Medtronic	
Study Title	Performance Evaluation of an Advanced Algorithm with CGM in Adults, Adolescents, and Pediatrics
NCT Number	NCT03966911
Document Description	Study Protocol (Version H)
Document Date	26-SEP-2019

Medtronic **Clinical Investigation Plan (CIP)**	
Study Title	Performance Evaluation of an Advanced Algorithm with CGM in Adults, Adolescents, and Pediatrics
CIP Identifier	324
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 Meter -referred to as the CONTOUR®NEXT LINK 2.4 study meter in this protocol ○ Abbott™*/Medisense™*Precision Xtra™* meter to be used for Ketone measurements only - referred to as the Precision Xtra™* ketone meter in this protocol ○ Oval Tape ○ Hypafix™* Tape 4in x10 yd ○ Tegaderm™* 4" x 4 ½" Dressing ○ Skin Tac™* Wipe
Description of CIP	This study will assess the use of Guardian™ Sensor (3) for the span of 170 hours (7 days) in an adult, adolescent, and pediatric population:

	○ Synopsis includes study devices, eligibility, study duration and statistical discussion ○ Adult and adolescent section includes study design and study procedures ○ Pediatric section includes study design and study procedures ○ Combined sections include: Safety, Device Performance, statistical section and Administrative sections
Sponsor	Medtronic MiniMed ("Medtronic") 18000 Devonshire St Northridge, CA 91325 866.948.6633
Document Version	Version H
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1. Glossary

Term	Definition
HbA1c	Glycosylated hemoglobin
AE	Adverse Event
ARE	Absolute Relative Error
AR1	Auto-regressive
ASIC	Application Specific Integrated Circuit
BG	Blood Glucose
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CEC	Clinical Events Committee
CEP	Clinical Evaluation Plan
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
CVA	Cerebrovascular Accident
DKA	Diabetic Ketoacidosis
eCRF	Electronic Case Report Form
EGA	Error Grid Analysis

Term	Definition
EIS	Electrochemical Impedance Spectroscopy
ER	Emergency Room
EOS	End of Study
exch	Exchangeable
FDA	United States Food and Drug Administration
FST	Frequent Sample Testing
GST	Glucose Sensor Transmitter
Hct	Hematocrit
HIPAA	Health Insurance Portability and Accountability Act of 1996
IB	Investigator's Brochure
ICF	Informed Consent/Assent Form
IDE	Investigational Device Exemption
IFU	Instructions for Use
IM	Intramuscular
IND	Independence
IRB	Institutional Review Board
ISIG	Interstitial Signal
IV	Intravenous
MC2	Medtronic Core Clinical Solutions
NGSP	National Glycohemoglobin Standardization Program
NS	Normal Saline
OC-RDC	Oracle Clinical Remote Data Capture

Term	Definition
PC	Personal Computer
PMA	Premarket Approval Application
POC	Point of Care
QIC	Quasi-AIC
QC	Quality Control
rDNA	Ribosomal DNA
RF	Radio Frequency
SAE	Serious Adverse Event
SGV	Sensor Glucose Value
SMBG	Self-Monitoring of Blood Glucose
SR	Significant Risk
SQ	Subcutaneous
TS	Technical Support
TIA	Transient Ischemic Attack
TLS	Transport Layer Security
UADE	Unanticipated Adverse Device Effect
WHO	World Health Organization
YSI™*	Yellow Springs Instrument

2. Synopsis

Title	Performance Evaluation of an Advanced Algorithm with CGM in Adults, Adolescents, and Pediatrics
Clinical Study Type	Pivotal study
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 Meter -referred to as the CONTOUR®NEXT LINK 2.4 study meter in this protocol ▪ Abbott™*/Medisense™*Precision Xtra™* meter to be used for Ketone measurements only - referred to as the Precision Xtra™* ketone meter in this protocol ▪ Oval Tape ▪ Hypafix™* Tape 4 in x10 yd ▪ Tegaderm™* 4" x 4 ½" Dressing *Commercially available device used outside their approved intended use in subjects 14 years or younger. **Commercially available device used outside their approved intended use in subjects 2-6 years.
Purpose	The purpose of this study is to demonstrate the performance of the Guardian™ Sensor (3) with an advanced algorithm in subjects age 2 – 80 years, for the span of 170 hours (7 days).
Objective(s)	The primary objective of the study is to demonstrate the accuracy of Guardian™ Sensor (3) when used over a period of 7 days (i.e., 170 hours) with the system in subjects 2-80 years of age.
Study Design	The study is a multi-center, randomly assigned, prospective, single-sample correlational design without controls. Subjects will be randomly assigned to sensor location, FST day, and FST time. A total of up to 460 previously-diagnosed type 1 and 2 diabetes subjects will be enrolled in order to have 244 subjects complete study. o N= 122 subjects 18-80 years old ▪ N= 15 minimum subjects age 18-29 years old ▪ N= 15 minimum subjects age 30-60 years old

	▪ N= 15 minimum subjects age 61-80 years old o N= 122 subjects 2-17 years old ▪ N= 15 minimum subjects 2-4 years old ▪ N= 15 minimum subjects 5-6 years old ▪ N= 20 minimum subjects 7-10 years old ▪ N= 20 minimum subjects 11-13 years old ▪ N= 24 minimum subjects 14-17 years old The study procedures may be done in a camp/hotel setting. For example, pediatric subjects may be brought together for 1-2 weeks during the week they undergo their FST sessions. The following are hotel/camp study requirements in order to support the safety of challenges which is equivalent to that provided in the in-clinic setting: **Staffing:** PI, sub- investigator and research support staff must provide the equivalent support to that performed in the in-clinic setting during Frequent Sample Testing. For example, the PI or sub-investigator are required to be present during all challenges. A research coordinator(s) must be on premises 24/7 during the entire hotel/camp stay. **Rescue Therapy:** Rescue therapy outlined in the protocol for hyperglycemia and hypoglycemia are required to be available during the entire hotel/camp stay as defined in the protocol. • Treatment with Glucagon and ampules of glucose for hypoglycemia are required to be available during the hotel/camp stay • Treatment with Saline, and IV regular insulin for hyperglycemia are required to be available during the hotel/camp stay. • Intravenous access is required during challenges for the hotel/camp study as it is for the in-clinic setting during Challenge procedures. **YSI:**

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- YSI is a portable machine that may be used in any setting – in-clinic or hotel/camp.
- YSI maintenance procedures will still be required during the hotel/camp.

See Section 8.1 for Subjects 14-80 years Study Design

See Section 9.1 for Subjects 2-13 years Study Design

</td></tr>
<tr><td>Random Assignment</td><td>

FST Timing for 14-80 years old:

<table>
<tr><th>Group</th><th>Sensor Wear Day</th><th>Timing of YSI™* FST & Start of Challenge (if applicable) from Sensor Insertion T=0</th></tr>
<tr><td>A1</td><td>Day 1, 3, 4 and 7</td><td>2-10 hours (+2), 50-58 hours (±6), 74-82 hours (±6), 146-154 hours (±6)</td></tr>
<tr><td>A2</td><td>Day 1, 3, 4 and 7</td><td>10-18 hours (±2), 58-66 hours (±6), 82-90 hours (±6), 154-162 hours (±6)</td></tr>
<tr><td>B1</td><td>Day 1, 3, 4 and 7</td><td>18-26 hours (±2), 66-74 hours (±6), 90-98 hours (±6), 162-170 hours (-6, +2)</td></tr>
<tr><td>B2</td><td>Day 2, 4, 5 and 6</td><td>24-32 hours (±2), 74-82 hours (±6), 98-106 hours (±6), 122-130 hours (±6)</td></tr>
<tr><td>C1</td><td>Day 2, 4, 5 and 6</td><td>32-40 hours (±2), 82-90 hours (±6), 106-114 hours (±6), 130-138 hours (±6)</td></tr>
<tr><td>C2</td><td>Day 2, 4, 5 and 6</td><td>40-48 hours (±2), 90-98 hours (±6), 114-122 (±6), 138-146 hours (±6)</td></tr>
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FST Timing for 7-13 years old:

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Group	Sensor Wear Day	Timing of YSI™* FST & Start of Challenge (if applicable) from Sensor Insertion T=0
A1	Day 1, 7	2-8 hours (+2), 146-152 hours (±6)
A2	Day 1, 7	20- 26 hours (±2), 164-170 hours (-6, +2)
B1	Day 2, 5	26-32 hours (±2), 116-122 hours (±6)
B2	Day 2, 5	44-50 hours (±2), 98-104 hours (±6)
C1	Day 3, 5	50-56 hours (±6), 116-122 hours (±6)
C2	Day 3, 5	68-74 hours (±6), 98-104 hours (±6)
D1	Day 4, 6	74 -80 hours (±6), 140-146 hours (±6)
D2	Day 4, 6	92-98 hours (±6), 122-128 hours (±6)

FST Timing for 2-6 years old:

Group	Sensor Wear Day	Timing of SMBG FST & Start of Challenge (if applicable) from Sensor Insertion T=0
A1	Day 1, 7	2-6 hours (+2), 148-152 hours (±6)
A2	Day 1, 7	20- 24 hours (±2), 166-170 hours (-6, +2)
B1	Day 2, 5	26-30 hours (±2), 118-122 hours (±6)
B2	Day 2, 5	44-48 hours (±2), 100-104 hours (±6)
C1	Day 3, 5	50-54 hours (±6), 118-122 hours (±6)
C2	Day 3, 5	68-72 hours (±6), 100-104 hours (±6)
D1	Day 4, 6	74 -78 hours (±6), 142-146 hours (±6)
D2	Day 4, 6	92-96 hours (±6), 124-128 hours (±6)

Subjects will be assigned to the following according to their age:

