Medtronic

Clinical Investigation Plan Title	Impact of Acetaminophen on Performance of Guardian™ Sensor (3) in Adults
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Medtronic **Clinical Investigation Plan (CIP)**	
Study Title	Impact of Acetaminophen on Performance of Guardian™ Sensor (3) in Adults
CIP Identifier	333
Study Product Name & Study Product Model	Investigational devices: • GST3C/4C Dock • GST Download Utility Software Non-Investigational devices: • Guardian™ Connect Transmitter • Guardian™ Sensor (3) • Tester • Charger • One-press Serter • USB cable and wall-powered adaptor for GST3C/4C Charger Dock • Medtronic CareLink™ Personal Therapy Management Software for Diabetes For Clinical Research –referred to as CareLink™ Personal For Clinical Research in this protocol • Ascensia CONTOUR®NEXT LINK 2.4 blood glucose (BG) meter -referred to as the CONTOUR®NEXT LINK 2.4 study meter in this protocol • Oval Tape • Hypafix™* Tape 4 in x10 yd • Tegaderm™* 4" x 4 ½" Dressing • Skin Tac™* Wipe
Description of CIP	This study will assess the impact of acetaminophen ingestion on the performance of Guardian™ Sensor (3) (i.e., C algorithm and Zeus algorithm) in an adult population.
Sponsor	Medtronic MiniMed ("Medtronic")

	18000 Devonshire St Northridge, CA 91325 866.948.6633
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Confidentiality Statement

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1. Glossary

Term	Definition
HbA1c	Glycosylated hemoglobin
AE	Adverse Event
BG	Blood Glucose
BMI	Body Mass Index
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CGMS	Continuous Glucose Monitoring System
CHF	Congestive Heart Failure
CI	Confidence Interval
CIP	Clinical Investigation Plan
DKA	Diabetic Ketoacidosis
eCRF	Electronic Case Report Form
EIS	Electrochemical Impedance Spectroscopy
ER	Emergency Room
EOS	End of Study
FDA	United States Food and Drug Administration
FST	Frequent Sample Testing
GST	Glucose Sensor Transmitter

Term	Definition
Hct	Hematocrit
HIPAA	Health Insurance Portability and Accountability Act of 1996
IB	Investigator's Brochure
ICF	Informed Consent Form
ID	Identification
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board
ISIG	Interstitial Signal
IV	Intravenous
MARD	Mean Absolute Relative Difference
MC2	Medtronic Core Clinical Solutions
NSR	Non-significant Risk
OC-RDC	Oracle Clinical Remote Data Capture
PC	Personal Computer
POC	Point of Care
QC	Quality Control
RF	Radio Frequency
SAE	Serious Adverse Event
SG	Sensor Glucose
SMBG	Self-Monitoring of Blood Glucose
SQ	Subcutaneous

Term	Definition
TS	Technical Support
TLS	Transport Layer Security
UADE	Unanticipated Adverse Device Effect
YSI™*	Yellow Springs Instrument

2. Synopsis

Title	Impact of Acetaminophen on Performance of Guardian™ Sensor (3) in Adults
Sponsor	Medtronic MiniMed, Inc. ("Medtronic") 18000 Devonshire St Northridge, CA 91325 866.948.6633
Indication Under Investigation	Type 1 diabetes, Type 2 diabetes
Devices	*Investigational Devices:* • GST3C/4C Dock • GST Download Utility Software *Non-Investigational Devices:* • Guardian™ Connect Transmitter • Guardian™ Sensor (3) • Tester • Charger • One-press Serter • USB cable and wall-powered adaptor for GST3C/4C Charger Dock • Medtronic CareLink™ Personal Therapy Management Software for Diabetes For Clinical Research –referred to as CareLink™ Personal For Clinical Research in this protocol • Ascensia CONTOUR®NEXT LINK 2.4 blood glucose (BG) meter -referred to as the CONTOUR®NEXT LINK 2.4 study meter in this protocol • Oval Tape • Hypafix™* Tape 4 in x10 yd • Tegaderm™* 4" x 4 ½" Dressing • Skin Tac™* Wipe
Purpose	The purpose of this study is to characterize the impact of acetaminophen ingestion on the performance of the Guardian™ Sensor (3) (i.e., C algorithm and Zeus algorithm) in subjects age 18 – 80 years.

Objective(s)	The primary objective of the study is to characterize the impact of acetaminophen ingestion on the accuracy of Guardian™ Sensor (3) (i.e., C algorithm and Zeus algorithm) with the system in subjects 18-80 years of age.
Study Design	The study is a multi-center, prospective, single-arm study without controls. See Section 5 for additional details on Study Design. A total of up to 150 previously-diagnosed type 1 or type 2 diabetes subjects will be enrolled in order to have 75 subjects complete the study. Up to 9 investigational centers in the US will be used during the study.
FST Timing & Sensor Locations	Subjects will wear two sensors (one sensor in the abdomen and one in the arm location) and undergo 6 hours of FST on Day 4 (74-98 hours) or Day 5 (98-122 hours).

Sample Size and Investigational Centers	A total of up to 150 previously-diagnosed type 1 or type 2 diabetes subjects will be enrolled in order to have 75 subjects complete the study.
	
	Up to 9 investigational centers in the US will be used during the study.
	
	Subjects will be grouped by diabetes classification:
	
	• **Diabetes cohorts based on type of diabetes**
	  ○ Type 1 = minimum 40 subjects
	  ○ Type 2 = minimum 20 subjects
	
	The investigational centers will be encouraged to include subjects of different ethnicities including Hispanic, Native American, Asian, and African-American.

Duration	The study is anticipated to last approximately 6 months from investigational center initiation to finalization of all data entry and monitoring procedures. The subject's maximum participation from study enrollment to study exit is approximately 90 days (including replacement sensor wear and repeat in clinic procedures if needed).
Inclusion/Exclusion Criteria	**Inclusion Criteria:** 1. Individual is 18 - 80 years of age at time of enrollment. 2. Subject has a clinical diagnosis of type 1 or type 2 diabetes for a minimum of 6 months duration as determined via medical record/ source documentation by an individual qualified to make a medical diagnosis. 3. Subject has adequate venous access as assessed by investigator or appropriate staff. **Exclusion Criteria:** 1. Subject has history of allergy to acetaminophen or has been told by a health care provider they may not ingest acetaminophen 2. Subject reports history of liver cirrhosis or liver problems that a health care provider told them they should not use acetaminophen because of liver disorder. 3. Subject will not tolerate tape adhesive in the area of Guardian™ Sensor (3) placement as assessed by a qualified individual. 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 an investigational study (e.g., drug or device) wherein he/she has received treatment from an investigational study (drug or device) in the last 2 weeks prior to Visit 1. (Please note participation in an observational study is acceptable.) 6. Subject is female of child-bearing potential and has a pregnancy screening test that is positive. 7. Subject is female of child-bearing potential and who is sexually active should be excluded if she is not using a form of contraception deemed reliable by investigator. 8. Subject is female and plans to become pregnant during the course of the study. 9. Subject is breast feeding.

	10. Subject has a chronic heavy alcohol use as determined by investigator. 11. Subject has a history of a seizure disorder. 12. Subject has a hematocrit (Hct) more than 10% below the lower limit of normal reference range (please note that patients may use prior blood draw from routine care as long as done within 6 months of screening and report of lab placed with subject source documents). 13. Subject has a history of adrenal insufficiency. 14. Subject is a member of the research staff involved with the study.
Study Visit Schedule:	Section 8.1.1 for Subjects Visit Schedule.
Device Deficiencies:	Subject and investigational center staff will report the device deficiencies by calling the 24-Hour Technical Support (TS) for device troubleshooting and device complaints. For additional information, see Section 12.
Starting Rules for Subjects for FST:	Subjects should fast at least 4 hours prior to start of YSI™* FST.
Stopping Rules for Subjects for FST :	The FST will be discontinued if the blood volume drawn reaches 4 mL/kg or 400 cc whichever is more during the FST.
Subject Stopping Rules for Study:	There are no subject stopping rules for this study.
Study Stopping Rules	There are no predefined study stopping rules.
Repeat Rules for In-Clinic Procedures	• Concurrent failure of both the primary and back-up YSI™* instruments during YSI™* FST. • If subject experiences unresolved IV occlusions during YSI™* FST requiring fingerstick measurements, the in-clinic procedures may be repeated per sponsor recommendation.
Statistical Analysis for Endpoints and Hypothesis:	*Primary Endpoints* Bias between the Guardian™ Sensor (3) values and YSI™* plasma glucose values during the 1 hour before and 5 hours after ingestion of acetaminophen will be described by each hour. Summary statistics will include its mean,

	standard deviation, median, 95% confidence interval (CI), minimum, and maximum. *Secondary Endpoints* Mean absolute relative difference (MARD) between the Guardian™ Sensor (3) values and YSI™* plasma glucose values during the 1 hour before and 5 hours after ingestion of acetaminophen will be described by each hour. Summary statistics will include its mean, standard deviation, median, 95% CI, minimum, and maximum. 20% mean agreement rate (±20 mg/dL (1.1 mmol/L) when reference YSI™* plasma glucose value less than or equal to (≤) 80 mg/dL (4.4 mmol/L) between the Guardian™ Sensor (3) values and YSI™* plasma glucose values during the 1 hour before and 5 hours after ingestion of acetaminophen will be described by each hour. Summary statistics will include its mean, standard deviation, median, 95% CI, minimum, and maximum. *Safety* Descriptive summary will be used to characterize adverse events. *Device Deficiencies* Descriptive summary will be used to characterize device deficiencies.

