Medtronic

Study Title	Feasibility Study of New Subcutaneous Glucose Sensor with Recording Devices- Phase 3 Group
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ATTACHMENT A

Medtronic **Clinical Investigation Plan (CIP)**	
CIP/Study Title	Feasibility Study of New Subcutaneous Glucose Sensor with Recording Devices- Phase 3 Group
CIP Identifier	CIP318
Study Product Name	**FDA Approved Devices Used in an Investigational Manner** • Guardian Sensor (3)- same sensor as the Enlite 3 Sensor, with only differences on packaging and labeling • Guardian Link (3) Transmitter • Guardian Connect Transmitter **Non-Investigational Devices** • Charger • Medtronic CareLink® Therapy Management Software for Diabetes – referred to as CareLink Clinical throughout this protocol • One-Press Serter-referred to as the Serter throughout the protocol • USB cable and wall-powered adapter • CONTOUR®NEXT LINK RF enabled Blood Glucose Meter, Referred to as the Study Meter throughout this protocol • CONTOUR®NEXT Blood Glucose Test Strips, referred to as Study Meter Strips throughout this protocol • CONTOUR®NEXT Control Solution, referred to as Control Solution • Oval Tape • Hypafix® Tape • BIOCLUSIVE Select Tape • Opsite® Flexifix Tape • Tegaderm Tape • Skin Tac™ Wipes

	• Mastisol® • Other off-the-shelf adhesives as needed
Sponsor/Local Sponsor	Medtronic MiniMed, Inc. ("Medtronic") 18000 Devonshire St Northridge, CA 91325 866.948.6633
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1. Glossary

Term	Definition
AE	Adverse Event
ADE	Adverse Device Effect
ASIC	Application Specific Integrated Circuit
BG	Blood Glucose
BLE	Bluetooth Low Energy
BMI	Body Mass Index
CBC	Complete Blood Count
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CGMS	Continuous Glucose Monitoring System
CIP	Clinical Investigation Plan
DKA	Diabetic Ketoacidosis
eCRF	Electronic Case Report Form
EIS	Electrochemical Impedance Spectroscopy
EMEA	Europe, the Middle East and Africa
EOS	End of Study
ER	Engineering Report
FDA	United States Food and Drug Administration
FST	Frequent Sample Testing
GST	Glucose Sensor Transmitter
HIPAA	Health Insurance Portability and Accountability Act
hs-CRP	high sensitivity C-reactive protein
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification
IFU	Instructions for Use

IRB	Institutional Review Board
ISO	International Organization for Standardization
MARD	Mean Absolute Relative Difference
NSR	Non-significant Risk
OC-RDC	Oracle Clinical Remote Data Capture
PC	Personal Computer
PI	Principal Investigator
QC	Quality Control
R&D	Research and Development
RF	Radio Frequency
RSO	Return Sales Order
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SG	Sensor Glucose
SMBG	Self-Monitoring of Blood Glucose
TLS	Transport Layer Security
UADE	Unanticipated Adverse Device Effect
USA	United States of America
USB	Universal Serial Bus

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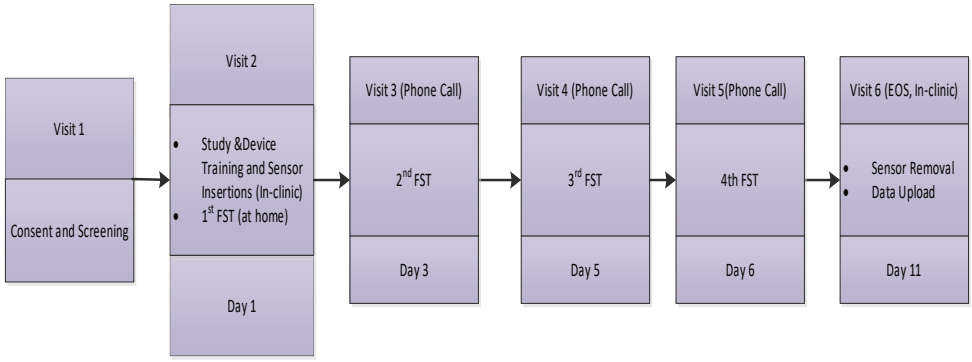
2. Synopsis

Title	Feasibility Study of New Subcutaneous Glucose Sensor with Recording Devices- Phase 3 Group
Clinical Study Type	Feasibility
Sponsor	Medtronic MiniMed, Inc. ("Medtronic") 18000 Devonshire St Northridge, CA 91325 866.948.6633
Indication under investigation	Type 1 diabetes, Type 2 diabetes
Devices	**FDA Approved Devices Used in an Investigational Manner** • Guardian Sensor (3)- same sensor as the Enlite 3 Sensor, with only differences on packaging and labeling • Guardian Link (3) Transmitter • Guardian Connect Transmitter **Non-Investigational Devices** • Charger • Medtronic CareLink® Therapy Management Software for Diabetes – referred to as CareLink Clinical throughout this protocol • One-Press Serter-referred to as the Serter throughout the protocol • USB cable and wall-powered adapter • CONTOUR®NEXT LINK RF enabled Blood Glucose Meter, Referred to as the Study Meter throughout this protocol

	• CONTOUR®NEXT Blood Glucose Test Strips, referred to as Study Meter Strips throughout this protocol • CONTOUR®NEXT Control Solution, referred to as Control Solution • Oval Tape • Hypafix® Tape • BIOCLUSIVE Select Tape • Opsite® Flexifix Tape • Tegaderm Tape • Skin Tac™ Wipes • Mastisol® • Other off-the-shelf adhesives as needed
Purpose	The purpose of Phase 3 Group is to collect data on the performance of Guardian Sensor (3)s each connected to the Guardian Link (3) Transmitter(s) and/or Guardian Connect Transmitter(s) during 11 days of wear (approximately 264 hours) in subjects with insulin requiring diabetes, 18-75 years of age.
Objective(s)	The primary objective of this feasibility study is to collect data to be used for development of Medtronic Diabetes devices and products.
Study Design	The study is a multi-center, prospective single-arm design without controls. All subjects will be assigned to treatment for 11 days of sensor wear. Each subject will wear 4 Guardian Sensor (3)s, and each will be connected to a Guardian Link (3) Transmitter and/or Guardian Connect Transmitter. The Investigational Center will be informed via email the specific details on the type and number of sensors connected to the transmitters. Subjects may not use SG values for diabetes management. Each subject may self-insert and self-tape their study glucose sensors once trained or have them inserted, connected, and taped by the trained Investigational Center staff in the abdomen and/ or arm area. During the study, each subject will undergo 4 Frequent Sample Testings (FSTs) obtained by self-monitoring of blood glucose (SMBG) from fingerstick from Study Meter BG readings. Subject will be assigned to Phase 3 Group (Phase 3 Group will include only subjects 18 years of age and older). Subjects will have all 4 FSTs occurring at home. Investigational Center staff will distribute and instruct subjects to take one gram of acetaminophen orally for FST Day 3, Day 5, and Day 6. During each FST, the subject will be asked to perform one SMBG measurement approximately every 20 minutes for 5 hours. On Day 11, approximately 264 hours after last study sensor has been inserted, devices will be removed; data uploaded from the study meter and transmitter or recorder; skin assessment will be performed; and subject's participation in the study will be completed.

Sample Size and Investigational Centers	Up to 20 subjects with type 1 or type 2 insulin requiring diabetes age 18-75 will be enrolled in the study. Up to 2 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 2 months from first Investigational Center initiation to finalization of all data entry and monitoring procedures. Subject participation is expected to be approximately 11 days.
Inclusion/ Exclusion Criteria	**Inclusion Criteria** 1. Subject is 18-75 years of age at time of screening 2. A clinical diagnosis of type 1 or type 2 diabetes as determined by investigator, for at least the last 12 months 3. Subject is using insulin to treat their diabetes 4. Subject agrees to comply with the study protocol requirements 5. Subject is willing to perform SMBG approximately every 20 minutes during FST **Exclusion Criteria** 1. Subject has history of allergy to acetaminophen or has been told by health care provider they may not ingest acetaminophen 2. Subject reports history of liver cirrhosis or problems with liver that a health care provider told them they should not use acetaminophen because of liver disorder. 3. Subject is unable to tolerate tape adhesive in the area of sensor placement 4. Subject has any unresolved adverse skin condition in the area of sensor or device placement (e.g. psoriasis, rash, Staphylococcus infection) 5. Subject is actively participating in or plans to enroll in an investigational study (drug or device), other than this study, wherein they have received treatment from an investigational drug or device 6. Subject has a positive urine pregnancy test at time of screening 7. 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 8. Subject is unwilling to participate in study procedures.
Study Timeline	Phase 3 Group subjects will participate in 6 planned study visits, as presented in Phase 3 Group Synopsis Figure 1 for 11 days of sensor wear with acetaminophen dosing. Details of the FST visit schedule are presented in Section 8.1.