Subjects 14 - 80 years

- Sensor Location (14-17 years) - **Random Assignment**
  - Arm/Arm/Buttock
    - N=4 minimum
  - Buttock/Buttock/Arm
    - N=4 minimum
- Sensor Location (18-80 years) - **Random Assignment**
  - Arm/Arm/Abdomen
    - N=26 minimum
  - Abdomen/Abdomen/Arm
    - N=26 minimum
- FST Schedule
  - Duration of FST and Challenges - **Random Assignment**
    - 4 x 8 hours FST
    - Hypoglycemic or Hyperglycemic challenges will be randomly assigned to each FST. These assignments are recommendations and investigator discretion may be used in selecting which challenge is to be performed for each FST.
      - Two Hyperglycemic Challenges
      - Two Hypoglycemic Challenges
      - Regardless of the order these challenges are performed, a total of 2 hyperglycemic challenges and 2 hypoglycemic challenges should be targeted.
    - A minimum of N=20 subjects will undergo observation

Subjects 7 - 13 years

- Sensor Location - **Random Assignment**

	▪ Arm/Arm/Buttock • N=10 minimum ▪ Buttock/Buttock/Arm • N=10 minimum ○ FST Schedule - **Random Assignment** ▪ 2x 6 hours FST **Subjects 2 - 6 years** ○ Sensor Location ▪ Arm/Arm • N=3 minimum ▪ Buttock/Buttock • N=3 minimum ▪ Arm/Buttock • N=6 minimum ▪ Subjects 2-6 years old may have their parents/guardians choose the area for their sensor placement. ○ FST Schedule - **Random Assignment** ▪ 2 x 4 hours FST SMBG only Based on the random assignment and sensor wear time it will be determined when subjects will be participating in the in-clinic YSI™*/SMBG FSTs.
Sample Size and Investigational Centers	A total of up to 460 previously-diagnosed type 1 and 2 diabetes subjects will be enrolled in order to have 244 subjects complete study. ○ N= 122 subjects 18-80 years old ▪ N= 15 minimum subjects age 18-29 years old ▪ N= 15 minimum subjects age 30-60 years old ▪ N= 15 minimum subjects age 61-80 years old ○ N= 122 subjects 2-17 years old ▪ N= 15 minimum subjects 2-4 years old ▪ N= 15 minimum subjects 5-6 years old

- N= 20 minimum subjects 7-10 years old
- N= 20 minimum subjects 11-13 years old
- N= 24 minimum subjects 14-17 years old

Up to 17 investigational centers in the US will be used during the study.

Subjects will be grouped by age, diabetes classification, body mass index (BMI)/ weight, CGM experience, glycosylated hemoglobin (HbA1c), exercise activity, and compression procedure.

- **Diabetes cohorts based on insulin requirement**
  - 18-80 years
    - Insulin requiring N = minimum 78 subjects
      - N= minimum of 52 type 1 insulin requiring
      - N= minimum of 26 type 2 insulin requiring
    - Non-Insulin requiring N = minimum 12 subjects
  - 14 - 17 years
    - Insulin requiring N = minimum 24 subjects
  - 2 - 13 years
    - Insulin requiring N = minimum 10 subjects

- **Diabetes cohorts based on Centers for Disease Control and Prevention (CDC) classification for 20 years old or younger**

  A description of the following 4 groups will be performed:
  - Underweight subjects (less than (<) 5th percentile): N=minimum of 1 subjects
  - Normal weight subjects (5th percentile to less than (<) 85th percentile): N= minimum of 40 subjects
  - Overweight (85th to less than (<) the 95th percentile): N= minimum of 8
  - Obese subjects (greater than or equal to (≥) the 95th percentile): N=minimum of 1 subjects

- **Diabetes cohorts based on BMI according to WHO criteria [World Health Organization, 2011] for subjects greater than 20 years old:**

  A description of the following 5 groups will be performed:

  - Underweight subjects (BMI less than (<)18.5 kg/m²): N=minimum of 1 subject
  - Normal weight subjects (BMI 18.5 to 24.99 kg/m²): N= minimum of 28 subjects
  - Overweight and obese subjects (BMI 25.00 to 40 kg/m²): N= minimum of 36 subjects
    - Overweight subjects (BMI 25.00 to 29.99 kg/m²)
    - Obese subjects (BMI 30.00 to 39.99 kg/m²)
  - Morbidly obese subjects (BMI greater than or equal to (≥)40 kg/m²): N=minimum of 1 subject

- **Diabetes cohorts based on prior real-time CGM experience (by self report)**
  - CGM naïve: N= minimum of 40 subjects (2-80 years)
  - CGM experienced: N= minimum of 40 subjects (2-80 years)

- **Diabetes cohorts based on HbA1c:**
  - Baseline HbA1c (by certified National Glycohemoglobin Standardization Program, NGSP, method) will be collected:
    - A description of the following 3 groups will be performed: HbA1c less than (<) 7%, HbA1c 7-9%, HbA1c greater than (>) 9%
  - Quartile comparison (lowest to the highest) based on HbA1c

- **Diabetes cohort based on exercise activity:**
  - 18 – 80 years
    - N=minimum of 22 subjects
  - 14 - 17 years
    - N= minimum of 6 subjects

	○ 2 - 13 years ○ N= minimum of 20 subjects ○ Sponsor may instruct site for exercise to be performed in order to obtain low glucose values • **Diabetes cohort based on compression procedure:** ○ 18 – 80 years ○ N=minimum of 22 subjects ○ 14 - 17 years ○ N= minimum of 6 subjects ○ 2 - 13 years ○ N= minimum of 10 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 14 months from investigational center initiation to finalization of all data entry and monitoring procedures. The subject's maximum participation from study start to completion is approximately 90 days (including replacement sensor wear and repeat in clinic procedures if needed).
Inclusion/Exclusion Criteria	**Inclusion Criteria:** 1. Individual is 2 - 80 years of age at time of enrollment 2. A clinical diagnosis of type 1 or 2 diabetes for a minimum of 6 months duration as determined via medical record or source documentation by an individual qualified to make a medical diagnosis 3. Adequate venous access as assessed by investigator or appropriate staff 4. Subjects participating in the high and low glucose challenges must have an insulin carbohydrate ratio(s) and insulin sensitivity ratio. Subjects without ratios may participate under observation only **Exclusion Criteria:** 1. Subject will not tolerate tape adhesive in the area of Guardian™ Sensor (3) placement as assessed by a qualified individual.

	2. Subject has any unresolved adverse skin condition in the area of sensor or device placement (e.g., psoriasis, rash, *Staphylococcus* infection) 3. Subject is actively participating in an investigational study (drug or device) wherein they have received treatment from an investigational study (drug or device) in the last 2 weeks 4. Subject is female and has a positive pregnancy screening test 5. Female of child bearing age and who is sexually active should be excluded if she is not using a form of contraception deemed reliable by investigator 6. Subject is female and plans to become pregnant during the course of the study 7. Subject has had a hypoglycemic seizure within the past 6 months prior to enrollment 8. Subject has had hypoglycemia resulting in loss of consciousness within the past 6 months prior to enrollment. 9. Subject has had an episode of diabetic ketoacidosis (DKA) within the past 6 months prior to enrollment. 10. Subject has a history of a seizure disorder 11. Subject has central nervous system or cardiac disorder resulting in syncope 12. Subject has a history of myocardial infarction, unstable angina, coronary artery bypass surgery, coronary artery stenting, transient ischemic attack (TIA), cerebrovascular accident (CVA), angina, congestive heart failure, ventricular rhythm disturbances or thromboembolic disease 13. Subject has a hematocrit (Hct) lower than the 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) 14. Subject has a history of adrenal insufficiency 15. Subject is a member of the research staff involved with the study.
Study Timeline:	The subject's maximum participation from study start to completion is 90 days (including replacement sensor wear and repeat in clinic procedures). See Section 8.2.2.1 for Subjects 14-80 years Visit Schedule. See Section 9.2.2.1 for Subjects 2-13 years Visit Schedule.

Device Deficiencies:	Subject and investigational center reports of device deficiencies will be collected by subject and/or investigational center staff by calling the 24-Hour Technical Support (TS) for device troubleshooting and device complaints. For additional information, see Section 14.
Starting Rules for Subjects:	The start of the YSI™*/SMBG FST: ○ With challenge can occur if subject's ketone level is less than or equal to (≤) 0.6 mmol/L. For example, should a subject arrive with ketone levels greater than (>) 0.6 mmol/L, per investigator discretion, IV or oral hydration may be provided to subject to bring ketone level less than or equal to (≤) 0.6 mmol/L. Once ketone level is less than or equal to (≤) 0.6 mmol/L, per investigator discretion, subject may start YSI™* FST. ○ With observation can occur if subject's glucose is between 60 mg/dL to 300 mg/dL.
Subject Stopping Rules	• Subject is exhibiting signs and symptoms of DKA (see DKA definition in Section 12.1) • Severe hypoglycemia (see severe hypoglycemia definition Section 12.1) • YSI™* glucose greater than (>) 500 mg/dL regardless of ketone level ○ For subjects 2-6 year olds, SMBG will be used. All applicable rules related to rescue therapy/low glucose guidelines, will be based on SMBG rather than YSI™*. • Ketone greater than or equal (≥) to 3 mmol/L regardless of blood glucose • Persistent ketone level greater than or equal to (≥) 1.5 mmol/L after hydration (see ketone management guidelines Section 10.5.4) • Subject develops nausea, vomiting or abdominal pain • Maximum blood volume drawn: ○ 4 mL/kg (inclusive of all YSI™* FST days) during this study or 400 cc whichever is more for subjects' age 14-80 years old. However, no more than 2 mL/kg of blood volume in a 24-hour period is to be drawn.