3. Introduction

3.1. Background

Current methods of continuous glucose monitoring (CGM) include the use of subcutaneous (SQ) 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. A CGM sensor is attached to a transmitter, which typically sends interstitial glucose information to a monitor (e.g., the Guardian™ Connect App) as radio frequency (RF) signals. The sensor is composed of a microelectrode with a thin coating of glucose oxidase beneath several layers of biocompatible membrane.

Previous in vitro testing has demonstrated that the presence of acetaminophen can be associated with a minimal increase in the positive bias of the sensor glucose reading relative to the true glucose concentration in the test solution. Clinical studies will further characterize the in vivo impact of acetaminophen ingestion on sensor accuracy.

Following completion of the study, raw sensor data collected by the Guardian™ Connect Transmitters will be processed using the C and Zeus algorithms. For the C algorithm, sensor glucose will be generated based on 2 calibrations per day. For the Zeus algorithm, sensor glucose will be generated based on 0 calibration and 2 calibrations on Day 1.

3.2. Purpose

The purpose of this study is to characterize the impact of acetaminophen ingestion on the performance of the Guardian™ Sensor (3) (i.e., C algorithm and Zeus algorithm) in subjects age 18 – 80 years.

4. Objectives and Endpoints

4.1. Objectives

4.1.1. Primary Objective(s)

The primary objective of the study is to characterize the impact of acetaminophen ingestion on the accuracy of Guardian™ Sensor (3) (i.e., C algorithm and Zeus algorithm) with the system in subjects 18-80 years of age.

4.2. Endpoints

4.2.1. Primary Endpoints

Bias between the Guardian™ Sensor (3) values and YSI™* plasma glucose values during the 1 hour before and 5 hours after ingestion of acetaminophen will be described by each hour. Summary statistics will include its mean, standard deviation, median, 95% confidence interval (CI), minimum, and maximum.

4.2.2. Secondary Endpoints

Mean absolute relative difference (MARD) between the Guardian™ Sensor (3) values and YSI™* plasma glucose values during the 1 hour before and 5 hours after ingestion of acetaminophen will be described by each hour. Summary statistics will include its mean, standard deviation, median, 95% CI, minimum, and maximum.

20% mean agreement rate (±20 mg/dL (1.1 mmol/L) when reference YSI™* plasma glucose value less than or equal to (≤) 80 mg/dL (4.4 mmol/L) between the Guardian™ Sensor (3) values and YSI™* plasma glucose values during the 1 hour before and 5 hours after ingestion of acetaminophen will be described by each hour. Summary statistics will include its mean, standard deviation, median, 95% CI, minimum, and maximum.

4.2.3. Safety

Descriptive summary will be used to characterize adverse events.

4.2.4. Device Deficiencies

Descriptive summary will be used to characterize device deficiencies.

5. Study Design

The study is a multi-center, prospective, single-arm study without controls.

Subjects will wear two sensors (one sensor in the abdomen and one in the arm location) and undergo 6 hours of FST on Day 4 (74-98 hours) or Day 5 (98-122 hours).

Subjects will wear the devices up to 7 day training period (optional for subjects who participated in prior Medtronic CGM trials, per PI discretion) followed by a 7 day study period. Investigational center staff will ensure 176-188 hours of sensor wear (sensors may be removed at that time or after that time to ensure that the devices are not removed pre-maturely). In the event that early sensor removal occurs during the training period, the subject can continue to the study period based on PI discretion.

The YSI™* FST will be approximately 6 hours during the in-clinic visit and will require subjects to be fasting. Subjects should also arrive to clinic fasting (i.e., subjects should target not have anything to eat at least 4 hours prior to arrival to clinic). Per investigator discretion, the investigator may provide recommendations to adjust medications the night before the YSI™* FST visit and prior to arrival to clinic to target 150 mg/dL upon arrival to clinic. Prior to and during the YSI™* FST, subjects may drink non-caloric fluid. Caffeine is acceptable. Investigator discretion may be used to provide carbohydrates if subject is experiencing symptoms consistent with hypoglycemia and/or documented hypoglycemia (< 70 mg/dL) or any other reason investigator feels there is a safety issue (e.g., impending syncope). Investigational center staff will enter any departures from fasting on an Activity Log. For details on maximum amount of blood drawn refer to Synopsis and Stopping Rules for Subjects for FST (section 8.11.1).

During the study period, each subject will undergo one YSI™* FST:

- 24 hours prior to start of YSI™* FST
  - Subject is to not take any medication containing acetaminophen.
- At least 4 hours prior to start of YSI™* FST
  - Subject is to fast.
- Start YSI™* FST
  - At the beginning of YSI FST, investigational center staff is to draw blood to measure baseline serum acetaminophen concentration and send to Central Laboratory for processing.
- One hour after the YSI™* FST start
  - Investigational center staff is to instruct subject to ingest acetaminophen (1000 mg).
- Two hours after the YSI™* FST start
  - Investigational center staff is to draw blood to measure serum acetaminophen concentration (1 hour after subject's acetaminophen ingestion) and send to Central Laboratory for processing.

During the YSI™* FST, intravenous (IV) blood samples will be drawn every 10-15 minutes and analyzed using the YSI™*:

- First 3 hours of YSI™* FST
  - every 10 minutes (window of 4-16 minutes)
- Last 3 hours of YSI™* FST

- every 15 minutes (window of 7-23 minutes)

Subjects and/or Sites are to call the 24-Hour Technical Support (TS) for device troubleshooting and device complaints (See Section 12).

Subjects will continue with their current diabetes regimen independent of the study devices. Subjects will be instructed by the investigational center that they are not to use the study devices (except for the study meter) for the management of their diabetes.

5.1. Duration

The study is anticipated to last approximately 6 months from investigational center initiation to finalization of all data entry and monitoring procedures. The subject's maximum participation from study enrollment to study exit is approximately 90 days (including replacement sensor wear and repeat in clinic procedures if needed).

5.2. Rationale

This study is required to characterize the impact of acetaminophen ingestion on the accuracy of Guardian™ Sensor (3) (i.e., C algorithm and Zeus algorithm) with the system in subjects 18-80 years of age.

6. Product Description

6.1. Investigational Devices

The investigational devices used in this study will be described in this section. Instructional materials will be provided.

6.1.1. GST3C/4C Dock

The GST3C/4C Dock is an investigational device. It creates a communication link between the Guardian™ Connect Transmitter(s) and a PC to be used for uploading the data stored on the devices and clearing the data.

For the purposes of this study, uploads of the Guardian™ Connect Transmitter(s) are performed only by the investigational center staff.

6.1.2. GST Download Utility Software

The GST Download Utility Software for use with Guardian™ Connect Transmitter(s) is an investigational PC-based program used to set time, upload data and clear data for the Guardian™ Connect Transmitter(s). Communication between the Guardian™ Connect Transmitter(s) and the PC is done via the GST3C/4C Dock.

6.2. Non-Investigational Devices

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

6.2.1. Guardian™ Sensor (3)

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

6.2.2. Guardian™ Connect Transmitter

The Guardian™ Connect Transmitter is a device that reads the electronic signal generated by the sensor, generates a sensor glucose value based on the sensor signals and calibration BG measurements and transmits that value to a mobile application. In addition, the transmitter contains a custom ASIC (Application Specific Integrated Circuit), which enables Electrochemical Impedance Spectroscopy (EIS). The EIS measurements are used as diagnostics for the sensor, which are incorporated into the sensor calibration logic.

In this study the Guardian™ Connect Transmitter will be connected to the Guardian™ Sensor (3) and will be a single-use device. The Guardian™ Connect Transmitter will not transmit to a mobile application, but will store recorded data that will be downloaded at the end of the study for analysis through the new sensor calibration algorithm.

6.2.3. Tester

The Tester (Figure 1) operates as a sensor simulator creating signal current at a level that is within the range of an in-vivo sensor during normal operation. It is used to test and clean the Guardian™ Connect Transmitter.

Figure 1. Tester

For the purposes of this study, Tester will be used only by the investigational center staff.

6.2.4. Charger

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

6.2.5. One-press Serter

The One-press Serter (Figure 2) is an insertion device that is used to ensure correct placement of the Guardian™ Sensor (3) into the user's subcutaneous tissue. Insertion is triggered when the two spring loaded buttons on the sides of the One-press Serter are pressed simultaneously.

The One-press serter is a single patient, non-sterile, multi-use device.

Figure 2. One-press Serter

6.2.6. USB Cable and Wall- Powered Adaptor for GST3C/4C Dock

The small end of the USB cable (MMT-7747) connects to the GST3C/4C Dock. The other end of the cable connects to a USB port on a computer and charge the transmitter(s). The USB cable can also be connected to an AC adapter.

