in reporting to ECs and regulatory authorities, if required.

13 Statistical Design and Methods

13.1 General Aspects of Analysis

All data collected from the time of screening until the end of the study will be collected either on eCRFs or electronically by uploading the various devices.

13.2 Subject Disposition

The number of subjects screened, enrolled, completed and withdrawn in the study will be presented. The reasons for subject's withdrawal will be summarized.

13.3 Subject Demographics and Baseline Characteristics

Subject characteristics, including age, gender, race, ethnicity, type of diabetes mellitus, and BMI (calculated based on provided height and weight) will be summarized by descriptive statistics.

13.4 Sample Size Considerations

Up to 500 subjects with insulin-requiring type 1 or type 2 diabetes age 2-80 who use multiple daily

injections (MDI) insulin therapy will be enrolled.

13.5 CIP Deviations

All CIP deviations will be presented in the listings.

13.6 Primary Endpoint

Descriptive statistics will be performed; no statistically powered analyses or hypothesis testing will be performed.

- Glycemic control: Percentage of Time in Range (SG <70 mg/dL, 70-180 mg/dL, and >180 mg/dL)

13.7 Other Descriptive Endpoints

- Summary of completed data collection/available data
- Summary of study questionnaire results

13.8 Safety Analysis

Descriptive summary will be used to characterize adverse events:

- Serious Adverse Events (SAE)
- Device Related AEs
- Procedure Related AEs
- Serious Adverse Device Effect (SADE)
- Unanticipated Adverse Device Effect (UADE)
- Severe hypoglycemia
- Diabetic Ketoacidosis (DKA)

13.9 Device Deficiencies

Descriptive summary will be used to characterize device deficiencies.

14 Ethics

14.1 Statement(s) of Compliance

IRB

This CIP, any subsequent amendments to this CIP, the ICF/Assent form (if applicable), subject materials, and any form of subject recruitment information (e.g., advertisements) relating to this study will be approved by the responsible IRB in accordance with 21 CFR Part 56.

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

Regulatory Compliance

This clinical study will be conducted in compliance with the Clinical Investigation Agreement; the CIP; United States CFR Title 21 Part 812.2(b) (abbreviated requirements under Investigational Device Exemptions), Part 50 (Protection of Human Subjects), Part 54 (Financial Disclosure by Clinical Investigators), Part 11 (Electronic Records; Electronic Signatures), and Part 56 (IRBs); and all other applicable federal and local regulatory requirements.

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

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

If the subject is not of legal age per local requirements, he/she should be informed about the study to the extent compatible with the subject's understanding. If the subject could give consent to decisions about participation in research, the investigator must obtain that consent in addition to the consent of their guardian.

Ethical Considerations

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

Sponsor's Support

Sponsor representatives may provide support as required for the study including providing study

training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities.

14.2 Investigator's Responsibilities

Per 21 CFR 56.102, an Investigator means "an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject) or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team." Each investigational center shall designate a primary investigator who will have overall responsibility for the conduct of the investigation at the investigational center.

The primary investigators (and co-investigators if applicable) are responsible for conducting the study in accordance with this investigational plan and 21 CFR 812.2(b) that apply to NSR device studies. These requirements include, but are not limited to:

- Obtaining informed consent and assent (if applicable) for all subjects prior to study participation as described in 21 CFR Part 50.
- Maintaining records of each subject's case history and exposure to the device as described in §812.140(a)(3)(i). Case histories include case report forms and supporting data, including signed and dated consent forms and medical records, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes.
- Making the following required reports:
- Unanticipated Adverse Device Effects [§812.150(a)(1)]
- Withdrawal of IRB Approval [§812.150(a)(2)]
- Failure to obtain informed consent [§812.150(a)(5)]
- Other reports requested by a reviewing IRB or FDA [§812.150(a)(7)]
- Providing sufficient financial information to allow the sponsor to submit certification or disclosure of financial interests. The investigator must update the information if any relevant changes occur during the course of the investigation and for one year following completion of the study. (§ 812.110)

Only authorized study personnel as listed on the Delegation of Authority Log are permitted to consent subjects, receive, dispense, dispose of and return investigational products, conduct subject visits, insert devices, and enter data on eCRFs. These tasks may be delegated by the Investigator. However, the Investigator is ultimately responsible to ensure investigational center-staff are qualified and perform the tasks that have been delegated to them correctly. In addition, the Investigator is responsible for the conduct of investigational center in the execution of the clinical trial.

15 Study Administration

15.1 Training of Clinical Staff

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

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

15.2 Monitoring

Monitoring visits may be conducted at the start, during and at the closure of the clinical study in accordance with Medtronic SOPs and the Monitoring Plan. At minimum, it will be verified whether signed and dated ICF and assent form (if applicable) have been obtained from each subject at the point of enrollment and that AEs discussed in **Section 11** were reported via completion of the AE eCRFs. More details regarding the monitoring activities (frequency of monitoring visits, planned extent of source data verification) are described in the Monitoring Plan.