	○ 3 mL/kg (inclusive of all YSI™* FST days) during this study for subjects' age 7-13 years old. ○ 50 mL will be maximum blood volume for subjects' age 2-6 years old. However, no more than 1 mL/kg of blood volume in a 24-hour period is to be drawn.
Stopping Rules for Entire Study	During the study, the following steps will be taken for: • DKA during Hypoglycemic and Hyperglycemic Challenges • Severe hypoglycemia with seizures or requiring glucagon during Challenges 1. Site will notify the sponsor within approximately 24 hours of receiving knowledge of the event. 2. Sponsor will notify Food and Drug Administration (FDA) within approximately 72 hours of knowledge of the event. 3. CEC is to review the event within 7 days from the time that the sponsor is notified. 4. CEC will act as DMC in this situation and will provide recommendation to the sponsor on the following: a) If enrollment and study may continue b) If enrollment should be stopped; enrolled subjects are still allowed to continue in study c) If the entire study must be stopped, including subjects who have already received study devices.
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 for a prolonged time period, the in-clinic procedures may be re-scheduled per sponsor recommendation. • If primary sensor dislodges and FST cannot be completed. Subject should replace all sensors and repeat any FSTs not completed.
Statistical Analysis for Endpoints and Hypothesis:	*Primary Endpoint for ZEUS Algorithms* A total of 16 primary endpoints will be independently evaluated in blocks of 16 in the study. Analysis will be done in the blocks of 16 as:

	• Adult (18 – 80 years), abdomen insertion location and 0 Calibration of Zeus algorithm • Adult (18 – 80 years), abdomen insertion location and two Calibrations of Zeus algorithm (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration) • Adult (18 – 80 years), abdomen insertion location and three Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration) • Adult (18 – 80 years), abdomen insertion location and daily Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, 14 hours after second calibration and 24 hours after the previous calibration until end of wear) • Adult (18 – 80 years), arm insertion location and 0 Calibration of Zeus algorithm • Adult (18 – 80 years), arm insertion location and two Calibrations of Zeus algorithm (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration) • Adult (18 – 80 years), arm insertion location and three Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration) • Adult (18 – 80 years), arm insertion location and daily Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, 14 hours after second calibration and 24 hours after the previous calibration until end of wear) • Peds (2 to 17 years), buttock insertion location and 0 Calibration of Zeus algorithm • Peds (2 to 17 years), buttock insertion location and two Calibrations of Zeus algorithm (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration) • Peds (2 to 17 years), buttock insertion location and three Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration) • Peds (2 to 17 years), buttock insertion location and daily Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, 14 hours after second calibration and 24 hours after the previous calibration until end of wear) • Peds (2 to 17 years), arm insertion location and 0 Calibration of Zeus algorithm

- Peds (2 to 17 years), arm insertion location and two Calibrations of Zeus algorithm (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Peds (2 to 17 years), arm insertion location and three Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Peds (2 to 17 years), arm insertion location and daily Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, 14 hours after second calibration and 24 hours after the previous calibration until end of wear)

Guardian™ Sensor (3) accuracy *for ZEUS Algorithms*

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 20% mean agreement rate (±20 mg/dL when SG less than (<) 80 mg/dL), μ, between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated against the null Hypothesis:

  H0: $\mu \leq 75\%$

  H1: $\mu > 75\%$

- Statistical testing

  A generalized estimating equation method model will be used. The one sided 95% lower confidence limit of the mean agreement rate will be tested against the threshold of 75%. For the GEE model, Exchangable (exch) or Auto-regressive (AR1) or Independence (IND) correlation structure will be used, based on quasi-AIC (QIC). Confidence intervals from bias-corrected and accelerated percentile bootstrap approaches will be provided, if applicable. In addition, the confidence intervals from GEE model and bootstrap approaches will be adjusted based on the proposed alpha level at the interim analyses.

  Site effect will be evaluated. If it is not significant (p-value greater than (>) 0.1), site will not be included in the model so as to obtain the adjusted confidence limit.

	Secondary Endpoint for ZEUS Algorithm: Within each block of 16, secondary endpoints (a total of 176) will be evaluated in a fixed sequence of testing for adjustment of multiplicity. The results will be compared to the iCGM Special Control criteria for sensor accuracy (SG limit of 50-400 mg/dL). For each of the endpoints, iCGM measurement refers to the sensor glucose value: ○ % of iCGM measurements that indicate a positive glucose rate of change greater than 1 mg/dL/min when the corresponding true negative glucose rate of change is less than -2 mg/dL/min as determined by the corresponding blood glucose measurements ○ % of iCGM measurements that indicate a negative glucose rate of change less than -1 mg/dL/min when the corresponding true positive glucose rate of change is greater than 2 mg/dL/min as determined by the corresponding blood glucose measurements ○ Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 20% mean agreement rate between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated ○ Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 15% mean agreement rate when SG >180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated ○ Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 40% mean agreement rate when SG >180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated ○ When iCGM values are greater than 180 mg/dL, corresponding blood glucose value read less than 70 mg/dL.

	○ Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 15% mean agreement rate when SG between 70 and 180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated ○ Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 40% mean agreement rate when SG between 70 and 180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated ○ When iCGM values are less than 70 mg/dL, no corresponding blood glucose value shall read above 180 mg/dL. ○ Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±15 mg/dL mean agreement rate when SG less than (<) 70 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated ○ Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±40mg/dL mean agreement rate when SG less than (<) 70 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated Within each block of 16, secondary endpoints (a total of 176) will be evaluated in a fixed sequence of testing for adjustment of multiplicity. The results will be compared to the iCGM Special Control criteria for sensor accuracy (SG limit of 40-400 mg/dL). For each of the endpoints, iCGM measurement refers to the sensor glucose value: • % of iCGM measurements that indicate a positive glucose rate of change greater than 1 mg/dL/min when the corresponding true negative glucose rate of change is less than -2 mg/dL/min as determined by the corresponding blood glucose measurements • % of iCGM measurements that indicate a negative glucose rate of change less than -1 mg/dL/min when the corresponding true positive glucose rate of change is greater than 2 mg/dL/min as determined by the corresponding blood glucose measurements

	• Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 20% mean agreement rate between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated • Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 15% mean agreement rate when SG >180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated • Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 40% mean agreement rate when SG >180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated • When iCGM values are greater than 180 mg/dL, corresponding blood glucose value read less than 70 mg/dL. • Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 15% mean agreement rate when SG between 70 and 180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated • Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 40% mean agreement rate when SG between 70 and 180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated • When iCGM values are less than 70 mg/dL, no corresponding blood glucose value shall read above 180 mg/dL. • Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±15 mg/dL mean agreement rate when SG less than (<) 70 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated • Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±40mg/dL mean agreement rate when SG less than (<) 70 mg/dL between Guardian™ Sensor (3) values

	and YSI™* plasma glucose values during YSI™* FST days will be evaluated *Safety* Descriptive summary will be used to characterize safety events • Skin assessment at Guardian™ Sensor (3) insertion sites • All adverse events *Device Deficiencies* Descriptive device deficiencies will include all reports of Guardian™ Sensor (3) damage, breakage or fracture.

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 typically attached to a transmitter, which 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. The monitor is the data collection/user interface of the system and provides continuous real-time glucose values to the user, as well as the option to set high/low glucose alerts according to the individual patient's needs.

The Medtronic MiniMed™, Inc. (d/b/a "Medtronic Diabetes") family of Continuous Glucose Monitoring Systems (CGMS) measures SQ glucose continuously over various ranges of time. The newest generation Medtronic MiniMed™ SQ Glucose Sensor (Guardian™ Sensor 3) was approved by the United States Food and Drug Administration (FDA) for commercialization as part of the MiniMed™ 670G System in September 2016. The Medtronic MiniMed Glucose Sensor is a glucose sensor designed to work in Medtronic CGM systems to help users manage their diabetes.

Medtronic has developed a new advanced sensor calibration algorithm, called the "Zeus" algorithm, for use with Guardian™ Sensor (3). The "Zeus" algorithm is intended to minimize or eliminate required calibrations, which will reduce user burden. This algorithm will be implemented into a new Transmitter based on the Guardian™ Connect transmitter.

In this study, sensor data from Guardian™ Sensor (3) will be collected in a blinded approach, where commercial Guardian™ Connect Transmitters will be used as a recorder for the purposes of data collection. There will not be any live data communication during the study as no mobile application will be used. At the end of the study, raw sensor data collected by the Guardian™ Connect Transmitters will be processed using the Zeus algorithm and various calibration schemes.

Testing on human subjects is necessary to characterize the accuracy of this sensor algorithm. For purposes of this study, subjects will wear the study devices with Guardian™ Sensor (3). Subjects will manage their diabetes independent of the Guardian™ Sensor (3) values. During YSI™*/SMBG FST, venous blood glucose concentrations or SMBG (subjects 2-6 years only) will be measured periodically; these values will be compared to sensor glucose values (SGVs) in order to determine sensor accuracy.

Accuracy data will be calculated based on comparing calibrated glucose sensor values to a "gold standard" (Yellow Springs Instrument [YSI™*] plasma glucose values) in subjects during YSI™* frequent sample testing (FST). The YSI™* glucose analyzer, Model 2300, has been the recognized standard for the measurement of blood glucose and will be utilized across the investigational centers for the tests.

3.2. Purpose

The purpose of this study is to demonstrate the performance of the Guardian™ Sensor (3) with an advanced algorithm in subjects age 2 – 80 years, for the span of 170 hours (7 days).

4. Objectives and Endpoints

4.1. Objectives

4.1.1. Primary Objective(s)

The primary objective of the study is to demonstrate the accuracy of Guardian™ Sensor (3) when used over a period of 7 days (i.e., 170 hours) with the system in subjects 2-80 years of age.