Phase 3 Group Synopsis Figure 1. Phase 3 Group: 11 Days of Sensor Wear with Acetaminophen Study Visit Schedule



- Phase 3 Group Visit 1: Consent and Screening
- Phase 3 Group Visit 2: Study & Device Training and Sensor Insertions:
  - Study Sensor Insertions (in-clinic)
  - 1st FST on Day 1 (at-home)
    - 5-hrs FST starting at approximately T=5 hours
- Phase 3 Group Visit 3 (Phone call): 2nd FST on Day 3 (approximately 72-90 hours) with 1gm Acetaminophen administered after first hour of FST at home
- Phase 3 Group Visit 4 (Phone call): 3rd FST on Day 5 (approximately 120-138 hours) with 1 gm Acetaminophen administered after first hour of FST at home
- Phase 3 Group Visit 5 (Phone call): 4th FST on Day 6 (approximately 144-162 hours) with 1 gm Acetaminophen administered after first hour of FST at home
- Phase 3 Group Visit 6 End of Study (EOS), In-clinic: Day 11 (approximately 264-282 hours)
  - Data upload
  - Return study devices and Subject EZ Reference Guide and Diary

Device Deficiencies	Subject and investigational center reports of device deficiencies will be collected by electronic Case Report Forms (eCRF) for device troubleshooting and device complaints. For additional information, see Section 12
Subject Stopping Rules	The subject will stop the study if there is an unanticipated adverse device effect (UADE).

Stopping Rules for Entire Study	The study will stop if there is an UADE.

Statistical Analysis for Endpoints and Hypothesis	**Primary Endpoint**
	Accuracy (Mean absolute relative difference [MARD]) between the primary sensor values and meter BG values during the two hours (approximately 6 paired points per FST event) after ingestion of acetaminophen per subject will be described. Summary statistics will include its mean, standard deviation, median, and 95% confidence interval.
	
	Safety
	Descriptive summary will be used to characterize safety events
	• Skin assessment of subject's glucose sensor insertion sites
	• Adverse events (AE) to include:
	  ○ Serious Adverse Events (SAE)
	  ○ Device Related AEs
	  ○ Procedure Related AEs
	  ○ Serious Adverse Device Effect (SADE)
	  ○ UADE
	  ○ Severe hypoglycemia
	  ○ Diabetic Ketoacidosis (DKA)
	
	Device Deficiencies
	Descriptive summary will be used to characterize device deficiencies:
	• All reports of device issues.
	• All Investigational Center/subject reports of sensor damage, breakage or fracture will be included.

3. Introduction

3.1. Background

The intent of this study is to gather data from both commercially available devices and investigational devices used independently or in combination with each other.

Frequent self-monitoring of blood glucose (SMBG) is an important part of diabetes management. Careful attention to blood glucose (BG) values throughout the day allows patients to more precisely adjust insulin dosages and to adjust their food intake and activity levels accordingly. However, because SMBG values are taken only at specific time points and measure brief instances of time within a 24-hour period, there are limits to the usefulness of this information. The addition of continuous interstitial glucose values allows identification (ID), assessment, and monitoring of BG trends.

Current methods of continuous glucose monitoring (CGM) include the use of subcutaneous glucose sensors worn by the user which convert glucose from the subject's interstitial fluid into an electronic signal, the strength of which is proportional to the amount of glucose present in the fluid. (Note that throughout the protocol, a reference of "sensor" is meant to imply glucose sensor unless noted otherwise). A CGM sensor is typically attached to a transmitter which sends interstitial glucose information to a monitor (e.g. Guardian® Glucose Monitor) as radio frequency (RF) or Bluetooth Low Energy (BLE) signals or a recorder which saves interstitial glucose information to be uploaded after use. The sensor is composed of a microelectrode with a thin coating of glucose oxidase beneath several layers of biocompatible membrane. In this study, a glucose sensor is paired with a glucose sensor recorder and/or transmitter capturing interstitial glucose information that will be uploaded from the device to a personal computer (PC) using appropriate software by the Investigational Center staff.

The Medtronic® MiniMed®, Inc. (d/b/a "Medtronic") family of Continuous Glucose Monitoring Systems (CGMS) measures subcutaneous glucose continuously over various ranges of time. The newest generation Guardian Sensor (3) was approved by the Food and Drug Administration (FDA) for commercialization as part of Medtronic MiniMed 670G system in September 2016. The Guardian Sensor (3) is intended for use with the MiniMed 670G system to continuously monitor glucose levels in persons with diabetes. It is intended to be used for detecting trends and tracking patterns in persons aged fourteen years and older, and to be used by the MiniMed 670G system to automatically adjust basal insulin levels.

In this study, Guardian Sensor (3) will be tested on human subjects. The sensors are inserted into the user's subcutaneous tissue with a single patient, multi-use One-Press Serter. The Guardian Sensor (3) has the traditional one working electrode for determining the subject's interstitial glucose value. The sensors are attached to a Glucose Sensor Transmitter (GST), referred to as the Guardian Link (3) or Guardian Connect Transmitter, which will store the raw sensor data until it is downloaded to the designated PC.

3.2. Purpose

The purpose of Phase 3 Group is to collect data on the performance of Guardian Sensor (3)s each connected to the Guardian Link (3) Transmitter(s) and/or Guardian Connect Transmitter(s) during 11 days of wear (approximately 264 hours) in subjects with insulin requiring diabetes, 18-75 years of age.

4. Objectives and 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 devices and products.

4.2. Endpoints

4.2.1. Accuracy Endpoints

4.2.1.1. Primary Endpoints

Accuracy (Mean absolute relative difference [MARD]) between the primary sensor values and meter BG values during the two hours (approximately 6 paired points per FST event) after ingestion of acetaminophen per subject will be described. Summary statistics will include its mean, standard deviation, median, and 95% confidence interval.

4.2.1.2. Exploratory Analysis

Accuracy (MARD) between the primary sensor values and meter BG values during the two hours (approximately 6 paired points per FST event) after ingestion of acetaminophen per measurement will be described. Summary statistics will include its mean, standard deviation, median, and 95% confidence interval.

The 20% mean agreement rate (±20 mg/dL (1.1 mmol/L) when Reference BG less than or equal to (≤) 80 mg/dL (4.4 mmol/L)) between the primary sensor values and meter BG values during the two hours (at least 6 paired points per FST event) after ingestion of acetaminophen per measurement will be

calculated. Summary statistics will include its mean, standard deviation, median, and 95% confidence interval.

4.2.2. Safety

Descriptive summary will be used to characterize safety events

- Skin assessment of subject's glucose sensor insertion sites
- Adverse events (AE) to include:
  - Serious Adverse Events (SAE)
  - Device Related AEs
  - Procedure Related AEs
  - Serious Adverse Device Effect (SADEs)
  - UADE
  - Severe hypoglycemia
  - Diabetic Ketoacidosis (DKA)

4.2.3. Device Deficiencies

Descriptive summary will be used to characterize device deficiencies:

- All reports of device issues.
- All Investigational Center/subject reports of sensor damage, breakage or fracture will be included.

5. Study Design

The study is a multi-center, prospective single-arm design without controls. All subjects will be assigned to treatment for 11 days of sensor wear. Each subject will wear 4 Guardian Sensor (3)s, and each will be connected to a Guardian Link (3) Transmitter and/or Guardian Connect Transmitter. The Investigational Center will be informed via email the specific details on the type and number of sensors connected to the transmitters. Subjects may not use SG values for diabetes management.

Each subject may self-insert and self-tape their study glucose sensors once trained or have them inserted, connected, and taped by the trained Investigational Center staff in the abdomen and/ or arm area.

During the study, each subject will undergo 4 Frequent Sample Testings (FSTs) obtained by self-monitoring of blood glucose (SMBG) from fingerstick from Study Meter BG readings. Subject will be

assigned to Phase 3 Group (Phase 3 Group will include only subjects 18 years of age and older).

Subjects will have all 4 FSTs occurring at home. Investigational Center staff will distribute and instruct subjects to take one gram of acetaminophen orally for FST Day 3, Day 5, and Day 6. During each FST, the subject will be asked to perform one SMBG measurement approximately every 20 minutes for 5 hours.