For the purposes of this study, uploads of transmitter(s) are performed only by the investigational center staff.

The USB cable serves as a communication link between the GST3C/4C Dock and the PC.

6.2.7. Medtronic CareLink® Personal Therapy Management Software for Diabetes For Clinical Research – Non-Investigational

Medtronic CareLink® Personal Therapy Management Software for Diabetes For Clinical Research is a web-based system which allows the device data to be viewed and easily evaluated by the physician. A PC links to the Medtronic CareLink® system via the Internet and allows for upload of data from Medtronic MiniMed insulin pump and third-party BG meters. The clinical support version of Medtronic CareLink™ Personal For Clinical Research software may be used by investigational center staff. For the purposes of this study, uploads are performed only by the investigational center staff.

All references to CareLink™ Personal For Clinical Research software are meant to imply the clinical support version of Medtronic CareLink™ and throughout the protocol will be referred to as CareLink™ Personal For Clinical Research software. The data contained in CareLink™ Personal For Clinical Research software is accessible to users using a standard browser, i.e., Microsoft® Internet Explorer, on an Internet enabled PC.

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

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

The CareLink™ Personal For Clinical Research software will be used only to upload the blood glucose measurements from the CONTOUR®NEXT LINK 2.4 study meter. These uploads will be used by Medtronic for data collection and analysis.

6.2.8. Ascensia CONTOUR®NEXT LINK 2.4 Blood Glucose Meter

An Ascensia CONTOUR®NEXT LINK 2.4 blood glucose (BG) meter, referred to as the CONTOUR®NEXT LINK 2.4 study meter, will be provided to all subjects for use. The meter determines the subject's capillary BG level using the Ascensia CONTOUR®NEXT Strips.

In this study, the blood glucose measurements from the CONTOUR®NEXT LINK 2.4 study meter will be uploaded to CareLink™ Personal For Clinical Research software.

The Ascensia CONTOUR®NEXT BG test strips, USB connector cables, and Ascensia CONTOUR®NEXT Control Solutions will be used in conjunction with the CONTOUR®NEXT LINK 2.4 study meter.

6.2.9. Oval Tape

The Oval tape is a medical grade adhesive tape that 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 ISO 10993-Biological Evaluation of Medical Device testing.

6.2.10. Hypafix™* Tape, Tegaderm™* Dressing or Skin Tac™* Wipe

Hypafix™* tape 4 in x10 yd, Tegaderm™ 4" x 4 ½" dressing or Skin Tac™* Wipe are off the shelf medical grade adhesive and dressing/wipe that may be used to secure the sensor and transmitter pair to the body.

6.3. Anticipated Device Changes

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

6.4. 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 devices being used in clinical research will not be shipped to any site unless all of the necessary approvals (e.g., Regulatory and IRB) have been received.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices. Additional details regarding device disposition requirements are provided in Table 1.

6.4.1. Receipt and Inventory of Investigational Devices by Investigational Center

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

6.4.2. 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 user guide/labeling.

6.4.3. Disbursement of Study Devices

Each time a study device is disbursed to a subject by the investigator or authorized member of the research team, eCRF (e.g., Sensor Insertion/Removal eCRF) and/or source documentation will be completed as required. Documentation may include:

- Date of disbursement
- Subject ID
- Lot number(s) (where applicable)
- Serial Number (where applicable)
- Device Type
- Amount dispensed

The investigator or authorized member of the research team is to record disbursement only for the study meter from subject on the Subject Device Identification eCRF.

6.4.4. Handling of Study Devices Upon Completion of Subject and Site Study

Requirements for return or disposal of study devices upon completion of subject and site participation in the study are listed in Table 1. All consumable products may be disposed of properly by the investigational center staff at end of study (EOS).

Table 1 Device Disposition by Subjects and Site

Device	Subject	Site
Guardian™ Sensor (3) (MMT-7020)	Return unused sensors only to site, unless required for return for a complaint	Unused sensors may be returned to sponsor or discarded by investigational center. Discard used sensors; sponsor may ask for used sensors associated with complaint to be returned.
Guardian™ Connect Transmitter* (MMT-7821)	Return device to site	Return used and unused devices to sponsor
GST3C/4C Dock (T8381-003)	NA	Return used and unused devices to sponsor
CONTOUR®NEXT LINK 2.4 study meter (MMT-1152/1352)	Device does not need to be returned to site.	Discard used devices. Unused devices may be returned to sponsor or discarded by investigational center.

*May be shipped as a starter kit (MMT-7820).

7. Selection of Subjects

7.1. Study Population

A total of up to 150 previously-diagnosed type 1 or type 2 diabetes subjects will be enrolled in order to have 75 subjects complete the study.

Up to 9 investigational centers in the US will be used during the study.

Subjects will be grouped by diabetes classification:

- **Diabetes cohorts based on type of diabetes**
  - Type 1 = minimum 40 subjects
  - Type 2 = minimum 20 subjects

The investigational centers will be encouraged to include subjects of different ethnicities including Hispanic, Native American, Asian, and African-American.

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 identification (ID) via the eCRF, which is a 9-digit code (333XXXXXX). The first three numbers refer to the CIP number (333), the next three numbers refer to the investigational center number, and the last 3 numbers refer to the subject number assigned during Visit 1 (e.g., 333002001 is subject 001 from site 002).

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

7.3. Inclusion Criteria

1. Individual is 18 - 80 years of age at time of enrollment.
2. Subject has a clinical diagnosis of type 1 or type 2 diabetes for a minimum of 6 months duration as determined via medical record/ source documentation by an individual qualified to make a medical diagnosis.
3. Subject has adequate venous access as assessed by investigator or appropriate staff.

7.4. Exclusion Criteria

1. Subject has history of allergy to acetaminophen or has been told by a health care provider they may not ingest acetaminophen
2. Subject reports history of liver cirrhosis or liver problems that a health care provider told them they should not use acetaminophen because of liver disorder.
3. Subject will not tolerate tape adhesive in the area of Guardian™ Sensor (3) placement as assessed by a qualified individual.
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 an investigational study (e.g., drug or device) wherein he/she has received treatment from an investigational study (drug or device) in the last 2 weeks prior to Visit 1. (Please note participation in an observational study is acceptable.)
6. Subject is female of child-bearing potential and has a pregnancy screening test that is positive.
7. Subject is female of child-bearing potential and who is sexually active should be excluded if she is not using a form of contraception deemed reliable by investigator.
8. Subject is female and plans to become pregnant during the course of the study.
9. Subject is breast feeding.
10. Subject has a chronic heavy alcohol use as determined by investigator.
11. Subject has a history of a seizure disorder.
12. Subject has a hematocrit (Hct) more than 10% below the lower limit of normal reference range (please note that patients may use prior blood draw from routine care as long as done within 6 months of screening and report of lab placed with subject source documents).
13. Subject has a history of adrenal insufficiency.
14. Subject is a member of the research staff involved with the study.

7.5. FST Timing & Sensor Locations

Subjects will wear two sensors (one sensor in the abdomen and one in the arm location) and undergo 6 hours of FST on Day 4 (74-98 hours) or Day 5 (98-122 hours).

8. Study Procedures

8.1. Schedule of Events

8.1.1. Visit Schedule

Each subject's participation will include the following visits below. The intent is for subjects to wear the study sensors and undergo one YSI™* FST.

One rescheduled visit can occur during the study period if the sensors dislodges and new sensors must be re-inserted (See Replacement Sensors Section 8.4 and 8.5).

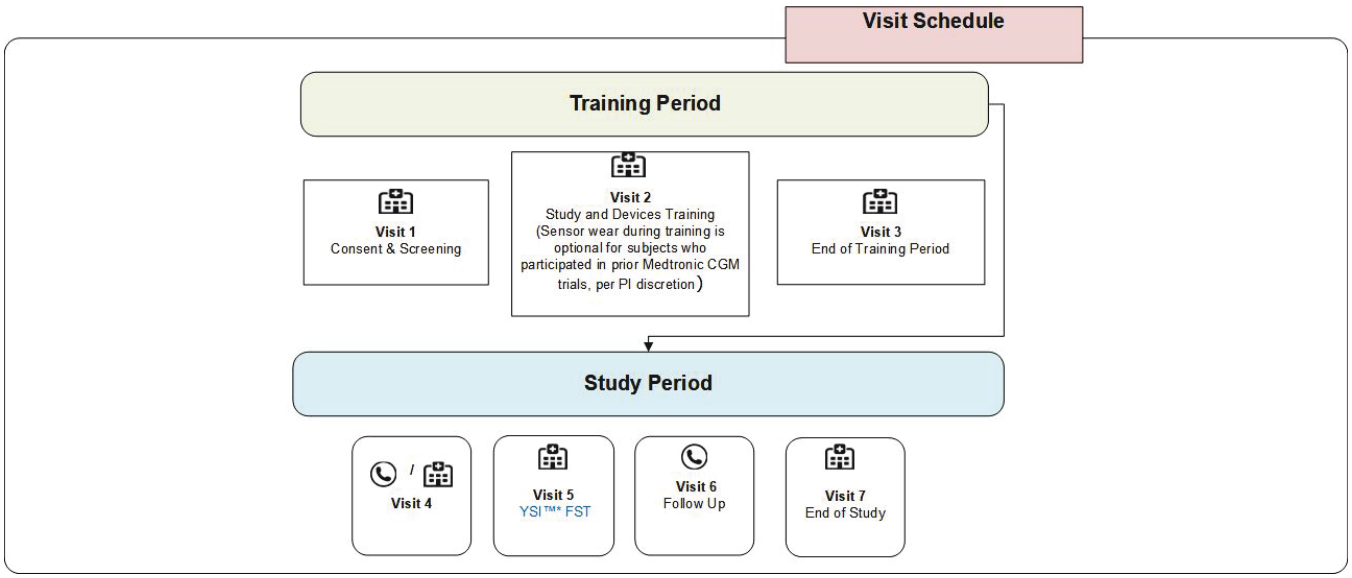
Screening and Training Period: To be completed in 30 days (Visit 1 to Visit 3)