4.2. Endpoints

4.2.1. Primary Endpoint(s)

4.2.1.1. Primary Endpoint for ZEUS Algorithm

A total of 16 primary endpoints will be independently evaluated in blocks of 16 in the study. Analysis will be done in the blocks of 16 as:

- Adult (18 – 80 years), abdomen insertion location and 0 Calibration of Zeus algorithm
- Adult (18 – 80 years), abdomen insertion location and two Calibrations of Zeus algorithm (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Adult (18 – 80 years), abdomen insertion location and three Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Adult (18 – 80 years), abdomen insertion location and daily Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, 14 hours after second calibration and 24 hours after the previous calibration until end of wear)
- Adult (18 – 80 years), arm insertion location and 0 Calibration of Zeus algorithm

- Adult (18 – 80 years), arm insertion location and two Calibrations of Zeus algorithm (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Adult (18 – 80 years), arm insertion location and three Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Adult (18 – 80 years), arm insertion location and daily Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, 14 hours after second calibration and 24 hours after the previous calibration until end of wear)
- Peds (2 to 17 years), buttock insertion location and 0 Calibration of Zeus algorithm
- Peds (2 to 17 years), buttock insertion location and two Calibrations of Zeus algorithm (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Peds (2 to 17 years), buttock insertion location and three Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Peds (2 to 17 years), buttock insertion location and daily Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, 14 hours after second calibration and 24 hours after the previous calibration until end of wear)
- Peds (2 to 17 years), arm insertion location and 0 Calibration of Zeus algorithm
- Peds (2 to 17 years), arm insertion location and two Calibrations of Zeus algorithm (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Peds (2 to 17 years), arm insertion location and three Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Peds (2 to 17 years), arm insertion location and daily Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, 14 hours after second calibration and 24 hours after the previous calibration until end of wear)

Guardian™ Sensor (3) accuracy *for ZEUS Algorithms*

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 20% mean agreement rate (±20 mg/dL when SG less than (<) 80 mg/dL), μ, between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated against the null Hypothesis:

  H0: $\mu \leq 75\%$

  H1: $\mu > 75\%$

- Statistical testing

A generalized estimating equation method model will be used. The one sided 95% lower confidence limit of the mean agreement rate will be tested against the threshold of 75%. For the GEE model, Exchangable (exch) or Auto-regressive (AR1) or Independence (IND) correlation structure will be used, based on quasi-AIC (QIC). Confidence intervals from bias-corrected and accelerated percentile bootstrap approaches will be provided, if applicable. In addition, the confidence intervals from GEE model and bootstrap approaches will be adjusted based on the proposed alpha level at the interim analyses.

Site effect will be evaluated. If it is not significant (p-value greater than (>) 0.1), site will not be included in the model so as to obtain the adjusted confidence limit.

4.2.2. Secondary Endpoint(s)

4.2.2.1. Secondary Endpoint for ZEUS Algorithm

Within each block of 16, secondary endpoints (a total of 176) will be evaluated in a fixed sequence of testing for adjustment of multiplicity. The results will be compared to the iCGM Special Control criteria for sensor accuracy (SG limit of 50-400 mg/dL). For each of the endpoints, iCGM measurement refers to the sensor glucose value:

- % of iCGM measurements that indicate a positive glucose rate of change greater than 1 mg/dL/min when the corresponding true negative glucose rate of change is less than -2 mg/dL/min as determined by the corresponding blood glucose measurements
- % of iCGM measurements that indicate a negative glucose rate of change less than -1 mg/dL/min when the corresponding true positive glucose rate of change is greater than 2 mg/dL/min as determined by the corresponding blood glucose measurements
- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 20% mean agreement rate between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated
- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 15% mean agreement rate when SG >180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated
- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 40% mean agreement rate when SG >180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

- When iCGM values are greater than 180 mg/dL, corresponding blood glucose value read less than 70 mg/dL.

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 15% mean agreement rate when SG between 70 and 180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

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- When iCGM values are less than 70 mg/dL, no corresponding blood glucose value shall read above 180 mg/dL.

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±15 mg/dL mean agreement rate when SG less than (<) 70 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±40mg/dL mean agreement rate when SG less than (<) 70 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

Within each block of 16, secondary endpoints (a total of 176) will be evaluated in a fixed sequence of testing for adjustment of multiplicity. The results will be compared to the iCGM Special Control criteria for sensor accuracy (SG limit of 40-400 mg/dL). For each of the endpoints, iCGM measurement refers to the sensor glucose value:

- % of iCGM measurements that indicate a positive glucose rate of change greater than 1 mg/dL/min when the corresponding true negative glucose rate of change is less than -2 mg/dL/min as determined by the corresponding blood glucose measurements

- % of iCGM measurements that indicate a negative glucose rate of change less than -1 mg/dL/min when the corresponding true positive glucose rate of change is greater than 2 mg/dL/min as determined by the corresponding blood glucose measurements

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 20% mean agreement rate between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 15% mean agreement rate when SG >180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

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- When iCGM values are less than 70 mg/dL, no corresponding blood glucose value shall read above 180 mg/dL.

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±15 mg/dL mean agreement rate when SG less than (<) 70 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±40mg/dL mean agreement rate when SG less than (<) 70 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

4.2.3. Safety

Descriptive summary will be used to characterize safety events

- Skin assessment at Guardian™ Sensor (3) insertion sites
- All adverse events

4.2.4. Device Deficiencies

Descriptive device deficiencies will include all reports of Guardian™ Sensor (3) damage, breakage or fracture.

5. Study Design

The study is a multi-center, randomly assigned, prospective, single-sample correlational design without controls. Subjects will be randomly assigned to sensor location, FST day, and FST time.

A total of up to 460 previously-diagnosed type 1 and 2 diabetes subjects will be enrolled in order to have 244 subjects complete study.

- N= 122 subjects 18-80 years old
  - N= 15 minimum subjects age 18-29 years old
  - N= 15 minimum subjects age 30-60 years old
  - N= 15 minimum subjects age 61-80 years old
- N= 122 subjects 2-17 years old
  - N= 15 minimum subjects 2-4 years old
  - N= 15 minimum subjects 5-6 years old
  - N= 20 minimum subjects 7-10 years old
  - N= 20 minimum subjects 11-13 years old
  - N= 24 minimum subjects 14-17 years old

The study procedures may be done in a camp/hotel setting. For example, pediatric subjects may be brought together for 1-2 weeks during the week they undergo their FST sessions.

The following are hotel/camp study requirements in order to support the safety of challenges which is equivalent to that provided in the in-clinic setting:

Staffing:

PI, sub- investigator and research support staff must provide the equivalent support to that performed in the in-clinic setting during Frequent Sample Testing. For example, the PI or sub-investigator are required to be present during all challenges. A research coordinator(s) must be on premises 24/7 during the entire hotel/camp stay.

Rescue Therapy:

Rescue therapy outlined in the protocol for hyperglycemia and hypoglycemia are required to be available during the entire hotel/camp stay as defined in the protocol.

- Treatment with Glucagon and ampules of glucose for hypoglycemia are required to be available during the hotel/camp stay
- Treatment with Saline, and IV regular insulin for hyperglycemia are required to be available during the hotel/camp stay.
- Intravenous access is required during challenges for the hotel/camp study as it is for the in-clinic setting during Challenge procedures.

YSI:

- YSI is a portable machine that may be used in any setting – in-clinic or hotel/camp.
- YSI maintenance procedures will still be required during the hotel/camp.

See Section 8.1 for Subjects 14-80 years Study Design

See Section 9.1 for Subjects 2-13 years Study Design

5.1. Duration

The study is anticipated to last approximately 14 months from investigational center initiation to finalization of all data entry and monitoring procedures. The subject's maximum participation from study start to completion is approximately 90 days (including replacement sensor wear and repeat in clinic procedures if needed).

5.2. Rationale

The clinical study is being conducted to demonstrate Guardian™ Sensor (3) performance in patients with type 1 or 2 diabetes during in-clinic and at home testing. The study will demonstrate the use of Guardian™ Sensor (3) with Guardian™ Connect Transmitter when used over a period of 7 days in subjects 2-80 years of age.

6. Product Description

6.1. Investigational Devices

The following 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 following 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 lastest 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 blood glucose 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 intended as 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 blood glucose 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 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 blood glucose level using the Ascensia CONTOUR®NEXT Strips, and this value may be used to calibrate the CGM systems.

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 blood glucose 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. Abbott™*/MediSense Precision Xtra™* Meter

The Abbott™*/Medisense™* Precision Xtra™* meter, referred to as Precision Xtra™* ketone meter, measures both blood glucose (sugar) and blood ß-Ketone. In this study, the meter will be used to collect ß-Ketone data, which will be collected for reporting and review (see Investigator Site Binder for details). This particular meter will be used because it is the only commercially available meter which allows quantification of blood ß-Ketone levels and is preferred patient method of testing over urine testing.

6.2.10. 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.