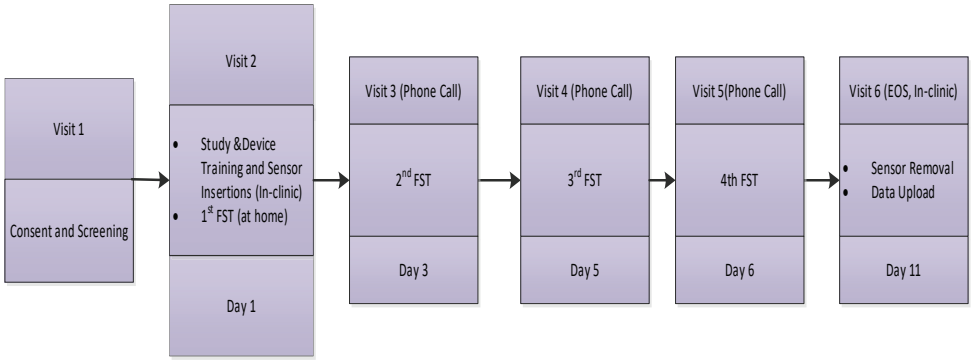
On Day 11, approximately 264 hours after last study sensor has been inserted, devices will be removed; data uploaded from the study meter and transmitter or recorder; skin assessment will be performed; and subject's participation in the study will be completed.

5.1. Study Timeline

Phase 3 Group subjects will participate in 6 planned study visits, as presented in Phase 3 Group Figure 1 for 11 days of sensor wear with acetaminophen dosing.

Details of the FST visit schedule are presented in Section 8.1.

Phase 3 Group Figure 1. Phase 3 Group: 11 Days of Sensor Wear with Acetaminophen Study Visit Schedule



- Phase 3 Group Visit 1: Consent and Screening
- Phase 3 Group Visit 2: Study & Device Training and Sensor Insertions:
    - Study Sensor Insertions (in-clinic)
    - 1st FST on Day 1 (at-home)
        - 5-hrs FST starting at approximately T=5 hours
- Phase 3 Group Visit 3 (Phone call): 2nd FST on Day 3 (approximately 72-90 hours) with 1gm Acetaminophen administered after first hour of FST at home
- Phase 3 Group Visit 4 (Phone call): 3rd FST on Day 5 (approximately 120-138 hours) with 1 gm Acetaminophen administered after first hour of FST at home
- Phase 3 Group Visit 5 (Phone call): 4th FST on Day 6 (approximately 144-162 hours) with 1 gm Acetaminophen administered after first hour of FST at home

- Phase 3 Group Visit 6 End of Study (EOS), In-clinic: Day 11 (approximately 264-282 hours)
    - Data upload
    - Return study devices and Subject EZ Reference Guide and Diary

5.2. Duration

The study is anticipated to last approximately 2 months from first Investigational Center initiation to finalization of all data entry and monitoring procedures. Subject participation is expected to be approximately 11 days

5.3. Rationale

The clinical study will evaluate SG values compared to BG values in patients with type 1 or 2 diabetes during in-clinic and at home testing. The study will evaluate the use of Guardian Sensor (3) with Guardian Link (3) Transmitter and Guardian Connect Transmitter.

Currently, only Guardian Sensor (3), Guardian Link (3) Transmitter, and Guardian Connect Transmitter are approved by FDA. This study is being done for Medtronic devices and product development.

6. Product Description

6.1. FDA Approved Devices Used in an Investigational Manner

The following devices are FDA approved in subjects 7 years and older but will be used in an investigational manner.

6.1.1. Guardian Sensor (3)

The Guardian Sensor (3) is a sensor that contains one microelectrodes 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.

In this study, the Guardian Sensor (3) IFU will be used for the Guardian Sensor (3). Those labeled as Guardian Sensor (3) will not include an investigational caution statement.

6.1.2. Guardian Link (3) Transmitter

The Guardian Link (3) Transmitter is a device that has the same housing and sensor interface as the MiniLink transmitter. However, the internal electronics and firmware of the Guardian Link (3) Transmitter are new. Like the MiniLink transmitter, the Guardian Link (3) Transmitter reads the electronic signal generated by the sensor. In addition, the transmitter contains a custom ASIC, which enables EIS. The EIS measurements are used as diagnostics for the sensor, which are incorporated into the sensor calibration logic.

In addition, the transmitter also contains the sensor calibration algorithm which converts the sensor signal to a SG value using calibration BG values from a meter relayed to the transmitter through the pump. The transmitter transmits the calculated glucose data to the pump via 2.4GHz RF technology (Tel-D communication protocol). The new algorithm is designed to improve and optimize performance when paired with the sensors.

In this study the Guardian Link (3) Transmitter may be connected to Guardian Sensor (3). The Guardian Link (3) Transmitter will also store recorded data and at the end of the study, it will be downloaded.

The Investigational Center will need to follow proper cleaning and disinfection procedures listed in the System Maintenance Guide for Guardian Link (3) Transmitter as it will be a multi-subject use device.

Figure 1. Guardian Link (3) Transmitter

6.1.3. Guardian Connect Transmitter

The Guardian Connect Transmitter is a device that has the same housing and sensor interface as the MiniLink transmitter. However, the internal electronics and firmware of the Guardian Connect Transmitter are new. Like the MiniLink transmitter, the Guardian Connect Transmitter 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.

In addition, the transmitter also contains the sensor calibration algorithm which converts the sensor signal to a SG value using calibration BG values from a meter relayed to the transmitter through the pump. The transmitter transmits the calculated glucose data to the pump via 2.4GHz RF technology (BLE).

In this study the Guardian Connect Transmitter may be connected to Guardian Sensor (3). The Guardian Connect Transmitter will also store recorded data and at the end of the study, it will be downloaded.

The Investigational Center will need to follow proper cleaning and disinfection procedures listed in the System Maintenance Guide for Guardian Connect Transmitter as it will be a multi-subject use device.

6.2. Non-Investigational Devices

The following non-investigational devices planned for use in the study will be described in this section.

6.2.1. Charger

The Charger is used to recharge the transmitters as needed. The system includes a battery charger that will recharge the device according to the user guide.

For the purposes of this study, charging is performed only by the Investigational Center staff.

6.2.2. CareLink Clinical

Medtronic CareLink® Therapy Management Software for Diabetes is an internet-based software system which allows the device data to be viewed and easily evaluated by the subject and his/her physician. A PC is used to access the Medtronic CareLink® system via the Internet, which then allows subjects to upload data from Medtronic MiniMed insulin pumps and a range of system-supported, third-party BG meters. The clinical support version of Medtronic CareLink used in this study was developed for use for Investigational Center staff only. For the purposes of this study, all references to CareLink Clinical in this document relate to the clinical support version of Medtronic CareLink and throughout the protocol will be referred to as CareLink Clinical. The data contained in CareLink Clinical is accessible to users using a standard browser, i.e., Microsoft® Internet Explorer, on an Internet enabled PC.

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

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

The Investigational center staff will upload the Study Meter into CareLink Clinical.

6.2.3. One-Press Serter

The One-Press Serter (Figure 2), referred to as the Serter throughout the protocol, is a device similar in design and function to the Enlite Serter. As the name implies the Serter requires only 1 button press, waiting 5 seconds for proper adhesion of the tape around the needle, and then can be lifted off of the sensor housing without the second button press. All other functionality and requirements are the same. The Serter is intended as a single patient, multi-use device.

Figure 2. One-Press Serter

6.2.4. USB Cable and Wall-Powered Adapter

The small end of the Universal Serial Bus (USB) cable connects to the Dock. The other end of the cable connects to a USB port on a computer, so that the user can upload data using the GST Download Utility Software and Prototype 2A Utility Software and charge the transmitter(s). The USB cable can also be connected to a wall- powered adapter.

The wall-powered adapter lets the user charge the transmitter(s) by connecting the Dock to a regular socket, instead of a computer. It comes with 4 interchangeable power plugs. The appropriate power plug to the wall-powered adapter needs to be connected.

6.2.5. CONTOUR®NEXT Link BG Meter

The commercial RF-enabled BG meter, CONTOUR NEXT LINK (referred to as Study Meter in this protocol) will be provided to all subjects. The meter determines the subject's capillary BG level. BG values obtained from the study meter will be paired with interstitial glucose information collected by the transmitters.

6.2.6. Study Meter Test Strips and Control Solution

The CONTOUR NEXT BG test strips (referred to as Study Meter Strips in the protocol) CONTOUR NEXT Control Solutions (referred to as Control Solution in the protocol) will be used in conjunction with the Study Meter. The Study Meter can be connected through the plug in USB port directly or via the cable to upload BG data to the PC.