- Visit 1: Consent and Screening
- Visit 2: Study and Device Training
    - Confirm eligibility. Please note that Hct eligibility criteria must be confirmed prior to Visit 2.
    - Visit 1 and 2 can be combined if eligibility criteria are met (see note above on Hct).
    - Subjects to insert one sensor in abdomen and one in the arm location (Sensor wear during the training period is optional for subjects who participated in prior Medtronic CGM trials, per PI discretion)
- Visit 3: End of Training Period - Investigational center Visit
    - Investigational center staff must remind subject to not ingest medication containing acetaminophen 24 hours prior to start of YSI™* FST
    - Investigational center staff must remind subject to fast at least 4 hours prior to start of YSI™* FST
    - Investigator may instruct subject to make any anti-diabetic medication adjustments, if applicable, including adjustment in insulin to avoid hypoglycemia.

Start of Study Period: To be completed in 60 days from Visit 4 to Visit 7

- Visit 4: Phone Visit or Optional Office Visit
  - Investigational center staff must remind subject to not ingest medication containing acetaminophen 24 hours prior to start of YSI™* FST
  - Investigational center staff must remind subject to fast at least 4 hours prior to start of YSI™* FST
  - Investigator may remind subject to make any anti-diabetic medication adjustments, if applicable, including adjustment in insulin to avoid hypoglycemia.
  - Investigational center staff must confirm that the sensor insertion was performed at the appropriate insertion time, insertion location, and SMBG reminder
- Visit 5: YSI™* FST
- Visit 6: Follow Up Phone Call
- Visit 7: End of Study Visit
  - Schedule after subject has worn sensors for T= 176-188 hours.
  - Upload the study devices

Figure 1. Visit Schedule



8.1.2. Visit 1: Consent and Screening

Overview General

Investigational center staff will:

- Obtain California Experimental Subject's Bill of Rights (if applicable), ICF, and HIPAA form from the subjects
- Assess subject eligibility to participate in the study
- Obtain demographic and baseline characteristics including:
  - Age
  - Gender
  - Race
  - Ethnicity
  - Prior medical history, to include diabetes classification (e.g., type 1, type 2) and date of diabetes diagnosis
  - Height and Weight

    Note: BMI will be calculated automatically in the study database, based on height and weight measurements entered.
  - Concomitant medications
  - CGM experience
- Complete required screening tests, if all eligibility criteria are met:
  - Perform urine test for pregnancy, female subjects of child-bearing age or capability
  - Obtain blood sample:
    - Hct
      - Send to Central Laboratory, or clinic's own lab for required screening tests. There is no point of care (POC) testing for Hct.
      - If patient has prior Hct from routine care done within 6 months of enrollment and the report of lab placed with subject source documents, then no blood test needs to be done.
      - **Note:** For all out of range lab results, a single re-test is permitted
    - HbA1c (not an eligibility criteria)
      - Send to Central Laboratory
- Enter data into electronic Case Report Forms (eCRF)s as appropriate
- Schedule next visit date and time

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, whether they are eligible or ineligible to participate. If a subject fails screening criteria (e.g., Hct or 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 Hct and pregnancy test results are available and all other eligibility criteria are met.

8.1.3. Visit 2: Study and Devices Training

For subjects who participated in prior Medtronic CGM trials, the training period is optional, per PI discretion. If subjects opt out of the training, subjects can combine Visit 2 and Visit 3.

Confirm all eligibility criteria has been met from Visit 1.

Prior to use, all devices will be prepared following the instructions in the users' guides. Before distributing to subjects at Visit 2, the Guardian™ Connect Transmitters and the CONTOUR®NEXT LINK 2.4 study meters need to be synchronized with the designated study clock at the investigational center. Subjects will be instructed not to change the clocks (except for daylight savings time changes) in these devices. Subjects will be provided an CONTOUR®NEXT LINK 2.4 study meter to be used to perform fingerstick (capillary SMBG) and all required calibrations of study devices. The investigational center staff will also have to register the subject into CareLink™ Personal For Clinical Research software and upload the subject's CONTOUR®NEXT LINK 2.4 study (see Investigator Site Binder for details) .

Guardian™ Connect Transmitter setup instructions

The investigational center staff will need to fully charge and set up the Guardian™ Connect Transmitter(s) prior to distribution to study subject.

- Refer to Section 8.1.3.1 for Procedures Including YSI™* FST Timing and SMBG Requirements

Overview of general study procedures

Investigational center staff will:

- Confirm eligibility
- Synchronize time on Guardian™ Connect Transmitters and CONTOUR®NEXT LINK 2.4 study meter using the investigational center's designated study clock
- Register study subjects in CareLink™ Personal For Clinical Research software
- Upload CONTOUR®NEXT LINK 2.4 study meter into CareLink™ Personal For Clinical Research software
- Train subjects on study devices
- Enter data into eCRFs as appropriate
- Schedule the next visit date and time

Overview of study devices and supplies

Investigational center staff will disburse the following to the subjects:

- Guardian™ Connect Transmitter(s)
- Guardian™ Sensor (3)(s)
- Chargers
- Tester
- One-press Serter
- CONTOUR®NEXT LINK 2.4 study meter(s)
- BG supplies (e.g., control solution, batteries, meter strips, lancet holder and lancets)
- Other study materials (e.g., study reference card, device user guides, and training materials)
- Other study supplies and adhesives (e.g., alcohol swabs, Oval tape, Hypafix™* tape, Tegaderm™* dressing, Skin Tac™* Wipe) as needed

Investigational center staff will record and track all study devices outlined in the device accountability section (see Section 6.4) on the appropriate eCRF.

Overview of training and instructions

Investigational center staff will:

- Train each subject on sensor insertions, taping and removal, study devices, and study procedures
  - Subject will be instructed to wash hands thoroughly with soap and water.
  - Subject will be instructed to clean the insertion site with alcohol and let the insertion site air dry prior to sensor insertion.
- Train subjects on use of CONTOUR®NEXT LINK 2.4 study meter
  - Subject will be instructed to wash his/her hands thoroughly with warm, soapy water, rinse and dry before testing BG
  - Consider best practice to use "second drop" technique, express first drop and wipe away, express second drop for meter BG testing
  - Subjects will be instructed to use only the CONTOUR®NEXT LINK 2.4 study meter during the course of the study to perform study defined SMBG measurements
- Perform applicable quality control (QC) testing (CONTOUR®NEXT LINK 2.4 study meter). Shake control solution bottle well prior to use.
- Instruct subjects to insert one sensor in the abdomen and one in the arm location.
- Have subject perform connection of Guardian™ Sensor (3)s to the Guardian™ Connect Transmitter(s).
- Instruct subjects to apply adhesives according to the Instructions for Use (IFU)
- Instruct subjects to perform fingersticks (capillary SMBGs)
- Recommend subjects to set alarm (e.g., on their phone) to check their fingersticks (SBMG) at insertion, 2 hours, 8 hours, 10 hours, 20 hours and 24 hours after insertion on Day 1 and also one approximately at the same time every day as time of the insertion
- Have subject perform the first calibration at the investigational center or a follow up call will be required to confirm this
- Instruct subjects to wear the devices up to 7 days training period. Instruct subjects to remove the sensors (at end of training period or at investigational center) after 7 days (T= 176-188 hours).
- Instruct subjects on Guardian™ Sensor (3)s return.
- Subjects will be provided information to help identify sensor fracture, breakage or damage (i.e., subject would note a sensor failure and upon removal would see that the sensor electrode is not fully or partially present when removing the sensor)
  - Subjects should notify site immediately of sensor breakage/fracture
  - Site should notify Medtronic when sensor breakage is suspected. (See Section 12 for notification process)

- Site may provide therapy recommendations for sensor breakage as per investigator discretion (i.e., ultrasound imaging, surgical removal)

- Instruct subjects to contact the 24-Hour TS for technical issues and support
- Remind subjects to bring in the CONTOUR®NEXT LINK 2.4 study meter for accuracy testing (with control solution per IFU to each visit)

In addition:

- Assess subjects for the occurrence of any adverse events or device deficiencies (see Section 10 and 12 at each visit and document on the appropriate source) and record event(s) on the appropriate eCRF

The main purpose of Visit 2 is to provide the subjects with study device training that would be comparable to training provided to patients in the actual clinical use. The subjects will receive training on the study requirements before completing the training visit. All subjects will be trained on the device(s) to be used in the study prior to leaving the investigational center. Investigational center staff will train the subjects on the appropriate use of the study devices. Each subject will receive training on sensor insertion and removal, other study devices, and study procedures. This training includes SMBG. The training is expected to last 15 minutes to 2 hours in duration on average, depending on the subject's experience. Training materials provided to the subject may include IFUs, Getting Started Guides, and Quick Reference Guide. This allows subject familiarization with study devices and procedures.