6.2.11. 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 changes to anticipate for 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 study device used in a research trial. It is expected that all study 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 study device being used in clinical research must be strictly accounted for. This includes keeping records of:

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

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

Table 1 Device Accountability Requirements

Device	Record on Site Received eCRF	Record Disbursement, Returned or Not Returned on Subject Device Disposition eCRF	Subject Return Device to Investigational Center	Record Returned or Not Returned on Site Returned eCRF	Site Return Device to Sponsor at Conclusion of Study
Guardian™ Sensor (3) (MMT-7020)	Yes	Yes	Unused Only, unless required for return for a complaint	Yes	Return unused sensors. Sponsor may ask for used sensors to be returned with complaint
Guardian™ Connect Transmitter* (MMT-7821)	Yes	Yes	Yes	Yes	Yes
GST3C/4C Dock (T8381-003)	Yes	NA	NA	Yes	Yes
CONTOUR®NEXT LINK 2.4 study meter (MMT-1152/1352)	Yes	Yes	No	Yes	Return unused to sponsor

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

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

6.4.1. Receipt and Inventory of Investigational Devices by Investigational Center

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

- Ship To
- Reference Number
- Device Type
- Quantity
- Quantity per package
- Lot number
- Serial number

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

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, all required eCRF and source documentation will be completed. Documentation may include:

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

6.4.4. Return or Disposal of Study Devices

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

Requirements for return of devices by subjects to the investigational center and return of device by the investigational center to the sponsor are listed in Table 1 Device Accountability Requirements. Study devices provided to the investigational center may be returned as subjects complete the study, at the end of study (EOS) or upon sponsor request. The quantity received by the investigational center and the quantity returned to sponsor should be equal. The investigational center will provide details of the disposition of all unreturned study devices in the eCRF.

Other consumable devices (i.e., alcohol wipes, CONTOUR ®NEXT LINK 2.4 study meter supplies, overtape, etc.), accessories (e.g., serter, charger, and tester) shipped in kits, supplies or materials may be returned to the sponsor or retained by investigational center for educational purposes only, or may be disposed of properly by the investigational center staff.

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

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

7. Selection of Subjects

7.1. Study Population

A total of up to 460 previously-diagnosed type 1 and 2 diabetes subjects will be enrolled in order to have 244 subjects complete study.

- N= 122 subjects 18-80 years old
  - N= 15 minimum subjects age 18-29 years old
  - N= 15 minimum subjects age 30-60 years old
  - N= 15 minimum subjects age 61-80 years old
- N= 122 subjects 2-17 years old
  - N= 15 minimum subjects 2-4 years old
  - N= 15 minimum subjects 5-6 years old
  - N= 20 minimum subjects 7-10 years old
  - N= 20 minimum subjects 11-13 years old
  - N= 24 minimum subjects 14-17 years old

Up to 17 investigational centers in the US will be used during the study.

Subjects will be grouped by age, diabetes classification, body mass index (BMI)/ weight, CGM experience, glycosylated hemoglobin (HbA1c), exercise activity, and compression procedure.

- **Diabetes cohorts based on insulin requirement**
  - 18-80 years
    - Insulin requiring N = minimum 78 subjects
      - N= minimum of 52 type 1 insulin requiring
      - N= minimum of 26 type 2 insulin requiring
    - Non-Insulin requiring N = minimum 12 subjects
  - 14 - 17 years
    - Insulin requiring N = minimum 24 subjects
  - 2 - 13 years
    - Insulin requiring N = minimum 10 subjects

- **Diabetes cohorts based on Centers for Disease Control and Prevention (CDC) classification for 20 years old or younger**

  A description of the following 4 groups will be performed:
  - Underweight subjects (less than (<) 5th percentile): N=minimum of 1 subjects
  - Normal weight subjects (5th percentile to less than (<) 85th percentile): N= minimum of 40 subjects
  - Overweight (85th to less than (<) the 95th percentile): N= minimum of 8
  - Obese subjects (greater than or equal to (≥) the 95th percentile): N=minimum of 1 subjects

- **Diabetes cohorts based on BMI according to WHO criteria [World Health Organization, 2011] for subjects greater than 20 years old:**

  A description of the following 5 groups will be performed:
  - Underweight subjects (BMI less than (<)18.5 kg/m²): N=minimum of 1 subject
  - Normal weight subjects (BMI 18.5 to 24.99 kg/m²): N= minimum of 28 subjects
  - Overweight and obese subjects (BMI 25.00 to 40 kg/m²): N= minimum of 36 subjects
    - Overweight subjects (BMI 25.00 to 29.99 kg/m²)
    - Obese subjects (BMI 30.00 to 39.99 kg/m²)
  - Morbidly obese subjects (BMI greater than or equal to (≥)40 kg/m²): N=minimum of 1 subject

- **Diabetes cohorts based on prior real-time CGM experience (by self report)**
  - CGM naïve: N= minimum of 40 subjects (2-80 years)
  - CGM experienced: N= minimum of 40 subjects (2-80 years)

- **Diabetes cohorts based on HbA1c:**
  - Baseline HbA1c (by certified National Glycohemoglobin Standardization Program, NGSP, method) will be collected:
    - A description of the following 3 groups will be performed: HbA1c less than (<) 7%, HbA1c 7-9%, HbA1c greater than (>) 9%
  - Quartile comparison (lowest to the highest) based on HbA1c

- **Diabetes cohort based on exercise activity:**
  - 18 – 80 years
    - N=minimum of 22 subjects
  - 14 - 17 years
    - N= minimum of 6 subjects
  - 2 - 13 years
    - N= minimum of 20 subjects
  - Sponsor may instruct site for exercise to be performed in order to obtain low glucose values
- **Diabetes cohort based on compression procedure:**
  - 18 – 80 years
    - N=minimum of 22 subjects
  - 14 - 17 years
    - N= minimum of 6 subjects
  - 2 - 13 years
    - N= minimum of 10 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 ICF/ Assent form.
A subject will be assigned a unique study subject identification (SID) via the eCRF, which is a 9-digit code (324XXXXXX). The first three numbers refer to the CIP number (324), 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., 324002001 is subject 001 from site 002).

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

7.3. Inclusion Criteria

1. Individual is 2 - 80 years of age at time of enrollment
2. A clinical diagnosis of type 1 or 2 diabetes for a minimum of 6 months duration as determined via medical record or source documentation by an individual qualified to make a medical diagnosis
3. Adequate venous access as assessed by investigator or appropriate staff
4. Subjects participating in the high and low glucose challenges must have an insulin carbohydrate ratio(s) and insulin sensitivity ratio. Subjects without ratios may participate under observation only

7.4. Exclusion Criteria

1. Subject will not tolerate tape adhesive in the area of Guardian™ Sensor (3) placement as assessed by a qualified individual.
2. Subject has any unresolved adverse skin condition in the area of sensor or device placement (e.g., psoriasis, rash, *Staphylococcus* infection)
3. Subject is actively participating in an investigational study (drug or device) wherein they have received treatment from an investigational study (drug or device) in the last 2 weeks
4. Subject is female and has a positive pregnancy screening test
5. Female of child bearing age and who is sexually active should be excluded if she is not using a form of contraception deemed reliable by investigator
6. Subject is female and plans to become pregnant during the course of the study
7. Subject has had a hypoglycemic seizure within the past 6 months prior to enrollment
8. Subject has had hypoglycemia resulting in loss of consciousness within the past 6 months prior to enrollment.
9. Subject has had an episode of diabetic ketoacidosis (DKA) within the past 6 months prior to enrollment.
10. Subject has a history of a seizure disorder
11. Subject has central nervous system or cardiac disorder resulting in syncope
12. Subject has a history of myocardial infarction, unstable angina, coronary artery bypass surgery, coronary artery stenting, transient ischemic attack (TIA), cerebrovascular accident (CVA), angina, congestive heart failure, ventricular rhythm disturbances or thromboembolic disease
13. Subject has a hematocrit (Hct) lower than the 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)
14. Subject has a history of adrenal insufficiency
15. Subject is a member of the research staff involved with the study.

7.5. Subject Consent

Informed Consent/Assent will be obtained in accordance with the Code of Federal Regulations (CFR) Title 21, Part 50. Prior to entry into the study the California Experimental Subject's Bill of Rights (if applicable), the (Institutional Review Board) IRB and Medtronic-approved ICF/Assent form, and the Health Insurance Portability and Accountability (HIPAA) Authorization Form will be given to each subject and legally authorized representative (if applicable) to complete. Subjects and legally authorized representative will be offered ample opportunity to review these documents before signing.

The Investigator or designee will explain the purpose and duration of the study, requirements of the subject and legally authorized representative during the study, as well as the potential risks involved with participation in this study. Every attempt will be made to answer subject's and legally authorized representative's questions during the informed consent/assent process. The consenting process must be documented in the subject's source files. The subject will receive copies of the fully executed documents. A subject's participation in study procedures cannot start before the consent process has been properly executed.

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

If the ICF/Assent form is amended during the course of the study, the IRB shall determine if active subjects and legally authorized representative must be re-consented at their next visit and whether subjects who have completed the study at the time of the amendment do not need to repeat the informed consent/assent process.

Subjects and legally authorized representative will be informed that authorities from the investigational center, Medtronic, and specific agencies, such as the FDA and 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/Assent violations to the sponsor:

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

7.6. Treatment Assignment

Investigational centers will receive random assignment from Medtronic.