6.2.7. Oval Tape

The Oval tape is a medical grade adhesive tape which can be applied over the glucose sensor and transmitter during normal sensor wear to assist with device adherence. The medical grade tape materials have passed International Organization for Standardization (ISO) 10993-Biological Evaluation of Medical Device testing.

6.2.8. Other Off-the-Shelf Adhesives, Including Hypafix® Tape, BIOCLUSIVE® Select Tape, Opsite® Flexifix Tape, or Tegaderm™ Tape

Hypafix® Tape, BIOCLUSIVE® Select Tape, and Opsite® Flexifix Tape are off the shelf medical grade adhesives that may be used to further secure the sensor and recorder pair to the body. Hypafix is the preferred overtape for this study. If a subject has a known problem with Hypafix®, then BIOCLUSIVE, Opsite®, or Tegaderm™ may be substituted.

6.2.9. Skin Tac™ Wipes

Skin Tac™ wipes may be used to prepare the skin for application of tapes and dressings. This unique "tacky" skin barrier is hypo-allergenic and latex free which makes it ideal for patients with sensitive skin.

6.2.10. Mastisol®

Mastisol® is a clear liquid adhesive that may be used to secure the device migration or accidental removal. It also minimizes risk of infection by creating a lasting occlusive dressing barrier

6.3. Anticipated Devices Change

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

6.4. Device Re-Use Disclosure

The following device in this study may have been previously used, but if so, they have been cleaned by the Investigational Center staff prior to re-use between subjects in this clinical study: transmitters

The investigational center will need to follow validated cleaning and disinfection procedures listed in the study documents.

6.5. Device Accountability

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

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

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

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

Table 1 Device Accountability Requirements

Device	Investigational Center Receipt (Packing Slip and eCRF)	Disbursement to Subject (eCRF)	Device Accountability at Conclusion of Study	Record Device Accountability (eCRF)
Guardian Sensor (3) (MMT-7020)	Yes	Yes	All used and unused sensors will be returned to Sponsor.	Yes
Guardian Link (3) Transmitter (MMT-7811)	Yes	Yes	Return to Sponsor	Yes (at EOS)
Guardian Connect Transmitter (MMT-7821)	Yes	Yes	Return to Sponsor	Yes (at EOS)
One-Press Serter (MMT-7512)	No	No	Dispose Used and Return Unused to Sponsor	No
Charger (MMT-7715)	No	N/A	Dispose Used and Return Unused to Sponsor	No
Study Meter (HMS-9740)	Yes	Yes	Dispose Used and Return Unused to Sponsor	Yes

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

6.5.1. Receipt and Inventory of Investigational Devices by Investigational Center

- Upon receipt of the study devices, investigational center staff take inventory of the shipment, making sure that information on the packing slips/invoices matches exactly the contents of the containers, as applicable, including:
    - Ship To
    - Reference Number
    - Device Type

- Quantity
- Quantity per package
- Lot number
- Serial number

- Ensure that devices and supplies received have not reached their expiration date
- Sign and date the packing slips/invoices, noting any discrepancies, and file in appropriate study binder
- Notify the study Monitor of any discrepancies
- Enter the study device information on the appropriate eCRF in the study database.

6.5.2. Storage of Study Devices at Investigational Center

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

6.5.3. Disbursement of Study Devices

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

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

6.5.4. Return or Disposal of Study Devices

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

As applicable and as described in Table 1, devices will be returned by subjects to the Investigational Center and then to the Sponsor. Study devices provided to the Investigational Center may be returned as subjects complete the study, at the EOS, or upon sponsor request. The quantity received by the Investigational Center and the quantity returned to sponsor should be equal. The Investigational Center will provide details of the disposition of all unreturned study devices (excluding the Study Meter) in the eCRF.

All glucose sensors (used or unused) are expected to be returned by subjects to the Investigational Center in the specimen containers and, therefore, are expected to be returned to the Sponsor.

Other consumable devices (i.e., alcohol wipes, BG meter supplies, sensor tapes, etc.), supplies or materials may be returned to the sponsor, retained by Investigational Center for educational purposes only, or may be disposed of properly by the Investigational Center staff.

Disposable devices and supplies that have been ***used*** by a subject will be disposed of properly by the subject or the Investigational Center staff during the conduct of the study. This includes study meter strips, control solution & supplies, and adhesive overtape.

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

7. Selection of Subjects

7.1. Study Population

Up to 20 subjects with type 1 or type 2 insulin requiring diabetes age 18-75 will be enrolled in the study. Up to 2 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.

7.2. Subject Enrollment

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

A subject will be assigned a unique study subject ID via the eCRF during Visit 1.

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

7.3. Inclusion Criteria

1. Subject is 18-75 years of age at time of screening
2. A clinical diagnosis of type 1 or type 2 diabetes as determined by investigator, for at least the last 12 months
3. Subject is using insulin to treat their diabetes
4. Subject agrees to comply with the study protocol requirements
5. Subject is willing to perform SMBG approximately every 20 minutes during FST

7.4. Exclusion Criteria

1. Subject has history of allergy to acetaminophen or has been told by health care provider they may not ingest acetaminophen
2. Subject reports history of liver cirrhosis or problems with liver that a health care provider told them they should not use acetaminophen because of liver disorder.
3. Subject is unable to tolerate tape adhesive in the area of sensor placement
4. Subject has any unresolved adverse skin condition in the area of sensor or device placement (e.g. psoriasis, rash, Staphylococcus infection)
5. Subject is actively participating in or plans to enroll in an investigational study (drug or device), other than this study, wherein they have received treatment from an investigational drug or device
6. Subject has a positive urine pregnancy test at time of screening
7. 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
8. Subject is unwilling to participate in study procedures.

8. Study Procedures

8.1. Schedule of Events for Phase 3 Group

8.1.1. Visit 1: Consent and Screening

General

Investigational Center staff will:

- Administer California Experimental Subject's Bill of Rights (if applicable), ICF form, and HIPAA
- Assess subject eligibility
- Obtain demographic information and baseline characteristics including:
    - Age
    - Gender
    - Race
    - Ethnicity
    - Date of diabetes diagnosis
    - Type of diabetes mellitus
    - Percentage of Body Fat (Note: If not collected at Visit 1, this should be collected at any point between Visit 1 and when subject exits the study. This value will be recorded on the Visit 1 eCRF.)
    - Height and weight

- Note: Body Mass Index (BMI) will be calculated automatically in the study database, based on height and weight measurements entered.
- Obtain blood sample(s) to complete a Complete Blood Count (CBC) and high sensitivity C-reactive protein (hs-CRP) lab test (not eligibility screening lab test)
- Obtain urine pregnancy test for females of child bearing age (required screening lab test)
- Provide subject with the opportunity to bring up study-related questions and concerns.
- Enter eCRFs into the study database as appropriate.
- Schedule next visit date and time
- Inform subject that observation or assistance by Sponsor may occur at any time during the study

The study is open to all individuals who meet the eligibility criteria of the study. The investigational center will be responsible for determining adequate source documents to verify subject eligibility. Subjects who do not meet the eligibility requirements for participation in the study will be entered into the database as screen failures. Applicable eCRF(s) will be completed for all subjects who signed an ICF form, whether they are eligible or ineligible to participate. If a subject fails screening criteria (e.g. pregnancy test), they will be notified regarding their ineligibility immediately, either in person or via telephone. Eligible subjects will return to the investigational center to begin study and device training at Visit 2.

Visit 2 may be completed on the same day as Visit 1, provided that pregnancy test results are available and all other eligibility criteria are met.