Subjects will continue on their current diabetes regimen (including glucose monitoring with their own meter when desired) independent of the study devices.

Subjects will be instructed by the investigational center that they are not to use the study devices (except for the study meter) for the management of their diabetes.

The subjects will not be blinded to the study devices used. However, the data generated from the study devices will be blinded to the subjects.

Overview of FST Timing and Sensor Location:

Subjects will wear two sensors (one sensor in the abdomen and one in the arm location) and undergo 6 hours of FST on Day 4 (74-98 hours) or Day 5 (98-122 hours).

8.1.3.1. Procedures Including YSI™* FST Timing and SMBG Requirements

SMBGs that are collected will be used retrospectively for calibration(s) of sensor as applicable.

SMBG Requirements

- On Day 1, a minimum of 6 fingerstick glucose readings (SMBG) at the times below will be requested with target of 7 total fingerstick glucose readings:
    - Time = 0 hour
        - Sensor insertions will be performed
        - The 0 hour represents the time after the last sensor has been connected to the Guardian™ Connect Transmitter
    - Time = 2 hours
        - T = 2 hours after the last sensor has been inserted connected to the Guardian™ Connect Transmitter
    - Time = 8 hours
        - T = 8 hours after the last sensor has been connected to the Guardian™ Connect Transmitter
    - Time = 10 hours
        - T = 10 hours after the last sensor has been connected to the Guardian™ Connect Transmitter
    - Time = 20 hours
        - T = 20 hours after the last sensor has been connected to the Guardian™ Connect Transmitter
    - Time = 24 hours
        - T = 24 hours after the last sensor has been connected to the Guardian™ Connect Transmitter
- On Day 2-7, a minimum of 4 fingerstick glucose readings (SMBG) per day will be requested with target of 7 fingerstick glucose readings (with one of them occurring at the same time of day as initial sensor insertion [±1 hour]). For example, if sensor was inserted at 8 am, then each day after that one SMBG will done at this same time.
- One SMBG should be taken upon arrival for FST (Day 4 or Day 5)
- At the end of FST, take one fingerstick glucose reading
- Consider best practice to use "second drop" technique: express first drop and wipe away, express second drop for meter BG testing.
- Subjects will be instructed to check SMBG 4-7 times spread throughout the day.

8.1.4. Visit 3: End of Training Period -Investigational Center Visit

Overview of general study procedures
Investigational center staff will:

- Instruct subject to self-remove the sensors that he/she is still wearing at this visit
- Upload study devices via:
    - CareLink™ Personal For Clinical Research software (CONTOUR®NEXT LINK 2.4 study meter)
    - GST Download Utility Software (Guardian™ Connect Transmitters) following instructions provided
- Determine if additional training is needed (e.g., if the subject is not following finger-stick monitoring requirements). If additional training is required, subjects will be retrained using training materials supplied during training visit 2 and research staff may focus on specific areas of opportunity for improvement.
- Enter data into the eCRFs as appropriate
- Review requirements of next study visit with subjects
- Disburse Guardian™ Sensor (3)s to subjects who will insert at home
- Disburse new Guardian™ Connect Transmitter(s) (Refer to "Guardian™ Connect Transmitter setup instructions" prior to distribution to study subject)
- Remind subject to not ingest medication containing acetaminophen 24 hours prior to start of YSI™* FST (Visit 5)
- Remind subject to fast at least 4 hours prior to start of YSI™* FST (Visit 5)
- Schedule the next visit dates and times (includes the first YSI™* FST)
- The subject will be instructed to insert sensors. Note: the subject will use the same CONTOUR®NEXT LINK 2.4 study meter provided at training visit. The subject will perform the connection of the Guardian™ Connect Transmitter to the study Guardian™ Sensor (3) (as will be done in real patient use). And the subject will apply adhesives according to the IFU.
- Remind subjects on Guardian™ Sensor (3)s return (see Table 1 Device Disposition by Subjects and Site)
- Schedule YSI™* FST visit so it is on Day 4 (74-98 hours) or Day 5 (98-122 hours)
- Enter all necessary device return information on the appropriate eCRF and any additional subject visits (unscheduled) on the appropriate eCRF.

In addition, Investigator may remind subject to make any anti-diabetic medication adjustments, if applicable, including adjustment in insulin to avoid hypoglycemia.
In the event the subject no longer wants to participate in the study after the training period or any time throughout the course of the study including the day of last FST, the subject will be withdrawn. This will

be documented in the subject study file including the reason for withdrawal and the Exit eCRF will be completed.

8.1.5. Visit 4: Phone Call or Optional Office Visit

The purpose of the Visit 4 (phone/clinic visit) is to verify that the sensor insertion was performed at the appropriate insertion time, insertion location, and SMBG reminder.

During the phone call or at the investigational center, the investigational center staff will:

- Remind subject to not ingest medication containing acetaminophen 24 hours prior to start of YSI™* FST (Visit 5)
- Remind subject to fast at least 4 hours prior to start of YSI™* FST (Visit 5)
- Confirm subject has inserted, connected and taped the sensors at the appropriate time and sensor location. Once the study period sensors are inserted, the subject should follow the YSI™* FST SMBG requirements (Section 8.1.3.1).
- Remind subject to bring medication, syringes, insulin, and infusion sets that might be needed for their personal pumps during the YSI™* FST visit.

In addition, Investigator may remind subject to make any anti-diabetic medication adjustments, if applicable, including adjustment in insulin to avoid hypoglycemia.

8.1.6. Visit 5: YSI™* FST

The YSI™* FST is a 6 hour frequent BG sampling session using IV blood samples and a laboratory BG analyzer, YSI™*. The investigational center staff will set up the YSI™*.

8.1.6.1. Prior to Arrival at the Clinic

These subjects should fast at home (i.e., subjects should target not have anything to eat for at least 4 hours) prior to arrival to clinic. Per investigator discretion, the investigator may provide recommendations to adjust medications the night before the YSI™* FST visit and prior to arrival to clinic to target 150 mg/dL upon arrival to clinic. Subjects may drink non-caloric fluid. Caffeine is acceptable. Investigator discretion may be used to provide carbohydrates if subject is experiencing symptoms consistent with hypoglycemia and/or documented hypoglycemia (< 70 mg/dL) or any other reason investigator feels there is a safety issue (e.g., impending syncope). Investigational center staff will enter any departures from fasting on an Activity Log. In addition, subjects should not take any medication containing acetaminophen 24 hours prior to start of YSI™ FST.

These subjects should also take any other medications at their usual times both at home and in clinic. Subjects should bring all medications they are taking with them to the clinic, even if they aren't scheduled to take that medication that day.

Insulin (if applicable), medication(if applicable), diet, diabetes monitoring/management and ketone monitoring/management may be performed per Investigator discretion (e.g., may reduce long acting insulin night before).

8.1.6.2. Upon Arrival to the Clinic for the Subject Undergoing FST

Per investigator discretion, the investigator may provide recommendations to adjust medications prior to arrival to clinic to target 150 mg/dL upon arrival to clinic.

During the in-clinic YSI™ FST, subjects will continue to fast for the duration of the YSI™* FST (6 hours). Subjects may drink non-caloric fluid. Caffeine is acceptable. Investigator discretion may be used to provide carbohydrates if subject is experiencing symptoms consistent with hypoglycemia and/or documented hypoglycemia (< 70 mg/dL) or any other reason investigator feels there is a safety issue (e.g., impending syncope). Investigational center staff will enter any departures from fasting on an Activity Log.