FST Timing for 14-80 years old:

Group	Sensor Wear Day	Timing of YSI™* FST & Start of Challenge (if applicable) from Sensor Insertion T=0
A1	Day 1, 3, 4 and 7	2-10 hours (+2), 50-58 hours (±6), 74-82 hours (±6), 146-154 hours (±6)
A2	Day 1, 3, 4 and 7	10-18 hours (±2), 58-66 hours (±6), 82-90 hours (±6), 154-162 hours (±6)
B1	Day 1, 3, 4 and 7	18-26 hours (±2), 66-74 hours (±6), 90-98 hours (±6), 162-170 hours (-6, +2)
B2	Day 2, 4, 5 and 6	24-32 hours (±2), 74-82 hours (±6), 98-106 hours (±6), 122-130 hours (±6)
C1	Day 2, 4, 5 and 6	32-40 hours (±2), 82-90 hours (±6), 106-114 hours (±6), 130-138 hours (±6)
C2	Day 2, 4, 5 and 6	40-48 hours (±2), 90-98 hours (±6), 114-122 (±6), 138-146 hours (±6)

FST Timing for 7-13 years old:

Group	Sensor Wear Day	Timing of YSI™* FST & Start of Challenge (if applicable) from Sensor Insertion T=0
A1	Day 1, 7	2-8 hours (+2), 146-152 hours (±6)
A2	Day 1, 7	20- 26 hours (±2), 164-170 hours (-6, +2)
B1	Day 2, 5	26-32 hours (±2), 116-122 hours (±6)
B2	Day 2, 5	44-50 hours (±2), 98-104 hours (±6)
C1	Day 3, 5	50-56 hours (±6), 116-122 hours (±6)
C2	Day 3, 5	68-74 hours (±6), 98-104 hours (±6)
D1	Day 4, 6	74 -80 hours (±6), 140-146 hours (±6)
D2	Day 4, 6	92-98 hours (±6), 122-128 hours (±6)

FST Timing for 2-6 years old:

Group	Sensor Wear Day	Timing of SMBG FST & Start of Challenge (if applicable) from Sensor Insertion T=0
A1	Day 1, 7	2-6 hours (+2), 148-152 hours (±6)
A2	Day 1, 7	20- 24 hours (±2), 166-170 hours (-6, +2)
B1	Day 2, 5	26-30 hours (±2), 118-122 hours (±6)
B2	Day 2, 5	44-48 hours (±2), 100-104 hours (±6)
C1	Day 3, 5	50-54 hours (±6), 118-122 hours (±6)
C2	Day 3, 5	68-72 hours (±6), 100-104 hours (±6)
D1	Day 4, 6	74 -78 hours (±6), 142-146 hours (±6)
D2	Day 4, 6	92-96 hours (±6), 124-128 hours (±6)

Subjects will be assigned to the following according to their age:

Subjects 14 - 80 years

- Sensor Location (14-17 years) - **Random Assignment**
  - Arm/Arm/Buttock
    - N=4 minimum
  - Buttock/Buttock/Arm
    - N=4 minimum
- Sensor Location (18-80 years) - **Random Assignment**
  - Arm/Arm/Abdomen
    - N=26 minimum
  - Abdomen/Abdomen/Arm

- N=26 minimum

- FST Schedule
  - Duration of FST and Challenges - **Random Assignment**
    - 4 x 8 hours FST
    - Hypoglycemic or Hyperglycemic challenges will be randomly assigned to each FST. These assignments are recommendations and investigator discretion may be used in selecting which challenge is to be performed for each FST.
      - Two Hyperglycemic Challenges
      - Two Hypoglycemic Challenges
      - Regardless of the order these challenges are performed, a total of 2 hyperglycemic challenges and 2 hypoglycemic challenges should be targeted.
    - A minimum of N=20 subjects will undergo observation

Subjects 7 - 13 years

- Sensor Location - **Random Assignment**
  - Arm/Arm/Buttock
    - N=10 minimum
  - Buttock/Buttock/Arm
    - N=10 minimum
- FST Schedule - **Random Assignment**
  - 2x 6 hours FST

Subjects 2 - 6 years

- Sensor Location
  - Arm/Arm
    - N=3 minimum
  - Buttock/Buttock
    - N=3 minimum
  - Arm/Buttock
    - N=6 minimum
  - Subjects 2-6 years old may have their parents/guardians choose the area for their sensor placement.

- FST Schedule - **Random Assignment**
  - 2 x 4 hours FST

    SMBG only

Once subject is assigned to the study group (if applicable), subjects will stay in that randomly assigned group during the study.

8. Subjects 14- 80 Years Study Design and Study Procedures

This section is presented as below:

- **Section 8.1:** Study Design
- **Section 8.2:** Study Procedures (Subjects 14-80 years)

8.1. Study Design

The study is a multi-center, randomly assigned, prospective, single-sample, correlational design without controls. Subjects will be randomly assigned to sensor location, FST day, and FST time.

Subjects will wear Guardian™ Sensor (3)s in the following configurations outlined in Table 2 or Table 3:

Table 2. Age 18-80 years, Sensor Wear Locations

Sensor	Guardian™ Sensor (3)		
Location*	Arm	Arm	Abdomen
Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter
Pairing	Function as Glucose Recorder	Function as Glucose Recorder	Function as Glucose Recorder
OR			
Sensor	Guardian™ Sensor (3)		
Location*	Abdomen	Abdomen	Arm
Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter
Pairing	Function as Glucose Recorder	Function as Glucose Recorder	Function as Glucose Recorder

*Sensors worn in the same insertion site location may be inserted on same side or opposite sides.

Table 3. Age 14-17 years, Sensor Wear Location

Sensor	Guardian™ Sensor (3)		
Location*	Arm	Arm	Buttock
Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter
Pairing	Function as Glucose Recorder	Function as Glucose Recorder	Function as Glucose Recorder
OR			
Sensor	Guardian™ Sensor (3)		
Location*	Buttock	Buttock	Arm
Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter
Pairing	Function as Glucose Recorder	Function as Glucose Recorder	Function as Glucose Recorder

*Sensors worn in the same insertion site location may be inserted on same side or opposite sides. Sensors may be inserted with the assistance of a caretaker.

Sensor wear location will be randomly assigned.

Subjects will wear the devices up to 7-day training period, 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.

During the study period, each subject will undergo four YSI™* FSTs.

During the YSI™* FST, intravenous (IV) blood samples will be drawn every 5-15 minutes and analyzed using the YSI™*.

The YSI™* FST will be approximately 8 hours during the in-clinic visit. For details on maximum amount of blood drawn refer to Synopsis and Subject Stopping Rules (section 10.10.1).

FST Timing for 14-80 years old:

Group	Sensor Wear Day	Timing of YSI™* FST & Start of Challenge (if applicable) from Sensor Insertion T=0
A1	Day 1, 3, 4 and 7	2-10 hours (+2), 50-58 hours (±6), 74-82 hours (±6), 146-154 hours (±6)
A2	Day 1, 3, 4 and 7	10-18 hours (±2), 58-66 hours (±6), 82-90 hours (±6), 154-162 hours (±6)
B1	Day 1, 3, 4 and 7	18-26 hours (±2), 66-74 hours (±6), 90-98 hours (±6), 162-170 hours (-6, +2)
B2	Day 2, 4, 5 and 6	24-32 hours (±2), 74-82 hours (±6), 98-106 hours (±6), 122-130 hours (±6)
C1	Day 2, 4, 5 and 6	32-40 hours (±2), 82-90 hours (±6), 106-114 hours (±6), 130-138 hours (±6)
C2	Day 2, 4, 5 and 6	40-48 hours (±2), 90-98 hours (±6), 114-122 (±6), 138-146 hours (±6)

Subjects will be assigned to the following sensor location and FST schedule:

Subjects **14 - 80 years**

- Sensor Location (14-17 years) - **Random Assignment**
  - Arm/Arm/Buttock
    - N=4 minimum
  - Buttock/Buttock/Arm
    - N=4 minimum
- Sensor Location (18-80 years) - **Random Assignment**
  - Arm/Arm/Abdomen
    - N=26 minimum
  - Abdomen/Abdomen/Arm
    - N=26 minimum
- FST Schedule
  - Duration of FST and Challenges - **Random Assignment**
    - 4 x 8 hours FST
    - Hypoglycemic or Hyperglycemic challenges will be randomly assigned to each FST. These assignments are recommendations and investigator discretion may be used in selecting which challenge is to be performed for each FST.
      - Two Hyperglycemic Challenges
      - Two Hypoglycemic Challenges
      - Regardless of the order these challenges are performed, a total of 2 hyperglycemic challenges and 2 hypoglycemic challenges should be targeted.
    - A minimum of N=20 subjects will undergo observation

Subjects and/or Sites are to call the 24-Hour Technical Support (TS) for device troubleshooting and device complaints (See Section 14)

Hypoglycemic and Hyperglycemic Challenges

During the YSI™* FST, subjects with a known insulin sensitivity ratio and insulin carbohydrate ratio will be randomly assigned to undergo hypoglycemic and hyperglycemic challenges (see Hypoglycemic and Hyperglycemic Challenge Guidelines).

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.

8.2. Study Procedures (Subjects 14-80 years)

8.2.1. Study Timeline

The subject's maximum participation from study start to completion is 90 days (including replacement sensor wear and repeat in clinic procedures).

8.2.2. Schedule of Events

8.2.2.1. Visit Schedule

Each subject's participation will include the following visits . The intent is for subjects to wear the study Guardian™ Sensor (3)s and devices and perform 4 YSI™* FSTs.

One rescheduled visit can occur if Guardian™ Sensor (3) primary sensors dislodges and new Guardian™ Sensor (3)s must be re-inserted (See Replacement Sensors Section 10.2 and 10.3).