8.1.2. Visit 2: Study & Device Training and 1st FST

Visit 2 can be done the same day as Visit 1

8.1.3. General procedures

Investigational Center staff will:

- Confirm subject eligibility prior to moving forward with any study procedures
- Collect Percentage of Body Fat if not collected at Visit 1. Record this value on the Visit 1 eCRF.
- Provide subject with the opportunity to bring up study-related questions and concerns
- Ask subject about the occurrence of AEs
- Record AEs on the appropriate eCRF if subject reports health status changes that result in a new medical condition or deterioration of an existing medical condition such as sickness or glycemic problems.
- Instruct subject to call the investigational center to report any changes to their health status (see AE definition).
- Ask subject about device deficiencies and if they called the Investigational Center staff to report them
- Enroll subject in CareLink Clinical

- Assign subject to Phase 3 Group (Phase 3 Group will include only subjects 18 years of age and older):
    - At home: 5-hrs FST starting at approximately T=5 hours
- Assign eligible subject to 11 days of sensor wear according to FST schedule: Day 1, 3, 5, and 6
- Review and disburse Subject EZ Reference Guide and Diary:
    - Including phone number(s) for study staff and after–hours telephone number(s) for study staff who are assigned to respond to calls from subjects who have questions or experience problems.
    - Instruct subject to record time of acetaminophen ingestion
- Dispense study devices (Refer to Section 8.1.4)
- Prepare all study devices following the instructions in the IFUs including the following:
    - Synchronize study laptop computer at the investigational center using investigational center's designated study clock
    - Fully charge the transmitter(s) prior to distribution to study subject
- Perform applicable Quality Control (QC) testing of the Study Meter per IFU. 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
- Insert or instruct trained subject to self-insert study sensors into the abdomen and/ or arm area.
- Apply or instruct trained subject to self-apply the sensor tape(s) or any other provided medical tapes per the taping IFU. It is recommended (not required) for study purposes (to further secure the sensor and recorder pair to the body).
- Instruct Phase 3 Group subject to perform 1st FST at home:
    - Refer to Phase 3 Group Table 1: FST Timing and SMBG Requirements for 11 Days of Sensor Wear with Acetaminophen Dosing for fingerstick testing at home
    - Instruct subject to avoid ingesting food, carbohydrate, or glucose during FST, other than standard of care
    - Instruct subjects to take one gram of acetaminophen orally for FST Day 3, Day 5, and Day 6
- Instruct subject to perform at-home FSTs based on FST schedule and sensor wear
- Schedule the next visit date and time for 2nd, 3rd, and 4th FST (all phone calls) and EOS Visit 6 (in-clinic).
- Enter eCRFs into the study database as appropriate.

8.1.4. Study devices and supplies

Investigational Center staff will disburse the following to the subject:

- Transmitter(s)

- Study sensor(s)
- Study Meter
- Acetaminophen (1 gm of acetaminophen for 2nd, 3rd, and 4th FST)
- Sensor tape(s) or other off-the-shelf adhesive(s)
- BG supplies (e.g. study meter strips, lancet holder, and lancets)
- Other study materials [e.g. Subject EZ Reference Guide and Diary, device IFUs (if applicable), training materials, subject materials, etc.]. The Subject EZ Reference Guide and Diary also contains important device instructions, helpful reminders, the investigator's contact information, and specific emergency instructions.
- Other study supplies as needed (e.g. alcohol swabs, adhesive remover, etc.)

Investigational Center staff will record and track all study devices outlined in device accountability section (see Section 6.5) on the appropriate eCRF.

8.1.5. Training and instructions

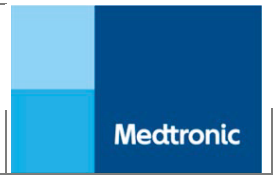
Investigational Center staff will:

- Train subject on study devices and study procedures (including sensor insertion, taping, and removal, as applicable). All such training will be documented in the subject source files.
- 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.
    - Subject will be instructed to use only the Study Meter during the course of the study
- Instruct Phase 3 Group subject to perform SMBG and self-administer 1 gm of acetaminophen orally 1-hour after starting FST on Day 3, Day 5, and Day 6 (See Phase 3 Group Table 1: FST Timing and SMBG Requirements for 11 Days of Sensor Wear with Acetaminophen Dosing)
- Instruct subject to perform additional approximate 6-8 times SMBGs throughout the day (outside of the FST days). Subject may obtain more than 8 SMBG readings per day.
- Instruct subject to follow their routine diabetes care. Qualified Investigational Center staff should follow routine diabetes management throughout the study.
- Train subject on Subject EZ Reference Guide and Diary
- Instruct subject to contact the Investigational Center staff in the event they experience problems with their study devices (Refer to Section 12).
- Remind subject to document time and reason of any study sensor early removal.

Phase 3 Group Table 1. FST Timing and SMBG Requirements for 11 Days of Sensor Wear with Acetaminophen Dosing

Visit	Sensor Wear	Timing of FST from T=0 represents the time when the last transmitter is connected to the final sensor	SMBG At Home	Acetaminophen Dosing
2 (At home -confirmed via Phone Call)	Day 1	T=5	• Subjects will be recommended to perform one SMBG per hour up to 5 hours • FST: Subjects will be asked to perform one SMBG measurement approximately every 20 minutes for 5 hours.	None
3 (At home-confirmed via Phone call)	Day 3	T=72-90 hours	• FST: Subjects will be asked to perform one SMBG measurement approximately every 20 minutes for 5 hours. • Additional approximate 6-8 SMBGs throughout the day including at recommended times: ○ After exercise ○ Prior to meals ○ At bedtime ○ If BG is under 75-mg/dL, it is recommended to take an extra glucose reading until BG is over 75-mg/dL	• 1 gram of Acetaminophen will be self-administered orally approximately 1-hour after starting FST (subject self-report)

Visit	Sensor Wear	Timing of FST from T=0 represents the time when the last transmitter is connected to the final sensor	SMBG At Home	Acetaminophen Dosing
4 (At home-confirmed via Phone call)	Day 5	T=120-138 hours	• FST: Subjects will be asked to perform one SMBG measurement approximately every 20 minutes for 5 hours. • Additional approximate 6-8 SMBGs throughout the day including at recommended times: ○ After exercise ○ Prior to meals ○ At bedtime ○ If BG is under 75-mg/dL, it is recommended to take an extra glucose reading until BG is over 75-mg/dL	• 1 gram of Acetaminophen will be self-administered orally approximately 1-hour after starting FST (subject self-report)
5 (At home-confirmed via Phone call)	Day 6	T=144-162 hours	• FST: Subjects will be asked to perform one SMBG measurement approximately every 20 minutes for 5 hours. • Additional approximate 6-8 SMBGs throughout the day including at recommended times: ○ After exercise ○ Prior to meals ○ At bedtime ○ If BG is under 75-mg/dL, it is recommended to take an extra glucose reading until BG is over 75-mg/dL	• 1 gram of Acetaminophen will be self-administered orally approximately 1-hour after starting FST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8.1.6. Visit 3 (Phone Call): 2nd FST

Investigational Center staff will, via phone call:

- Provide subject with the opportunity to bring up study-related questions and concerns
- Ask subject about the occurrence of AEs.
- Record AEs on the appropriate eCRF if subject reports health status changes that result in a new medical condition or deterioration of an existing medical condition.
- Instruct subject to call the investigational center to report any changes to their health status (see AE definition).
- Ask subject about device deficiencies and if they called the Investigational Center staff to report them
- Instruct subject to perform 2nd FST:
    - Refer to Phase 3 Group Table 1: FST Timing and SMBG Requirements for 11 Days of Sensor Wear with Acetaminophen Dosing for fingerstick testing at home
    - Remind subject to avoid ingesting food, carbohydrate, or glucose during FST, other than standard of care
- Remind subject to perform additional approximate 6-8 times SMBGs throughout the day (outside of the FST days). Subject may obtain more than 8 SMBG readings per day.
- Remind subject to contact the Investigational Center staff in the event they experience problems with their study devices (Refer to Section 12).
- Remind subject to check on the adequacy of their supplies
- Remind subject to continue filling out the Subject EZ Reference Guide and Diary (remind subject to record time of acetaminophen ingestion)
- Review the next visit (phone call) date and time for FST
- Enter eCRFs into the study database as appropriate.

8.1.7. Visit 4 (Phone call): 3rd FST

Investigational Center staff will, via phone call:

- Provide subject with the opportunity to bring up study-related questions and concerns.
- Ask subject about the occurrence of AEs.
- Record AEs on the appropriate eCRF if subject reports health status changes that result in a new medical condition or deterioration of an existing medical condition.
- Instruct subject to call the investigational center to report any changes to their health status (see AE definition).
- Ask subject about device deficiencies and if they called the Investigational Center staff to report them
- Instruct subject to perform 3rd FST

- Refer to Phase 3 Group Table 1: FST Timing and SMBG Requirements for 11 Days of Sensor Wear with Acetaminophen Dosing for fingerstick testing at home
- Instruct subject to avoid ingesting food, carbohydrate or glucose during FST, other than standard of care

- Remind subject to perform additional approximate 6-8 times SMBGs throughout the day (outside of the FST days). Subject may obtain more than 8 SMBG readings per day.
- Remind subject to contact the Investigational Center staff in the event they experience problems with their study devices (Refer to Section 12).
- Remind subject to check on the adequacy of their supplies.
- Remind subject to continue filling out the Subject EZ Reference Guide and Diary (remind subject to record time of acetaminophen ingestion)
- Enter eCRFs into the study database as appropriate.