8.1.6.3. In-Clinic Procedures

Overview of general study procedures

Investigational center staff will:

- Collect concomitant medications (medication containing acetaminophen only)
- Set up the YSI™* instruments (see Investigator Site Binder for details)
- Perform applicable QC testing (CONTOUR®NEXT LINK 2.4 study meter)
- Synchronize YSI™* devices at the investigational center with the designated study clock
- Verify that sensor insertions were performed at the appropriate insertion time, insertion location and SMBG reminders.
- Conduct SMBG testing upon subject arrival
- Refer to Section 8.1.3.1 for instructions on Procedures Including YSI™* FST Timing and SMBG Requirements
- Apply heating pad (optional) around subject's IV site, per investigator's discretion

- Conduct YSI™* FST procedures
    - 24 hours prior to start of YSI™* FST
        - Subject is to not take any medication containing acetaminophen.
    - At least 4 hours prior to start of YSI™* FST
        - Subject is to fast.
    - Start YSI™* FST
        - At the beginning of YSI FST, investigational center staff is to draw blood to measure baseline serum acetaminophen concentration and send to Central Laboratory for processing.
    - One hour after the YSI™* FST start
        - Investigational center staff is to instruct subject to ingest acetaminophen (1000 mg).
    - Two hours after the YSI™* FST start
        - Investigational center staff is to draw blood to measure serum acetaminophen concentration (1 hour after subject's acetaminophen ingestion)
- Upload study devices following completion of each YSI™* FST:
    - CONTOUR®NEXT LINK 2.4 study meter via CareLink™ Personal For Clinical Research software
- Upload YSI™* data to sponsor's secure site
- Calculate time for T=176-188 hours where the sensor may be removed at that time or after that time to ensure that the devices are not removed pre-maturely
- Subjects will continue to wear sensors past the end of this visit to achieve sensor wear for T=176-188 hours
- Review requirements of next study visit (phone and EOS visit) with subjects
- Enter data into eCRFs as appropriate
- Remind subjects on Guardian™ Sensor (3)s return (see Table 1 Device Disposition by Subjects and Site)
- Record all adhesives used on appropriate eCRF

Overview of study devices and supplies

Investigational center staff will disburse the following to subjects as needed:

- Acetaminophen (1000 mg of acetaminophen for the YSI™ FST)
- BG supplies (e.g., batteries, meter strips, lancet holder and lancets)
- Other study supplies and adhesives (e.g., alcohol swabs, Oval tape, Hypafix™* tape, Tegaderm™* dressing, Skin Tac™* Wipe) as needed

Investigational center staff will record and track all study devices outlined in device accountability section (see Section 6.4) on the appropriate eCRF.

Overview training and instructions

Investigational center staff will:

- Remind subjects to perform fingersticks (capillary SMBG)
- Remind subjects to contact the 24-Hour TS for technical issues and support
- Fingerstick will be performed at home as stated in Section 8.1.3.1.

8.1.6.3.1. Blood Glucose Monitoring During the YSI™* FST

The frequency of blood draws for YSI™* FST sampling is dependent on the average value of YSI-B and YSI-W probes of the previous sample, according to the following ranges:

- First 3 hours of YSI™* FST
  - every 10 minutes (window of 4-16 minutes)
- Last 3 hours of YSI™* FST
  - every 15 minutes (window of 7-23 minutes)

8.1.6.3.2. YSI™* FST Not Available (For Example, IV Occlusion)

In the event that YSI™* BG values are not immediately available, for safety purposes, the investigational center may use a CONTOUR®NEXT LINK 2.4 study meter to measure glucose. The fingerstick glucose values will be recorded on the appropriate eCRF and not used for analysis.

Venous blood samples should still be drawn for YSI™* FST.

8.1.6.3.3. End of FST and Discharge

Subject will be discharged per investigator discretion. The following are additional discharge activities:

- Investigational center staff will provide 24-hour contact information to the subjects
- Investigational center will contact the subject within 24 hours after discharge to assess subject status
- Subjects will be requested to continue to monitor their glucose at home with a minimum of 4 fingerstick glucose readings a day and a target of 7 fingersticks a day.

8.1.7. Visit 6: Follow-up Phone Call

The investigational center staff will follow-up with the subject after the YSI™* FST within 24 hours from discharge to address any questions, concerns and ask questions (e.g., most recent BG reading, ketone testing (as applicable), and assessing for AE) to determine how the subject has been doing. If subject is unable to be reached, then this should be documented and at least one second attempt to reach subject be performed.

8.1.8. Visit 7: End of Study

- Investigational center staff will ensure sensor wear time has been met (T=176-188 hours) and the sensor may be removed at that time. It is recommended to have subject remove sensor at clinic to ensure it is removed at proper time.
- Subjects will return to the clinic to address any questions, concerns, and collect adverse events or device deficiencies.
- For subjects who are still wearing the sensor(s), instruct subjects to remove them
- Upload study devices via:
    - CareLink™ Personal For Clinical Research software (CONTOUR®NEXT LINK 2.4 study meter)
    - GST Download Utility Software (Guardian™ Connect Transmitters) following instructions provided
- Return study sensors, devices, unused supplies and study guides from subjects (refer to Section 6.4)
- An Exit eCRF will be completed at this 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's Bill of Rights (if applicable), the (Institutional Review Board) IRB and Medtronic-approved ICF, and an Authorization Form required by the Health Insurance Portability and Accountability Act (HIPAA) Authorization Form will be presented to each subject to review and sign as applicable. The subject 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 of the study, the duration of the study, the requirements expected to be adhered to by the subject during the study, and the potential risks/ possible benefits associated with participation in the study. Every attempt will be made to answer the subject's questions during the informed consent process. The language used shall be as non-technical as possible and must be understandable to the subject.

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

Subjects will complete California Experimental Subject's Bill of Rights (if applicable), the HIPAA Form, and the ICF. The consenting process must be documented in the subject's source documents. 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.

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

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

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

- Whether or not active subjects must 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), specific 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 the 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 on file for all subjects who have provided informed consent.
- Use of an ICF that has not received approval from the IRB.
- Use of an incorrect version of the ICF.

8.3. Assessment of Safety

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

8.4. Replacement Sensors

8.4.1. Training Period Sensor Wear Rules

During the training period, if a sensor dislodges prior to completing, the subject may continue with the remaining sensor(s) until the end of the training period.

8.4.2. Study Period Sensor Wear Replacement Rules

A subject can replace their sensors once. Subject will wear the replacement sensors for 7 days (T= 176-188 hours) and complete the required YSI™* FST visits.

The following examples are when to replace the sensors:

- If a sensor dislodges before the YSI™* FST, the subject should replace both sensors and complete the FST.

  For example, if a subject loses a sensor inserted in the arm location on Day 3 (prior to YSI™* FST), subject should replace sensors in both insertion locations and complete the FST 98-122 hours after the insertion of the replacement sensors.
- If a sensor dislodges after the FST completion, it is not necessary to replace the sensor.

Scheduling should be performed so that subjects remain in the 90-day window period (i.e., between Visit 1 – Visit 7).

8.5. Repeat Rules for In-Clinic Procedures

- Concurrent failure of both the primary and back-up YSI™* instruments during YSI™* FST.
- If subject experiences unresolved IV occlusions during YSI™* FST requiring fingerstick measurements, the in-clinic procedures may be repeated per sponsor recommendation.

8.6. Medical Oversight

In order to conduct the YSI™ FST, staffing with the appropriate training is required:

- A physician or mid-level provider, such as a nurse practitioner or a physician assistant, who has managed diabetic patients must be available during the entire FST.
- The Investigator (or designee) will need to have one of the following qualifications; endocrinology fellowship, management in patients with diabetes in a clinical practice. The provider must be qualified to treat diabetic emergencies.

8.7. Glucose and Glycemia Measurements

During the course of the study, the subjects' BG, SG levels, HbA1c and alternate POC BG values will be assessed using the following methods:

- **Daily BG-** Values will be assessed during the study by all subjects using the CONTOUR®NEXT LINK 2.4 study meter. The control solution test will be done following the manufacturer's IFU. Subjects will be trained on the use of the CONTOUR®NEXT LINK 2.4 study meter per the manufacture's IFU.
- **YSI™* FST BG values -**During the YSI™* FSTs at the investigational center, blood plasma glucose will be determined using the laboratory BG analyzer (YSI™*).
- **Sensor Glucose (SG) Values** - Assessed using the following methods:
    - SG values collected by subject's Guardian™ Connect Transmitter
- **HbA1c** - Collected at baseline (Visit 1) and will be used as demographic information.
- **Alternate POC BG values**- During the YSI™* FST at the investigational center, alternate POC BG measurements will be used (CONTOUR®NEXT LINK 2.4 study meter) and the values recorded on the appropriate eCRF (not used for analysis). A QC test will be performed on the CONTOUR®NEXT LINK 2.4 study meter device before each YSI™* FST. The results of the QC test will be documented in the subject's source documents. The QC test will be done following the manufacturer's IFU.

8.8. Recording Data

All data required for analysis will be captured on eCRFs using OC-RDC's module. Original eCRFs will not be considered as source data and supporting documentation will be required.

Electronic device data will be collected from the CONTOUR®NEXT LINK 2.4 study meter using CareLink™ Personal For Clinical Research software. The system uses Secure Sockets Layers (TLS) technology, which encrypts all data it stores (21 CFR Part 11 compliant). Data from the Guardian™ Sensor (3) will be collected using the GST Download Utility Software. Certain data points stored in the uploaded information may also be captured on the appropriate eCRF. These data files will be sent to the sponsor electronically using the internet and a secure cloud-based site (Box).

Electronic data files will be collected from the YSI™* devices for each subject. These data files will be sent to the sponsor electronically using the internet and a secure cloud-based site (Box).

Laboratory results will be recorded on eCRFs.

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

Medtronic will only consider eCRFs to be complete when all discrepancies between source data and eCRF have been resolved and eCRF content has been reviewed by 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.

8.9. Deviation Handling

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

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

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

The following provides further guidance on what is or what is not a CIP deviation:

- FST timing:
  Out of window protocol deviations related to start of FST time will be given ONLY if the FST is not performed on the scheduled testing day.