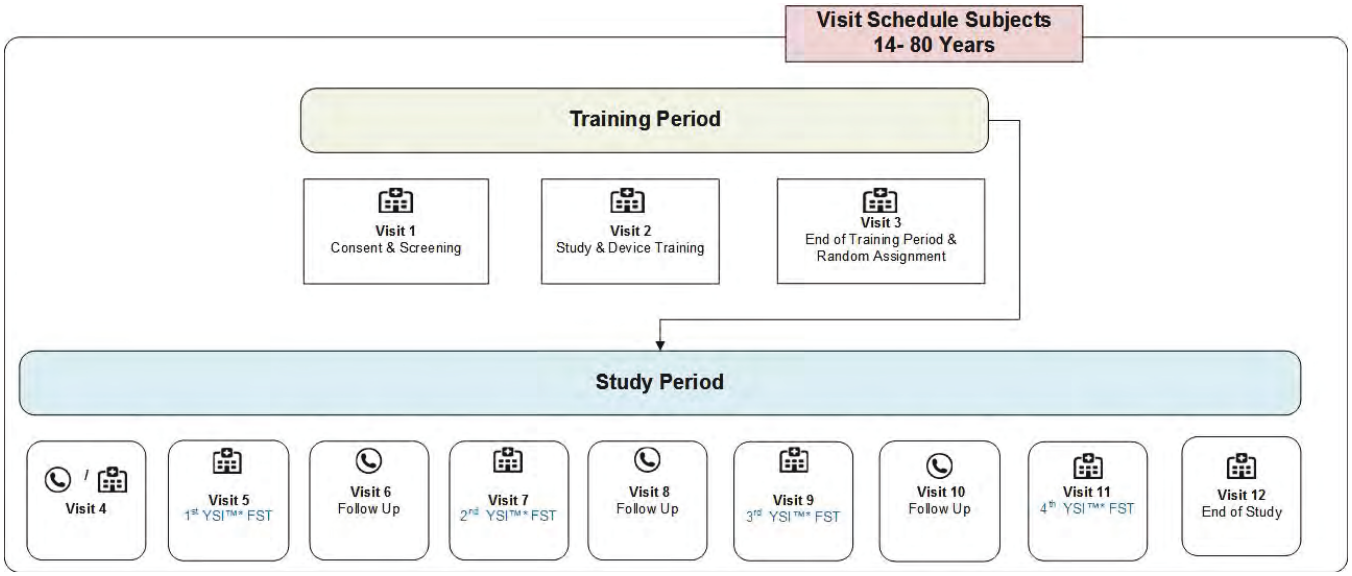
Screening and Training Period: To be completed in 30 days (Visit 1 to Visit 3)

- 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).
- Visit 3: End of Training Period and Random Assignment - Investigational center Visit

Start of Study Period: To be completed in 60 days from Visit 4 to Visit 12; Additional 15 days for sensor replacements (e.g. 75 days)

- Visit 4: Phone Visit or Optional Office Visit
  - **Group A1**- May be combined with Visit 5 (e.g., if sensor insertion for Day 1 is done at Visit 5)
  - **Group A2,B1, B2, C1 and C2-**Investigational center must confirm that the Guardian™ Sensor (3) insertion was performed at the appropriate insertion time, insertion location, and SMBG reminder.
- Visit 5: YSI™* 1st FST
- Visit 6: Follow Up Phone Call
- Visit 7: YSI™* 2nd FST
- Visit 8: Follow Up Phone Call
- Visit 9: YSI™* 3rd FST
- Visit 10: Follow Up Phone Call
- Visit 11: YSI™* 4th FST
- Visit 12: End of Study Visit
  - Subject has worn sensors for T= 176-188 hours.
  - Visit 11 and Visit 12 may be combined (e.g., FST occurs on day 7 and end of the sensor wear)

Figure 3. Visit Schedule Subjects 14-80 years



8.2.2.2. Visit 1: Consent and Screening

Overview General

Investigational center staff will:

- Obtain California Experimental Subject's Bill of Rights (if applicable), Informed Consent Form (ICF) /Assent form, 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
  - Height and Weight

    Note: BMI will be calculated automatically in the study database, based on height and weight measurements entered.
  - Concomitant medications (Screening Only)
  - Date of diabetes diagnosis
  - Insulin carbohydrate ratio and insulin sensitivity for subject's insulin requiring, if applicable
- 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 needs to be done.
    - HbA1c (not an eligibility criteria)
      - Send to Central Laboratory
- **Note:** For all out of range lab results, a single re-test is permitted
- Per Investigator's discretion, subjects may participate in the exercise cohort. Exercise cohort subjects will be asked to exercise for a minimum of 30 minutes a day during the hyperglycemic challenge YSI™* FSTs.

- Enter electronic Case Report Forms (eCRF)s into the study database 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/Assent form, 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.

8.2.2.3. Visit 2: Study and Device Training

Visit 2 can be done the same day as Visit 1 as long as eligibility is confirmed, including having an eligible Hct value.

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 meter need to be synchronized with a 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 a 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 meter (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 8.2.2.3.1 for Procedures Including YSI™* FST Timing and SMBG Requirements

Overview general study procedures

Investigational center staff will:

- Confirm eligibility
- Synchronize time on Guardian™ Connect Transmitters and CONTOUR®NEXT LINK 2.4 study meter using 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
- Confirm Guardian™ Sensor (3) sensor locations according to subject's age (see Sensor Wear Location Table)
- Enter eCRFs into the study database as appropriate
- Schedule the next visit date and time

Overview study devices and supplies

Investigational center staff will disburse the following to the subject:

- 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 device accountability section (see Section 6.4) on the appropriate eCRF.

Overview training and instructions

Investigational center staff will:

- Train each subject on Guardian™ Sensor (3) insertions, taping and removal, study devices, and study procedures
- 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 blood glucose
    - 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 Guardian™ Sensor (3) calibrations
- 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 Guardian™ Sensor (3)s in the sensor locations according to their age (Investigational center staff may choose from either combination of sensor wear location based on tables below):

Age 18-80 years, Sensor Wear Locations

Sensor	Guardian™ Sensor (3)		
Location*	Arm	Arm	Abdomen
Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter
Pairing	Function as Glucose Recorder	Function as Glucose Recorder	Function as Glucose Recorder
OR			
Sensor	Guardian™ Sensor (3)		
Location*	Abdomen	Abdomen	Arm
Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter
Pairing	Function as Glucose Recorder	Function as Glucose Recorder	Function as Glucose Recorder

*Sensors worn in the same insertion site location may be inserted on same side or opposite sides.

Age 14-17 years, Sensor Wear Location

Sensor	Guardian™ Sensor (3)		
Location*	Arm	Arm	Buttock
Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter
Pairing	Function as Glucose Recorder	Function as Glucose Recorder	Function as Glucose Recorder
OR			
Sensor	Guardian™ Sensor (3)		
Location*	Buttock	Buttock	Arm
Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter
Pairing	Function as Glucose Recorder	Function as Glucose Recorder	Function as Glucose Recorder

*Sensors worn in the same insertion site location may be inserted on same side or opposite sides. Sensors may be inserted with the assistance of a caretaker.

- 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, 10 hours, and 24 hours 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 remove the Guardian™ Sensor (3)s (at end of training period or at investigational center) after 7 days.
- 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 14 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 12 and 14 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 Guardian™ Sensor (3) 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.

Guardian™ Sensor (3) wear duration during training period:

All subjects should spend time bending and twisting even if they don't undergo aerobic exercise. Subjects will be told to remove the Guardian™ Sensor (3)s (at home or at the investigational center) after 7 days.

8.2.2.3.1. 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

- One SMBG should be taken approximately at the same time of the day of insertion (e.g., 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
- Time = 0 hour
    - Guardian™ Sensor (3) insertions will be performed
    - The 0 hour represents the time after sensors have been connected to the last of the Guardian™ Connect Transmitter(s)
- Time = 2 hours
    - YSI™* FST period begins.
    - T = 2 hours after the Guardian™ Sensor (3)s have been connected to the Guardian™ Connect Transmitter(s).
- Time = 10 hours
    - T = 10 hours after the Guardian™ Sensor (3)s have been connected to the Guardian™ Connect Transmitter(s).
- Time = 24 hours
    - T = 24 hours after the Guardian™ Sensor (3)s have been connected to the Guardian™ Connect Transmitter(s).
    - Approximately 4 fingerstick glucose readings (SMBG) per day will be requested with target of 7 fingerstick glucose readings (with fingersticks at 2 hours, 10 hours, and 24 hours after the Guardian™ Sensor (3) have been connected to the Guardian™ Connect Transmitter(s)).
- 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.
- At the end of FST take one fingerstick glucose reading.

8.2.2.4. Visit 3: End of Training Period and Random Assignment -Investigational Center Visit

Overview general study procedures
Investigational center staff will:

- Instruct subject to self-remove the Guardian™ Sensor (3)s that he/she is still wearing at this visit
- Perform a Skin Assessment on the area of each of the Guardian™ Sensor (3) insertion sites and document in subject source and complete the Skin Assessment eCRFs
- Upload study devices via:
    - CareLink™ Personal For Clinical Research software (CONTOUR®NEXT LINK 2.4 study meter)
    - GST Download Utility Software (Guardian™ Connect Transmitter) following instructions provided
- Determine if additional training is needed (e.g., if the subject is following finger-stick monitoring requirements). If additional training is required, subjects will be retrained using training materials supplied during training visit and research staff may focus on specific areas of opportunity for improvement (Visit 2).
- Randomly assign eligible subjects
- Enter eCRFs into the study database 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)
- Schedule the next visit date and time (first YSI™* FST)
- The subject will be instructed to insert Guardian™ Sensor (3)s. Note that the subject will use the same insertion device and 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 Accountability Requirements)

This study will involve random assignment and 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 assignment

FST Timing for 14-80 years old:

Group	Sensor Wear Day	Timing of YSI™* FST & Start of Challenge (if applicable) from Sensor Insertion T=0
A1	Day 1, 3, 4 and 7	2-10 hours (+2), 50-58 hours (±6), 74-82 hours (±6), 146-154 hours (±6)
A2	Day 1, 3, 4 and 7	10-18 hours (±2), 58-66 hours (±6), 82-90 hours (±6), 154-162 hours (±6)
B1	Day 1, 3, 4 and 7	18-26 hours (±2), 66-74 hours (±6), 90-98 hours (±6), 162-170 hours (-6, +2)
B2	Day 2, 4, 5 and 6	24-32 hours (±2), 74-82 hours (±6), 98-106 hours (±6), 122-130 hours (±6)
C1	Day 2, 4, 5 and 6	32-40 hours (±2), 82-90 hours (±6), 106-114 hours (±6), 130-138 hours (±6)
C2	Day 2, 4, 5 and 6	40-48 hours (±2), 90-98 hours (±6), 114-122 (±6), 138-146 hours (±6)