8.1.8. Visit 5 (Phone call): 4th FST

Investigational Center staff will, via phone call:

- Provide subject with the opportunity to bring up study-related questions and concerns.
- Ask subject about the occurrence of AEs.
- Record AEs on the appropriate eCRF if subject reports health status changes that result in a new medical condition or deterioration of an existing medical condition.
- Instruct subject to call the investigational center to report any changes to their health status (see AE definition).
- Ask subject about device deficiencies and if they called the Investigational Center staff to report them
- Instruct subject to perform 4th FST
  - Refer to Phase 3 Group Table 1: FST Timing and SMBG Requirements for 11 Days of Sensor Wear with Acetaminophen Dosing for fingerstick testing at home
  - Instruct subject to avoid ingesting food, carbohydrate or glucose during FST, other than standard of care
- Remind subject to perform additional approximate 6-8 times SMBGs throughout the day (outside of the FST days). Subject may obtain more than 8 SMBG readings per day.
- Remind subject to contact the Investigational Center staff in the event they experience problems with their study devices (Refer to Section 12).
- Remind subject to check on the adequacy of their supplies.
- Remind subject to continue filling out the Subject EZ Reference Guide and Diary (remind subject to record time of acetaminophen ingestion)
- Remind subject on study devices return (Refer to Table 1 in CIP318)
- Enter eCRFs into the study database as appropriate.

8.1.9. Visit 6 (End of Study): In-clinic

Investigational Center staff will:

- Collect Percentage of Body Fat if not collected at previous visits in the study. Record this value on the Visit 1 eCRF.
- Provide subject with the opportunity to bring up study-related questions and concerns.
- Ask subject about the occurrence of AEs.
    - Record AEs on the appropriate eCRF if subject reports health status changes that result in a new medical condition or deterioration of an existing medical condition.
- Ask subject about device deficiencies and if they called the Investigational Center staff to report them
- Collect study sensors if they have been self-removed or fell off the subject prior to Visit 6 in the provided container
- Collect Subject EZ Reference Guide and Diary (verifies for completeness and legibility)
- Perform the following for Phase 3 Group subject on Day 11 (approximately 264-282 hours after sensor insertion), as specified by Sponsor
    - Remove study devices
    - Remove and return all subject worn sensors to Sponsor for visual inspection in the provided container.
- Perform Skin Assessment for each sensor insertion site, document in subject source, and complete the Skin Assessment eCRFs. Photographs taken by subjects will not be used in placement of skin assessments performed in person by the Investigational Center staff.
- Upload following devices to and/or using:
    - CareLink Clinical (Study Meter)
    - Medtronic Box
        - Transmitter data
- Return study devices, unused supplies, and study guides from subject (Refer to Table 1 in CIP318)
- Enter eCRFs into the study database as appropriate.
- 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.

8.1.10. 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. The Investigational Center staff will also upload the transmitter(s) when necessary at these unscheduled visits.

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

If the subject comes to the Investigational Center at an unscheduled visit (e.g., for reasons specified above), the subject's body fat percentage can also be collected at this time if not completed at an earlier visit.

8.2. Subject Consent

Informed Consent 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 Bill of Rights (if applicable), the Institutional Review Board (IRB) and Medtronic approved ICF form, and Authorization Form required by the Health Insurance Portability and Accountability Act (HIPAA) will be presented to each subject to complete. Subjects 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 by the Investigator or designee: the purpose, duration of the study, requirements of the subject during the study, and the potential risks involved with participation in this study. Every attempt will be made to answer the subject's questions during the informed consent process. Subjects will complete California Experimental Subject's Bill of Rights (if applicable), the HIPAA Form, and the ICF form. The consenting process must be documented in the subject's source files. The subject will receive copies of the fully executed documents. A subject's participation in study procedures cannot begin before the consent process has been properly executed.

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

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

Subjects will be informed that qualified personnel from the Investigational Center, the sponsor (Medtronic), agencies such as the FDA 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 violations to their IRB and Sponsor:

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

8.3. Assessment of Safety

AE information is collected in this study. See Section 10 for further information on the collection of AEs and safety information.

8.4. Study Devices Replacement

Subjects will be instructed to wear study sensors approximately 264 hours (11 days).

In the event that any sensor falls off or is removed during the first 24 hours after the first sensor is inserted, the subject may return to the Investigational Center for an unscheduled visit to replace the non-functional sensor (s). New transmitter(s) will be connected to the new (replacement) sensor(s).

Replacement sensors will be worn through the last study visit and removed. A replaced sensor will not be worn any longer than the scheduled EOS. If the replaced sensor falls off early, the replacement sensor will not be replaced.

In the event that any sensor falls off or is removed more than 24 hours after the first sensor is inserted, the subject will continue to wear the remaining sensor(s) for the duration of the subject's sensor wear time or until all sensors are no longer adhered to the subject's skin, whichever event comes first.

Sensors that fall off early will be recorded on an eCRF. Specimen containers will be provided to the Investigational Center for subjects to place scheduled or accidentally removed sensor(s).

Subjects will be instructed by the Investigational Center staff on sensor/device return:

- If a subject experiences irritation or infection of the sensor site(s) and cannot come in for the removal visit, he/she is required to self-remove the affected sensor(s) and corresponding study device(s). Instructions and supplies to help subjects remove sensors and other study devices on their own will be provided.
- Subjects will be instructed to return the removed sensor and study devices to the Investigational Center at their next scheduled visit.

Sensors and study devices should be removed during Visit 5 (as close to 264 hours of wear as possible). Note: Only the sensor should be placed in the container. It must be disconnected from the transmitters. The transmitter(s) should be placed in a ziplock bag and returned to the Investigational Center at the next visit.

In the event that all sensors fall off more than 24 hours after the first sensor is inserted, the subject's participation will be considered complete and the Investigational Center staff should complete an Exit eCRF upon subject's return to the Investigational Center.

8.5. Glucose Measurements

During the course of the study, the subject's SMBG and SG levels will be assessed using the following methods in this section.

8.5.1. Daily Blood Glucose

Values will be assessed during the study by all subjects using the Study Meter. Control solution testing will be performed on the Study Meter assigned to each subject before being dispensed (Visit 2) and any time additional study meter strips are given to the subject. The results of the control solution test will be documented in the subject's source documents. The control solution test will be done following the manufacturer's IFU. Subjects will be trained on the use of the Study Meter per the manufacturer's IFU.

8.5.2. FST Blood Glucose Values

During the FST at the Investigational Center and at home, the BG will be obtained by SMBG from Study Meter BG readings. Subjects may also use the Study Meter SMBG readings for diabetes management.

8.5.3. Sensor Glucose Values

SG will be assessed using the following methods:

- SG data collected by subject's transmitter(s)

8.6. Recording Data

Data, excluding Subject EZ Reference Guide and Diary and 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.

Blood glucose data will be collected from the Study Meter using CareLink Clinical. The 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 and will be saved to the Medtronic Box.

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 procedures.

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

8.7. Deviation Handling

A deviation is any instance(s) of the failure of the Investigator and Investigational Center staff 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:

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

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

The investigator or person designated by the investigator will document and explain any deviation from the approved protocol that occurs during the course of the clinical trial. The date and reason for each deviation will be documented. (21 CFR 812.140 Records)

The investigator should not implement any deviation from, or changes to, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB of an amendment, 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.

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

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

21 CFR 812.150 (4) states "….except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB in accordance with 21 CFR 812.35(a) also is required."

In any emergency situation the investigator shall exercise his/her judgment to safeguard the subject's interest. The investigator shall report a deviation as soon as possible to Medtronic and the reviewing IRB according to IRB reporting guidelines, as applicable. Medtronic will inform the regulatory authorities, if required.

Emergency deviations must be reported to the sponsor and IRB within 5 days.

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. Examples (the list of examples is intended as a guide and is not all-inclusive):

- Failure to obtain informed consent, i.e., there is no documentation of informed consent
- Informed consent obtained after initiation of study procedures

- Enrollment of a subject who did not meet all inclusion/exclusion criteria
- Performing study procedure not approved by the IRB
- Failure to report serious AE to the IRB and sponsor
- Investigational study device dispensed without obtaining informed consent

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

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

Medtronic will submit any significant amendment to the CIP, including a justification for this amendment, to the appropriate regulatory authorities (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 authority (if applicable), and sponsor. Administrative amendments to the CIP will be submitted to the IRB for notification. Furthermore, investigators shall sign any approved amendment for agreement.

FST timing:

- Deviations will be issued for FST testing that is initiated more than 2 hours before or after the endpoints of the specified FST windows.

FST Samples:

It is noted that collecting FST samples every 20 minutes may be challenging. Deviations will not be issued for situations in which subjects do not perform SMBG per frequency recommended as stated in the study protocol.