- FST Sample:

  It is noted that collecting YSI™* FST every 10– 15 minutes may be challenging. Deviations for missing YSI™* FST samples will only be issued for the following reasons:

  - If there are 2 consecutive YSI™* FST samples missing (unless they were missed for safety issues, IV or YSI™* FST device issues).
    - Example of 2 missing YSI™* FST collected every 10 minutes:
      - YSI™* FST at 8 A.M.
      - YSI™* FST at 8:30 A.M.

    Since the samples need to be taken at 8:10 AM and 8:20 A.M. but the 2nd sample is at 8:30 AM, there are at least 2 missing samples.
  - A total of 3 or more YSI * FST samples missing during YSI™* FST (unless they were missed for safety issues, IV or YSI™* FST device issues).

  In the event that samples are not able to be collected or analyzed for technical reasons (YSI™* or IV line problems) reasons must be recorded on the eCRF and will not be considered deviations.

- SMBG:

  As subjects may not follow the fingerstick recommendations perfectly, no study deviation will be given unless site did not train subject on SMBG study procedures.

- Fasting:

  If the investigator feels that subject should have mixed meal (carbohydrate, protein, fat) for safety reasons, subjects may be administered a mixed meal and no study deviation will be given.

8.9.1. Documenting Requirements for Study Deviations

8.9.1.1. Unplanned CIP Deviations

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

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

CIP deviations should be reported as follows:

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

8.9.1.2. Reporting Requirements for Study Deviations

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

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

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

- Failure to obtain informed consent, i.e., there is no documentation of informed consent
- Informed consent obtained after initiation of study procedures
- Continuation of a subject who did not meet all inclusion/exclusion criteria
- Performing study procedure not approved by the IRB
- Failure to inform IRB and sponsor of reportable AEs (see Section 10)
- Investigational study device dispensed without obtaining informed consent
- Device dispensing error (i.e., use of an investigational device on a non-study subject)
- Study visit conducted outside of required timeframe that, in the opinion of the PI, may affect subject safety

Reporting of all other study deviations should comply with:

- IRB policies and/or
- local laws and/or

- regulatory agency requirements

They must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation. Refer to Investigator Reports, Section 15.8.2, for specific deviation reporting requirements and timeframes for reporting to Medtronic, IRB and regulatory agency (if applicable).

8.9.2. Analyzing Deviations

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

8.10. Subject Withdrawal or Discontinuation

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

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

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

- In the opinion of the Investigator, the subject's health or safety would be compromised by continuing in the study
- In the opinion of the Investigator, it is in the subject's best interest to discontinue participation in the study
- The subject is found to no longer meet all inclusion criteria, or is found to meet one or more exclusion criteria
- The subject fails to comply with one or more study requirements

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

8.11. Stopping Rules

8.11.1. Stopping Rules for Subjects for FST

The FST will be discontinued if the blood volume drawn reaches 4 mL/kg or 400 cc whichever is more during the FST.

8.11.2. Subject Stopping Rules for Study

There are no subject stopping rules for this study.

8.11.3. Study Stopping Rules

There are no predefined study stopping rules.

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 • Anxiety associated with insertion	Prevention and mitigation include: • Follow the provided user guides. • If a sensor site becomes infected or inflamed, the sensor will be removed and another placed in a new location
Risks with Transmitter	**Prevention and Mitigation**
Risks with Transmitter may include: • Skin irritation or reaction to adhesives • Bruising • Discomfort • Redness • Pain • Rash • Infection	Prevention and mitigation include: • Follow the provided user guide. • Train on the proper use of the transmitters.

• 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	
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 guide for insertions and care of device. • Train on the 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 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. • Train on the proper use of the meter and fingerstick testing.
Risks with IV Catheter Insertion	**Prevention and Mitigation**
Risks with IV catheter insertion may include: • Pain • Bruising • Infection • Irritation • Syncopal episode secondary to catheter insertion • Swelling. • Discomfort • Anxiety	Prevention and mitigation include: • Qualified individual to perform IV catheter insertion • Constant observation and monitoring of the subject during FSTs • Sterile technique will be used to insert the IV Treatment of these risks include: • Removal of IV catheter if subject experiences significant discomfort • Removal of IV catheter if infection develops • Antibiotics will be given, if needed
Risks for indwelling IV catheter	**Prevention and Mitigation**
Risks with indwelling IV catheters may include: • Infection • Irritation • Swelling • Thrombosis • Phlebitis • Bruising	Prevention and mitigation include: • Management of IV per investigational center protocol • Use of universal precautions to avoid infection • Qualified investigator will be present during experiment • Constant observation and monitoring of the subject

	during FSTs • Observation for redness at IV insertion site by qualified staff Treatment of these risks include: • Removal of IV catheter if infection develops and antibiotics will be given.
Risks with Blood Draw	**Prevention and Mitigation**
Risks with drawing blood may include: • Discomfort and bruising • Insertion of an IV catheter and drawing blood may also result in faintness, inflammation of the blood vessel, pain and bruising at the needle site • There is also a slight possibility of infection.	Prevention and mitigation include: • Qualified staff to perform blood draw
Risks with IV Saline Infusion	**Prevention and Mitigation**
Risks with saline infusion may include: • Edema • Congestive heart failure • Third spacing	Prevention and mitigation include: • Qualified investigator will be present during experiment • Constant observation and monitoring of the subject during FSTs Treatment of these risks include: • Reduction of IV fluid if subject shows signs of CHF, lower extremity edema, crackles on lung auscultation or S3 heart sound Subjects who still exhibit signs of fluid overload at time of discharge will be transported to the emergency room (ER) or follow guidelines of the local institution for the disposition of subject.
Risks with Acetaminophen Use	**Prevention and Mitigation**
Potential risks with acetaminophen may include: • Liver damage, liver failure and/or rare but fatal liver failure can occur • Skin rash and/or serious and potentially fatal skin reactions have been reported • Allergic reactions including those which are serious and potentially fatal can occur • Kidney disease • Lowered blood counts (red cells and white cells)	Prevention and mitigation include: • Acetaminophen dosage not to exceed the labeling • Subjects will be instructed to not take acetaminophen 24-hours prior to the FST • Subject with a history of allergy to acetaminophen or has been told by health care provider they may not ingest acetaminophen will be excluded • Subject who has a history of liver cirrhosis or problems with liver that a health care provider told them they should not use acetaminophen because of liver disorder will be excluded

9.2. Potential Benefits

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

9.3. Risk-Benefit Rationale

The benefit of new CGM technology may potentially improve overall diabetes management and glucose control. This benefit outweighs the risks of using the study device and study procedures.

9.4. Risk Determination

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

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

The devices to be used are the same as or similar, in manufacturing, material and intended use as those approved for commercial distribution as part of the Continuous Glucose Monitoring Systems. Specifically, we will use sensors and transmitters approved by FDA. The NSR determination is also based on the commensurate safety experience of continuous glucose monitoring in commercial use. Furthermore, no diagnostic or treatment decisions will be made, and no insulin will be administered during the study.

10. Adverse Event Assessments

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

10.1. 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 2.7/3 revision 3 guidelines for classifying causality levels; but will apply these causality definitions across all events, not only serious adverse events and definitions have been adapted accordingly.

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

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

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

- Blood glucose greater than (>) 250 mg/dL or greater than (>) 13.9 mmol/L
- Serum ketones or large/moderate urine ketones
- Symptoms such as polyuria, polydipsia, nausea, or vomiting
- Treatment provided in a health care facility

Adverse Event (AE) (ISO 14155-2011)

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

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

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

Adverse event that

a) Led to a death

b) Led to a serious deterioration in the health of the subject, that either resulted in

1. a life-threatening illness or injury, or
2. a permanent impairment of a body structure or a body function, or
3. in-patient* or prolonged hospitalization, or

4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) Led to foetal distress, foetal death or a congenital abnormality or birth defect

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

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

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

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

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

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.

10.2. Reporting of Adverse Events

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

- *Procedure* related AE: bruising at IV insertion site

Subjects participating in the study have diabetes and are expected to experience hypoglycemia and or hyperglycemia. These normal events are not expected to be reported to sponsor 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 SADE to Medtronic. For the previously mentioned events, the AE eCRF will be completed with all known details as soon as possible, this will serve as notification to Medtronic. If the study database cannot be accessed due to technical problems, contact the sponsor via email at dl.diabetesclinicalresearchsafety@medtronic.com and provide the known details of the event. Once the access issue has been corrected, the event should be entered onto an AE eCRF.

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

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. 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. It should also be noted that should a subject utilize a non-Medtronic device (such as an insulin pen) these would not be considered device related.

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.

10.6. Anticipated or Unanticipated

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

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

10.7. AEs Related to Glucose Sensor Insertion Sites

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

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

10.8. Documentation of Symptoms During Frequent Sample Testing

All symptoms experienced by the subject during FST must be recorded on the appropriate log. Those symptoms that are minor and directly associated with the requirements of the FST would be recorded on the log only. Examples include:

- headache
- shakiness/tremors
- discomfort associated with IV insertion

Events that are more serious should be noted on the log and reported as AEs. This would include:

- Severe Hypoglycemia
- Diabetic ketoacidosis
- Seizure
- Vomiting
- Chest pain
- Syncope/Fainting
- Shortness of breath unrelated to physical activity

11. Data Review Committees

11.1. Clinical Events Committee

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

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

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

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

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

12. Device Deficiencies and Troubleshooting

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

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

All device deficiencies reported directly to the investigational center staff by a subject should either be reported to the TS by the subject or investigational center staff. Any device deficiency the investigational

center may have should be reported to the TS. 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**)

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

It is the responsibility of the Investigator to follow their 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 downloading the various devices and used as source data for analysis. Data and analysis will be summarized in a Clinical Study Report.