15.3 Accessibility of Investigational Center Staff and Study Materials

The PI(s), his/her delegate(s) and the study coordinator(s) shall be accessible to Medtronic field personnel, regulatory agency personnel and the Clinical Study Manager. This accessibility is of particular importance for reviewing data in the eCRF. Direct access to subject's medical files for source data verification will need to be granted and prepared prior to any monitoring visits.

15.4 Audits and Investigational Center Inspections

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

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

15.5 Investigational Center Disqualification

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

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

A written statement fully documenting the reasons for such a termination will be provided to sponsor, the IRB, investigational center(s) and other regulatory authorities, as required.

15.6 Data Management

15.6.1 Data Collection

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

15.6.1.1 Electronic Case Report Forms (eCRFs)

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

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

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

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

15.6.1.2 CareLink Personal Software

During the course of the study, subject's BG values may be assessed from the study meter. The system uses TLS technology, which encrypts all data it stores (21 CFR Part 11 compliant). The data in the different databases are linked to each other via the subject IDs to prevent patient identification by the sponsor.

15.6.1.3 Time Windows for Completion and Submission of Case Report Forms

It is expected that eCRFs are completed in a timely manner with the exception of the reportable AEs (see **Section 11.2**). After data entry, eCRFs should be submitted (i.e., saved) so that sponsor can proceed with data verification without delay.

15.6.1.4 Data Review and Processing

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

Collected data will be reviewed for completeness, correctness, and consistency by sponsor. In case of issues, queries will be entered on the respective eCRF for the investigator to complete, correct, or comment on the data.

15.7 Direct Access to Source Data/Documents

The subject's clinic file, CareLink data, and source documents are handled as source data.

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

15.8 Confidentiality

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

15.9 Liability

Subjects will be paid for participation. Refer to the ICF on the details of the subject's compensation.

15.10 CIP Amendments

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

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

15.11 Records and Reports

15.11.1 Investigator Records

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

- All essential study documents and correspondence that pertains to the clinical study
- CIP and, if applicable, any amendments
- User guide(s)
- Medtronic and IRB approved Subject ICF and assent form (if applicable)
- IRB and Regulatory authority approval or notification
- Fully signed clinical study agreements (i.e. including Form of Investigator Statement, Clinical Trial Agreement, Financial Disclosure and Confidential Disclosure Agreement)
- Completed Delegation of Authority Log
- Training documentation of all investigational center staff
- Subject Screening log and/or Subject ID log
- Signed, dated and fully executed Subject ICF and assent forms (if applicable)
- Source documentation
- Fully executed eCRFs and corrections
- Report of AEs and Device Deficiencies

- Device accountability records
- CIP Deviation/CIP Non-Compliance, if any
- Clinical Bulletins- A brief official update or summary of current study news on a matter of immediate interest and high importance to investigational center surrounding the CIP.
- Current signed and dated curriculum vitae (CV) of PI (and key study team members if required per local requirements)
- Study Reports

15.11.2 Investigator reporting responsibilities

Table 3. Investigator Reporting Responsibilities

Report	Submit to	Description/Constraints
AEs and Device Deficiencies	Sponsor, IRB, and regulatory authority, where applicable	Refer to **Sections 11** for reporting requirements.
Withdrawal of IRB approval (either suspension or termination)	Sponsor	An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
Progress report	Sponsor and IRBs	The investigator must submit this report to the sponsor and IRB at regular intervals but in no event less than yearly.
Study deviations	Sponsor and IRBs	Notice of deviations from the CIP to protect the life or physical wellbeing of a subject in an emergency shall be given as soon as possible but no later than 5 working days after the emergency occurred.
Failure to obtain informed consent and assent prior to investigational device use	Sponsor and IRBs	If an investigator uses a device without obtaining informed consent and assent, the investigator shall report such use within 5 working days after device use.
Final report	Sponsor, IRBs and Regulatory Authorities (as applicable)	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation.
Other	Sponsor, IRB and FDA	An investigator shall, upon request by a reviewing IRB, FDA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation.

15.12 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.

15.13 Suspension or Early Termination

Sponsor or a Regulatory Authority may decide to suspend or prematurely terminate the clinical study (e.g. if information becomes available that the risk to study subject is higher than initially indicated, lack of enrollment or because of a business decision). If the clinical study is terminated prematurely or suspended, sponsor shall promptly inform the investigators of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing IRB and the study subjects.

15.14 Early Investigational Center Suspension or Termination

Sponsor, IRB or a Regulatory Authority may decide to suspend or prematurely terminate an investigational center (e.g., in case of expiring approval of the reviewing IRB, non-compliance to the CIP, or lack of enrollment). The suspended clinical studies cannot be resumed without permission from IRB. If an investigational center is suspended or prematurely terminated, sponsor shall promptly inform the investigator(s) of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing IRB and the study subjects.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definite outcomes, investigators must assess whether to continue, modify, or immediately stop the clinical study in the respective investigational center and immediately inform the sponsor and IRB, if applicable.