8.8. Subject Withdrawal or Discontinuation

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

If a subject chooses to end his or her study participation or if the subject is removed from the study at the Investigator's discretion or for failure to meet the study requirements, the reason for withdrawal must be documented both in source documents and Exit eCRF. All study devices and supplies must be returned and returned 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, the subject demonstrates that he/she is not able to comprehend instructions for study procedures, as evaluated by the appropriate research staff.
- During the study, (female) subject becomes pregnant.

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

8.9. Stopping Rules

8.9.1. Subject Stopping Rules

The subject will stop the study if there is an unanticipated adverse device effect (UADE).

8.9.2. Stopping Rules for Entire Study

The study will stop if there is an UADE.

9. Risks and Benefits

9.1. Potential Risks

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	Prevention and mitigation include: • Follow the provided user guides for insertions and care of sensors. • If a sensor site becomes infected or inflamed, the sensor should be removed and another placed in a new location • Base diabetes management on fingerstick readings and not sensor glucose values.

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

Potential risks with acetaminophen may include: • False elevation of sensor glucose readings. The level of inaccuracy depends on the amount of acetaminophen active in subject's body and may be different for each subject	Prevention and mitigation include: • Follow the user guide • Subjects should be instructed to consider avoiding the use of products containing acetaminophen • If acetaminophen is taken, subjects should use additional BG meter readings (they are not to calibrate with those readings) to verify their glucose levels • Subjects should consider exiting Auto Mode

10. Adverse Events Assessments

10.1. Adverse Events

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

10.2. Reporting of Adverse Events

The Investigator or designee will record AEs that are SAEs, device related, study procedure related, 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 (e.g. IV insertion pain, FST exercise injuries). This includes study procedures such as FST and lab draws.

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

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

10.3. Notification of Adverse Events

Sponsor Notification:

As soon as possible (desired within 24 hours of investigator or study coordinator awareness), the Investigational Center staff must report all Severe Hypoglycemia, DKA, SAE, and SADEs 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.

10.4. 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.

10.5. Definitions and Classification of Adverse Events

Medtronic uses the definitions provided in ISO 14155:2011 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. Medtronic follows MEDDEV 2.3/3 revision 3 guidelines for classifying causality levels; but will apply these causality definitions across all events, not only serious adverse events and definitions have been adapted accordingly.

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

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

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

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

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

Adverse Event (AE) (ISO 14155-2011)

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

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

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

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

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

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

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

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

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

An adverse event that

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

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

Note 2: 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. (International Conference on Harmonisation (ICH) Topic E 2 A Clinical Safety Data Management: Definitions & Standards for Expedited Reporting. Europe, the Middle East and Africa (EMEA) 2006)

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

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

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.

10.6. Causality Assessment

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

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

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

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

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

- **Unlikely:** the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but a relationship to the device cannot be completely ruled out.

- **Possible:** the relationship with the use of the investigational device is weak. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed should also be classified as possible.

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

- **Causal relationship:** the event is associated with the investigational device or with procedures

beyond reasonable doubt when:

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

10.7. Anticipated or Unanticipated

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

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

10.8. Skin Assessment: Glucose Sensor Insertion Sites

Skin irritation may be associated with the insertion of the device or device wear and may be associated with the adhesives and tapes used to secure the study devices. The area of skin associated with device insertion and wear will be assessed following the removal of each device by Investigational Center staff. Either subject or investigational center may remove a device if they are concerned with skin irritation or skin discomfort. The Investigational Center staff will complete a skin assessment each time a study device is removed from a subject, independent of the length of time inserted or the amount of time elapsed between device removal and the assessment.

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. These events are to be documented and captured on the Skin Assessment eCRF. An AE eCRF will only be completed if the skin assessment observation meets the following criteria:

- Infection
- Any observation that meets the criteria of moderate or severe per the skin assessment case report form (for example: bruising equal to or greater than 6 cm in longest diameter; rash that requires prescription medication)

Subjects will not be required to return to the Investigational Center for examination to document resolution of Skin Assessment observations. The subject should be instructed to contact the Investigational Center for follow-up if there is any worsening or change that concerns the subject. Worsening should be assessed to determine if AE reporting is necessary.

11. Data Review Committees

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, and may 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

The Sponsor will notify the Investigator of any disagreement in assessment of an event by the CEC.

12. Device Deficiencies and Troubleshooting

The subjects will be instructed to contact the Investigational Center staff for questions or concerns regarding study devices.

All device deficiencies reported directly to the Investigational Center staff by a subject or those potentially identified by review of a Subject EZ Reference Guide and Diary will be reported on the appropriate eCRF. 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. (**Adapted from ISO14155:2011**)

Device returns will follow the Return Sales Order (RSO) instructions. To return a study device as part of a device deficiency, the subject is to contact the Investigational Center staff, and the Investigational Center is to contact Sponsor.

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

13. Statistical Design and Methods

13.1. General Considerations

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.

Data and analysis will be summarized in a Clinical Study Report. Additional data generated will be summarized in an Engineering Report (ER) by Research and Development (R&D).

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, duration of insulin requiring diabetes mellitus, type of diabetes mellitus, body fat percentage, and BMI (calculated based on provided height and weight) will be summarized by descriptive statistics.

13.4. Sensor Insertion and Removal Information

The sensor insertion and removal information will be presented. Detailed Analysis Plan will be described in Biostatistical Plan.

13.5. General Considerations for Data Analysis

Primary sensor will be assigned to sensor number one (inserted in arm) on the eCRF.

13.6. Sample Size and Power

Given that this study is not statistically powered, no sample size calculation is performed. Up to 20 subjects will be enrolled in Phase 3 Group and demonstrate a feasibility study using the study sensors and transmitters.

13.7. CIP Deviations

All CIP deviations will be presented in the listings.

13.8. Accuracy Endpoints

13.8.1. Primary Endpoints

Accuracy (Mean absolute relative difference [MARD]) between the primary sensor values and meter BG values during the two hours (approximately 6 paired points per FST event) after ingestion of acetaminophen per subject will be described. Summary statistics will include its mean, standard deviation, median, and 95% confidence interval.

13.8.2. Exploratory Analysis

Accuracy (MARD) between the primary sensor values and meter BG values during the two hours (approximately 6 paired points per FST event) after ingestion of acetaminophen per measurement will be described. Summary statistics will include its mean, standard deviation, median, and 95% confidence interval.

The 20% mean agreement rate (±20 mg/dL (1.1 mmol/L) when Reference BG less than or equal to (≤) 80 mg/dL (4.4 mmol/L)) between the primary sensor values and meter BG values during the two hours (at least 6 paired points per FST event) after ingestion of acetaminophen per measurement will be calculated. Summary statistics will include its mean, standard deviation, median, and 95% confidence interval.

13.9. Safety Analysis

Descriptive summary will be used to characterize safety events

- Skin assessment of subject's glucose sensor insertion sites
- AEs to include:
  - Serious Adverse Events (SAE)
  - Device Related AEs
  - Procedure Related AEs
  - SADE
  - UADE
  - Severe hypoglycemia
  - Diabetic Ketoacidosis (DKA)

13.10. Device Deficiencies

Descriptive summary will be used to characterize device deficiencies:

- All reports of device issues.
- All Investigational Center/subject reports of sensor damage, breakage or fracture will be included

14. Ethics

14.1. Statement(s) of Compliance

IRB

This protocol, any subsequent amendments to this protocol, the ICF/Assent form, subject material, 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 study will not start until IRB approval has been granted, the Sponsor has cleared the Investigational Center to begin the study, and the investigational clinical staff has been appropriately trained to conduct the study. Copies of all relevant correspondence between the Investigational Center and the IRB will be retained on-site with copies forwarded to the Sponsor for their files.

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 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, IRB approval, study training, clinical trial registration, preclinical testing, risk benefit assessment, publication policy, etc.

14.2. Investigator's Responsibilities

This study will be conducted at the Investigational Centers where all study-related activities will be performed and will be led by a Principal Investigator (PI). 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."