13.2. Subject Disposition

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

13.3. Sensor Disposition

The number of sensor insertions and sensor removals for every subject enrolled in the study will be presented.

A descriptive analysis of sensor disposition including sensor dislodgement and reasons why it dislodged will be included in the Final Report. Sensor insertion and removals will be characterized by the following:

- Sensor location
- Duration of sensor wear by investigational center subject report
- The number and percentage of sensors remaining in place at study end.
- Duration of sensor wear (subject report) by insertion site.
- Reason for removal: for example, scheduled removal, adverse event, fell out.

The functional life of the sensor will also be characterized. The duration of sensor performance from the time of first valid Interstitial Signal (ISIG) to the last glucose reading (i.e., time to end of sensor life) will be described with Kaplan-Meier curves.

13.4. Subject Demographics and Baseline Characteristics

Subject characteristics, including age, gender, race, ethnicity, medical diagnosis (includes date of diabetes diagnosis and type of diabetes), height, weight, CGM experience, baseline HbA1c and BMI will be summarized by descriptive statistics (mean, standard deviation, minimum, median, and maximum) for continuous variables and by counts and percentages for categorical variables.

13.5. Sample Size and Power

Given that this study is not statistically powered, no sample size calculation is performed. Due to potential attritions of sensor data, up to 150 subjects will be enrolled at up to 9 investigational centers in order to have up to 75 subjects who complete the study.

13.6. Analysis Populations

All enrolled subjects who have at least one paired sensor and YSI™* measurement will be included in the efficacy analysis population. All enrolled subjects who have a sensor inserted will be included in the safety analysis population.

13.7. Assignment to Day of YSI™* FST

Subjects will be required to attend one 6 hour session of frequent sampling in which agreement between YSI™* and sensors will be summarized.

13.8. General Considerations for Data Analysis

13.8.1. Datasets Expected

The following datasets will be generated by the combination of:

- Algorithm:
    - C algorithm
    - Zeus algorithm
        - 0 Calibration
        - Two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)

- Location
  - Abdomen
  - Arm

13.8.2. Pairing Scheme

All YSI™* values collected will be presented. However, the sensor accuracy endpoint analysis will only include sensor values of 50-400 mg/dL and paired YSI™*.

YSI™* values will be paired with the closest sensor value between [0, 5) minutes. Fingerstick values that were not used for calibration will be paired with the closest sensor value within [0, 5) minutes.

13.8.3. YSI™* Retention

All YSI™* values will be captured and retained in OC-RDC database.

13.9. Primary Endpoints

Bias between the Guardian™ Sensor (3) values and YSI™* plasma glucose values during the 1 hour before and 5 hours after ingestion of acetaminophen will be described by each hour. Summary statistics will include its mean, standard deviation, median, 95% confidence interval (CI), minimum, and maximum.

13.10. Secondary Endpoints

Mean absolute relative difference (MARD) between the Guardian™ Sensor (3) values and YSI™* plasma glucose values during the 1 hour before and 5 hours after ingestion of acetaminophen will be described by each hour. Summary statistics will include its mean, standard deviation, median, 95% CI, minimum, and maximum.

20% mean agreement rate (±20 mg/dL (1.1 mmol/L) when reference YSI™* plasma glucose value less than or equal to (≤) 80 mg/dL (4.4 mmol/L) between the Guardian™ Sensor (3) values and YSI™* plasma glucose values during the 1 hour before and 5 hours after ingestion of acetaminophen will be described by each hour. Summary statistics will include its mean, standard deviation, median, 95% CI, minimum, and maximum.

13.11. Safety

Descriptive summary will be used to characterize adverse events.

13.12. Device Deficiencies

Descriptive summary will be used to characterize device deficiencies.

14. Ethics

14.1. Statement(s) of Compliance

IRB

This CIP, any subsequent amendments to this CIP, the ICF, subject materials and any form of subject recruitment information (e.g., advertisements) relating to this study will be approved by the responsible IRB in accordance with 21 CFR Part 56. The investigational center will not initiate any subject activities until IRB approval has been granted, the sponsor has cleared the investigational center to begin the study, and the investigational center staff has been appropriately trained to conduct the study.

Regulatory Compliance

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

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

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

Ethical Considerations

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

14.2. Investigator's Responsibilities

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

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

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

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

15. Study Administration

15.1. Training of Clinical Staff

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

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

15.2. Monitoring

Monitoring visits may be conducted at the start, during and at the closure of the clinical study in accordance with Medtronic SOPs and the Monitoring Plan. At minimum, it will be verified whether signed and dated ICF have been obtained from each subject at the point of enrollment and that AEs discussed in Section 10 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, FDA personnel and the Clinical Study Manager. This accessibility is of particular importance for reviewing data in the eCRF. Direct access to subject medical files for source data verification will need to be granted and prepared prior to any monitoring visits.

15.2.2. Audits and Investigational Center Inspections

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

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

15.2.3. Investigational Center Disqualification

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

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

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

15.3. 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 Delegated Task List included in the Investigator Site Binder. The OC-RDC system maintains an audit trail on entries, changes and corrections in eCRFs.

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

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

15.3.1.1. CareLink™ Personal For Clinical Research 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™ Personal For Clinical Research software 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 subject IDs to prevent patient identification by the sponsor.

15.3.1.2. GST Download Utility Software

The investigational center will use the GST Download Utility Software to set time, check software/firmware version, upload data and clear data from transmitters. Communication between the transmitters and the computer is done via the GST3C/4C Dock. Once the transmitter data is downloaded, each investigational center will access a specified database and upload the device data.

15.3.2. Time Windows For Completion and Submission of eCRFs

It is expected that eCRFs are completed in a timely manner with the exception of the reportable AEs (see Section 10.3). After data entry, eCRFs should be submitted (i.e., saved) so that Monitors can proceed with data verification without delay.

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 subject's clinic file, laboratory reports, YSI™* data and source documents are handled as source data.

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

15.5. 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. All records will be kept locked and all computer entry and networking programs will be done with coded numbers only.

15.6. Liability

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

15.7. CIP Amendments

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

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

15.8. Records and Reports

15.8.1. Investigator Records

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

- All essential study documents and correspondence that pertains to the clinical study
- CIP and, if applicable, any amendments
- Report of Prior Investigations and/or user guide
- Medtronic and IRB-approved Subject ICFs
- IRB and Regulatory authority approval or notification

- Fully signed clinical study agreements (i.e. including Investigator Statement , Clinical Trial Agreement, Financial Disclosure and Confidential Disclosure Agreement)
- Completed Delegated Task List
- Training documentation of all investigational center staff
- Subject Screening log and/or Subject ID log
- Signed, dated and fully executed Subject ICFs
- Source documentation
- Fully executed eCRFs and corrections
- Report of AEs and Device Deficiencies
- Device accountability records
- CIP Deviation/ CIP Non-Compliance, if any
- Clinical Bulletins- A brief official update or summary of current study news on a matter of immediate interest and high importance to investigational center surrounding the CIP.
- Current signed and dated curriculum vitae (CV) of PI (and key study team members if required per local requirements)
- Study Reports

15.8.2. Investigator Reporting Responsibilities

Table 2. Investigator Reporting Requirements

Report	Submit to	Description/Constraints
AEs and Device Deficiencies	Sponsor, IRB, and regulatory authority, where applicable	Refer to section 10 and 12 for reporting requirements.
Withdrawal of IRB approval (either suspension or termination)	Sponsor	An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
Progress report	Sponsor and 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.
Failure to obtain informed consent prior to investigational device use	Sponsor and IRBs	If an investigator uses a device without obtaining informed consent, the investigator shall report such use within 5 working days after device use.

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	Sponsor, IRB and FDA	An investigator shall, upon request by a reviewing IRB, FDA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation.

15.9. Record Retention

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

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 CIP 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 this study 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. 28:1245-1249, 2005

17. Appendices

17.1. Appendix A: Names and addresses

17.1.1. Investigational Centers

At the time of this CIP was finalized, a list of the names and addresses of the participating Investigational Centers were not identified. Refer to ClinicalTrials.gov for the names and address of the participating Investigational Centers.

17.1.2. IRB

At the time of this CIP was finalized, a central IRB was identified to be used for the study:

IRB Name	Address	Chairperson
Advarra	1501 Fourth Avenue Suite 800 Seattle, WA 98101	See current IRB Membership Roster

However, the Investigational Centers can also use their own local IRB with Sponsor approval.

17.1.3. Monitors Contact Information

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

[redacted]

Clinical Monitoring Manager, MC2 Global Monitoring

Medtronic

710 Medtronic Parkway

Minneapolis, MN 55432

17.2. Appendix B: Labeling and IFUs of Devices

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

17.3. Appendix C: Sample Consent Materials

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

18. Version History

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