15.14.1 Subject Follow-up in Case of Termination

In case of early investigational center suspension or termination, all subjects should be contacted to plan an early Termination visit at the investigational center. All efforts will be made to complete and report all study observations at the time of termination. The subject will return the study devices to the investigational center.

15.15 Study Close Out

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

regulations.

15.16 Publication and Use of Information

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

The identity of the subjects may not be disclosed, unless required by law, to any persons not immediately involved in the study or the study procedures. The study will be publicly registered on http://clinicaltrials.gov prior to subject enrollment.

16 References

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2. *Medtronic data on file.*
3. Beck RW, R.T., Ruedy K, et al., *Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections.* JAMA, 2017. **317**: p. 371-378.
4. Garg SK, W.S., Tamborlane WV, et al., *Glucose outcomes with the in-home use hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes.* Diabetes Technology Therapeutics, 2017. **19**: p. 1-9.
5. Bergenstal RM, G.S., Weinzimer SA, et al., *Safety of a hybrid closed-loop insulin delivery system in Patients with type 1 diabetes.* JAMA, 2016. **316**: p. 1407-1408.
6. Cryer, P., *Defining and reporting hypoglycemia in diabetes: A report from the American diabetes association workgroup on hypoglycemia.* Diabetes Care, 2005. **28**(5): p. 1245-1249.
7. *Hyperglycemic Crises in Diabetes.* Diabetes Care., 2004. **27**: p. S94-S102.
8. EMEA, *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.* ICH Topic E2A, 2006.

17 Appendices

17.1 Names and addresses

17.1.1 Investigational Centers and IRB

Table 4 below provides a list of the investigators and investigational centers currently approved to participate in the study.

Table 4. Investigators and Investigational Centers

Investigational Center No.	Principal Investigator Name	Investigational Center 's Name & Address	IRB Name	IRB Chairperson and Address	Site Status
001	Ronald Brazg, MD	Rainier Clinical Research Center 800 SW 39th St., Ste 110 Renton, WA 98057	Advarra	6100 Merriweather Dr., Ste 600 Columbia, MD 21044	Active
004	Kashif Latif, MD	AM Diabetes and Endocrinology Center 3025 Kate Bond Rd. Bartlett, TN 38133	Advarra	6100 Merriweather Dr., Ste 600 Columbia, MD 21044	Active
006	Nicolas Kissell, MD	Salinas Valley Memorial Healthcare System 450 E Romie Ln. Salinas, CA 93901	Advarra	6100 Merriweather Dr., Ste 600 Columbia, MD 21044	Active
010	Robert Slover, MD	Barbara Davis Center for Childhood Diabetes 1775 Aurora Ct., Bldg M20 Rm 2404 Aurora, CO 80045	Advarra	6100 Merriweather Dr., Ste 600 Columbia, MD 21044	Active

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

17.1.2 Monitors Contact Information

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

[redacted]
Clinical Monitoring Manager, MC2 Global Monitoring
Medtronic
710 Medtronic Parkway
Minneapolis, MN 55432

17.2 Labeling and IFUs of Devices

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

17.3 Sample Consent Materials

Samples of the following consent forms/materials will be provided in a separate cover which includes the California Experimental Subject's Bill of Rights (if applicable), ICF and assent form, and the HIPAA Authorization.

18 Version History

Version	Summary of Changes	Author(s)/Title
A	Not Applicable, New Document.	[redacted]

B	▪ Device updates
	  ○ Added InPen Basal smart cap
	  ○ Removed CONTOUR NEXT LINK 2.4 study meter and DIABNEXT devices
	  ○ Updated Guardian Connect regulatory status
	  ○ Updated part numbers for several devices
	  ○ Updated Potential Risks (Section 10.1)
	▪ Updated "Version Date" year from 2020 to 2021 to correct version date of previous CIP version
	▪ Clarified subjects that are 13 years of age and older may do optional video injection site capture
	▪ Updated "weekly surveillance report" to "data surveillance report"
	▪ Updated visit activities table (Section 9.2)
		[redacted]

C	▪ Device updates
	  ○ Added adapters
	  ○ BodyGuardian MINI
	▪ Updated study design to include optional BodyGuardian MINI cardiac monitoring
	▪ Updated sample size from 250 to 260
	▪ Updated exclusion criteria
	▪ Updated study visit schedule and visit schedule figure
	▪ Updated glossary (Section 1.1)
	▪ Updated list of trademarks (Section 1.2)
	▪ Updated Return or Disposal of Study Devices (Section 6.6.3)
	▪ Updated potential risks (Section 10.1)
	▪ Updated Investigational Centers and IRB (Section 17.1.1)
	▪ Updated CIP to match most current corporate CIP template
	▪ Typo/formatting corrections throughout document
		[redacted]