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

- Conduct of the investigation in accordance with the CIP, the abbreviated regulations as outlined in 21 CFR 812.2(b) that apply to NSR studies and other applicable regulations, and any conditions of approval imposed by the reviewing IRB
- Conduct of investigation in accordance to draft guidance from FDA, "Protecting the Rights, Safety, and Welfare of Study Subjects - Supervisory Responsibilities of Investigators", to meet responsibilities with respect to protect human subjects and ensuring the integrity of the data from clinical investigations. This guidance is also intended to clarify FDA's expectations concerning the investigator's responsibility:
    1) to supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other third parties, and
    2) to protect the rights, safety, and welfare of study subjects.
- Supervision of all testing of the device involving human subjects
- Ensuring that the requirements for obtaining informed consent/assent are met in accordance with 21 CFR 50
- Allowing study devices to be used only with subjects under the Investigator's supervision and to supply study devices only to persons authorized to receive it
- Ensuring that Investigational Center staff are adequately trained to perform their assigned duties
- Maintenance of accurate, complete, and current records relating to the Investigator's part of an investigation, to include:
    - all relevant correspondence with Medtronic and IRB
    - records of each subject's case history and exposure to the device
    - the CIP, with documents showing the dates of and reasons for each deviation from the CIP
- Preparation and submission to Medtronic and, when required, the reviewing IRB, the following complete, accurate, and timely reports:

- any reportable AEs (see Section 10) occurring during an investigation
- progress reports on the investigation as required by the IRB
- any deviation from the CIP made to protect the life or physical well-being of a subject in an emergency
- any use of the device without obtaining informed consent/assent
- any further information requested by the IRB about any aspect of the investigation

- Meeting with the monitor to discuss study progress and findings
- Ensuring that Investigational Center resources are adequate to fulfill the obligations of the study
- Ensuring completion of eCRF to include entry and addressing discrepancies in a timely fashion and approving selected eCRFs.

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

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

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 protocol is implemented. All participating physicians and coordinators will be familiarized with the system. Other members of the Investigational Center staff may require training depending on their role listing in 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 Standard Operating Procedures (SOPs) and the Monitoring Plan. At minimum, it will be verified whether signed and dated ICFs/Assent forms have been obtained from each subject at the point of enrollment and that AEs discussed in Section 10.2 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.

15.2.1. Accessibility of Investigational Center Staff and Study Materials

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

15.2.2. Audits and Investigational Center Inspections

In addition to regular monitoring visits, Medtronic 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 bodies 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 Medtronic and regulatory bodies direct access to source data and documents, taking into account any restrictions due to local law, to perform clinical study-related monitoring, audits, IRB review, and regulatory inspections.

15.2.3. Investigational Center Disqualification

Medtronic and/or the IRB retain the right to disqualify an Investigational Center and remove all study materials at any time. Specific instances, which may precipitate Investigational Center disqualification, include but are not limited to:

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

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

15.3. Data Management

15.3.1. Data collection

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

15.3.1.1. Electronic Case Report Forms (eCRFs)

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

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

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

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

15.3.1.2. CareLink Clinical Software

During the course of the study, subject's BG values may be assessed from the study meter. The study meter data will be uploaded in CareLink Clinical by the investigator or designated Investigational Center staff. The systems 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 SIDs to prevent patient identification by the sponsor.

15.3.1.3. Subject EZ Reference Guide and Diary

The Subject EZ Reference Guide and Diary will be collected on paper that will be kept at the Investigational Center. The Investigator or designated Investigational Center staff will make a copy and provide to the Sponsor. It is important that the investigator or designated Investigational Center staff verifies the Subject EZ Reference Guide and Diary completeness and legibility.

15.3.2. 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 adverse events (see Section 10.3), which need to be recorded within 24 hours in the eCRF after awareness of the investigator or Investigational Center staff of the event. Most eCRFs should be submitted in final form, i.e. saved as complete, upon data entry, so that Monitors can proceed with data verification without delay. Exceptions to this rule may apply to eCRF that need to be accessed on multiple occasions before they can be finalized.

15.3.3. Data review and processing

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

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

15.4. Direct Access to Source Data/Documents

The patient's clinic file, CareLink Clinical data, data from GST Download Utility Software, data from Prototype 2A Utility Software, source worksheets, and data collected on the Subject EZ Reference Guide and Diary 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, if applicable, for the purposes of monitoring, audit, or inspection. If applicable, where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the Investigational Center team with a statement that it is a true and complete reproduction of the original source document.

15.4.1. Quality Audits

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

15.5. Confidentiality

The investigator will ensure that the subject's anonymity is maintained. Subjects will not be identified in any publicly released reports of this study. All records will be kept confidential to the extent provided by federal, state and local law. The study monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records. The investigator will inform the subjects that the above-named representatives will review their study-related records without violating the confidentiality of the subjects. All laboratory specimens, evaluation forms, reports, and other records that leave the 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.

15.6. 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.

Medtronic 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 from the IRB, regulatory agency (if applicable), and sponsor. Administrative amendments to the CIP will be submitted to the IRB for notification. Furthermore, investigators shall sign any approved amendment for agreement.

15.7. Records and reports

15.7.1. Investigator Records

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

- Medtronic Contact Information
- CV's & Medical Licenses
- Agreement(s)
- Delegation of Authority Log
- Training Records
- Subject Screening/Enrollment Logs
- Randomization Documentation (if applicable)
- Laboratory Documentation
- eCRFs & Instructions
- Sponsor/Monitor Visit Log
- Protocol and Amendments
- Device IFUs
- IRB Documentation & Approvals
- IRB Approved Consent Documents
- Reports
- Essential Correspondence
- Product Accountability
- Regulations and Guidance Documents
- Site Study Materials
- Subject Study Materials

- Note to File
- Miscellaneous

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

- Source Documents
- Signed and dated ICF/Assent form
- Adverse Event Notifications, if any
- Study Logs, if any

15.7.2. Investigator reporting responsibilities

Table 2. Investigator Reporting Requirements

Report	Submit to	Description/Constraints
AEs	Sponsor, IRB, and local regulatory authority, where applicable	Refer to section 10.2, 10.3, 10.4, and 12 for reporting requirements.
Withdrawal of IRB approval (either suspension or termination)	Sponsor	The investigator must report a withdrawal of approval by the reviewing IRB of the investigator's part of the investigation within 5 working days.
Progress report	Sponsor and IRB	The investigator must submit this report to the sponsor and IRB at regular intervals but in no event less than yearly.
Study deviations	Sponsor and IRB	Notice of deviations from the CIP to protect the life or physical wellbeing of a subject in an emergency shall be given as soon as possible but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations. If the deviation may affect the scientific soundness of the plan or the rights, safety, and welfare of the subjects, the deviation must be approved by Medtronic, the IRB, and if applicable, the FDA/applicable regulatory authorities. If the deviation does not affect these issues then only Medtronic must approve it.
Failure to obtain informed consent/assent prior to investigational device use	Sponsor and IRBs	If an investigator uses a device without obtaining informed consent/assent, the investigator shall report such use within 5 working days after device use.

Report	Submit to	Description/Constraints
Final report	Sponsor IRBs Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation.
Other	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.

15.8. 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.

15.9. Liability

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

15.10. Suspension or Early Termination

Sponsor or a Regulatory Authority may decide to suspend or prematurely terminate the clinical study (e.g. if information becomes available that the risk to study subject is higher than initially indicated, lack of enrollment, if interim analysis indicates that the results significantly differ from expectations relative to study objectives or statistical endpoints, 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.

15.10.1. Early Investigational Center suspension or termination

Sponsor, IRB or a Regulatory Authority may decide to suspend or prematurely terminate an Investigational Center (e.g. in case of expiring approval of the reviewing IRB, non-compliance to the Clinical Investigation Plan, or lack of enrollment). 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.

15.10.2. Subject follow-up in case of termination

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

15.11. Study Close Out

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

15.12. Publication and Use of Information

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

The identity of the subjects may not be disclosed, unless required by law, to any persons not immediately involved in the study or the study procedures. The results for Phase 3 Group will be published on ClinicalTrials.Gov.

16. References

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

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

17. Appendices

17.1. Names and addresses

17.1.1. Investigational Centers

At the time of this Phase 3 Group CIP was finalized, a list of the names and addresses of the participating Investigational Centers were not identified.

17.1.2. IRB

IRB Name	Address	Chairperson
Quorum	1501 Fourth Avenue Suite 800 Seattle, WA 98101	Stephen Rosenfeld, MD, MBA
Western Institutional Review Board	1019 39th Avenue SE Suite 120 Puyallup, WA 98374-2115	See current WIRB Membership Roster

17.1.3. Monitors Contact Information

The study will be monitored by the MCO Global Monitoring and monitoring duties to be entrusted under:

[redacted]

Clinical Monitoring Manager, MCO Global Monitoring

Medtronic

710 Medtronic Parkway

Minneapolis, MN 55432

At the time of this CIP was finalized, the following names and address of the monitors are:

Monitor's Name	Monitor 's Address
[redacted]	710 Medtronic Parkway Minneapolis, MN 55432
[redacted]	
[redacted]	
[redacted]	
[redacted]	
[redacted]	

17.2. Labeling and IFUs of Devices

The current labeling and IFU for the study devices will be provided to the investigators in a 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/Assent form, and the HIPAA Authorization.