Subjects will be randomly assigned to the following

Subjects 14 - 80 years

- Sensor Location (14-17 years) - **Random Assignment**
  - Arm/Arm/Buttock
    - N=4 minimum
  - Buttock/Buttock/Arm
    - N=4 minimum
- Sensor Location (18-80 years) - **Random Assignment**
  - Arm/Arm/Abdomen
    - N=26 minimum
  - Abdomen/Abdomen/Arm

- N=26 minimum

- FST Schedule
  - Duration of FST and Challenges - **Random Assignment**
    - 4 x 8 hours FST
    - Hypoglycemic or Hyperglycemic challenges will be randomly assigned to each FST. These assignments are recommendations and investigator discretion may be used in selecting which challenge is to be performed for each FST.
      - Two Hyperglycemic Challenges
      - Two Hypoglycemic Challenges
      - Regardless of the order these challenges are performed, a total of 2 hyperglycemic challenges and 2 hypoglycemic challenges should be targeted.
    - A minimum of N=20 subjects will undergo observation

The YSI™* FST visits should be scheduled at this visit by the investigational center staff. The visits will be scheduled so that YSI™* FST timing and fingerstick glucose reading requirements are conducted as displayed in 8.2.2.3.

The study coordinator will enter all necessary device return information on the appropriate eCRF and any additional subject visits (unscheduled) on the appropriate eCRF.

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.

8.2.2.5. Visit 4: Phone Call or Optional Office Visit

The purpose of the visit 4 (phone/clinic visit) is to verify that the Guardian™ Sensor (3) insertion was performed at the appropriate insertion time, insertion location, and SMBG reminder.

For Group A1 subjects: this visit may be combined with Visit 5

For Group A2, B1, B2, C1 and C2 subjects: During the phone call or at the investigational center, the investigational center staff will confirm subject has inserted, connected, and taped the Guardian™ Sensor

(3)s at the appropriate time and sensor location. Once the study period Guardian™ Sensor (3)s are inserted, the subject should follow the YSI™* FST SMBG requirements (Section 8.2.2.3.1).

In addition, subjects should be reminded to bring medication, syringes, insulin, and infusion sets that might be needed for their personal pumps during the YSI™* FST visit.

8.2.2.6. Visit 5, 7, 9, and 11: YSI™* FSTs

The YSI™* FST is a 8 hour frequent blood glucose sampling session using IV blood samples and a laboratory blood glucose analyzer, YSI™*. The investigational center staff will set up the YSI™*. Meals will be provided to the subjects.

Additionally, on Visit 11 reminder that subject should keep the sensor in for at least 176 hours.

8.2.2.6.1. At Home, Prior to Arrival at the Clinic for the Challenges

Subjects who are going to undergo hyperglycemic or hypoglycemic challenges will be recommended to take their basal and correction insulin the night before leading up to YSI™* FST visit as per investigator discretion.

Subjects may be instructed by investigator to fast prior to YSI™* FST (e.g., in preparation for hypoglycemic challenge) however insulin management and SMBG testing should be adjusted by investigator to account for fasting and supplemental carbohydrates given as needed. For example, correction targets for glucose may be higher at 150 mg/dL to avoid hypoglycemia, or basal insulin lowered to avoid hypoglycemia.

Subjects who are going to undergo hyperglycemic or hypoglycemic challenges will be recommended to take all other medications at their usual times both prior to arrival at clinic and during the YSI™* FST as per investigator discretion. Subjects will be recommended to bring all medications they are taking with them to the clinic, even if they aren't scheduled to take that medication that day.

Subjects may eat unlimited protein prior to coming in to the clinic if they are hungry. No bolus insulin dose is required for protein intake.

8.2.2.6.2. Upon Arrival to the Clinic

Upon arrival to the clinic, subjects would be safe to undergo observation if glucose is between 60 mg/dL to 300 mg/dL.

For subjects who will undergo challenges, ketones are in the range below:

- The start of the YSI™* FST with challenge can occur if subject's ketone level is less than or equal to (≤) 0.6 mmol/L.

  For example, should a subject arrive with ketone levels greater than (>) 0.6 mmol/L, per investigator discretion, IV or oral hydration may be provided to subject to bring ketone level less than or equal to (≤) 0.6 mmol/L.

  Once ketone level is less than or equal to (≤) 0.6 mmol/L, per investigator discretion, subject may start YSI™* FST.

- If subject feels ill, then subjects should not fast or delay insulin, but should eat and take insulin as per their usual routine and should not undergo hypo or hyperglycemic challenges that day. They may undergo observation only if the investigator feels it is appropriate.

8.2.2.6.3. In-Clinic Procedures

Overview general study procedures

Investigational center staff will:

- Assess the last time that subject gave short/rapid acting insulin. Rapid acting insulin should only be given by investigator in clinic at least 3 hours from the last dose taken by subject.
- Set up the YSI™* instruments (see Investigator Site Binder for details)
- Perform applicable QC testing (CONTOUR®NEXT LINK 2.4 study meter and Precision Xtra™* ketone meter)
- Synchronize YSI™* devices at the investigational center with the designated study clock
- Verify that Guardian™ Sensor (3) insertion was performed at the appropriate insertion time and, insertion location, and SMBG reminder.
- Conduct ketone testing upon subject arrival, when YSI™* blood glucose is above 300 mg/dL, and prior to discharge
- Conduct SMBG testing upon subject arrival
- Refer to Section 8.2.2.3.1 for instructions on Procedures Including YSI™* FST Timing and SMBG Requirements
- Conduct YSI™* FST procedures
- Conduct the hypoglycemic or hyperglycemic challenge for subjects with known insulin sensitivity ratio and insulin carbohydrate ratio.
- 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 (**Visit 11 only**)
- Subjects will continue to wear Guardian™ Sensor (3)s past the end of this visit
- Review requirements of next study visit (phone visit) with subjects
- Review the next visit date and time for YSI™* FST
- Enter eCRFs into the study database as appropriate
- Subjects should be reminded to bring extra infusion sets for their personal pump to next YSI™* FST in case they are asked to change them due to occlusion or suspicion of occlusion.
- Remind subject to bring medication, syringes, insulin, infusion sets that might be needed during the YSI™* FST visit.
- Remind subjects on Guardian™ Sensor (3)s return (see Table 1 Device Accountability Requirements)
- Record all adhesives used on appropriate eCRF

Overview study devices and supplies

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

- Guardian™ Sensor (3)(s)
- 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
- Will follow the Discharge Criteria Guidelines
- Fingerstick will be performed at home as stated in 8.2.2.3.1.

Hydration:

- In order to avoid ketosis, subjects will be encouraged to ingest unlimited sugar free fluids to maintain hydration.

Meals/Medication:

- The Hypoglycemic and Hyperglycemic Challenge Guidelines has guidelines for meal schedule.
- Should a subject want to eat a meal for any reason and no longer participate in the challenge, the subject may stop the challenge and eat. The investigational center will remind the subject of the last dose and time they took insulin, as subject may want to adjust their insulin to lower the amount. The subject will administer what they normally would take for the meal and for insulin correction if indicated (with their prior dose of insulin in mind) as they normally do at home.
- Unlimited protein may be given at any point during the YSI™* FST if subject is hungry and glucose is above 75 mg/dL.

Insulin Administration for Challenges:

- Insulin will only be delivered SQ unless subject is exhibiting signs and symptoms of DKA.
- Insulin which is given SQ during the challenges will be with a rapid analog (Lispro/Humalog, Aspart/Novo; or Glulisine/Apidra).
- The frequency at which insulin SQ may be administered should be at least 3 hours after the last SQ insulin dose whether the last insulin dose was given at home or in the clinic.

PROCEDURE GUIDELINES FOR SUBJECTS UNDERGOING OBSERVATION ONLY

Per investigator discretion Type 1 or Type 2 subjects who do not have an insulin to carb ratio and insulin sensitivity factor at Visit 1 should not undergo hypoglycemic or hyperglycemic challenges but may undergo observation.

Upon arrival to the clinic, subjects would be safe to undergo observation if glucose is between 60 mg/dL to 300 mg/dL.

These subjects should eat and take their insulin at home as per their usual diabetes management prior to coming to clinic.

These subjects should also take any other medications at their usual times both in 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.

During the in-clinic observation they should continue to eat as they would at home using their usual BG targets.

Subjects may exercise during observation period if their glucose is between 100-300 mg/dL.

Ketones may be checked per investigator discretion. If subjects develop ketones, they should be managed as per the study ketone protocol (Section 10.5.4).

PROCEDURE GUIDELINES FOR SUBJECTS UNDERGOING HYPOGLYCEMIC AND HYPERGLYCEMIC CHALLENGES

Subject Criteria

- Only subjects with a known insulin sensitivity ratio and insulin carbohydrate ratio (Type 1 or Type 2 subjects) may participate in the hypoglycemic/hyperglycemic challenges.
    - These ratios may be developed for use in study by qualified investigator
- Subjects without a known insulin sensitivity ratio and insulin carbohydrate ratio (Type 1 or Type 2 subjects) will not participate in the hypoglycemic/hyperglycemic challenges, but will participate in the YSI™* FST with observation only

HYPOGLYCEMIC CHALLENGE:

For details, please refer to the Hypoglycemic Challenge Guidelines.

HYPERGLYCEMIC CHALLENGE:

For details, please refer to the Hyperglycemic Challenge Guidelines

These are guidelines only and investigator discretion may be used.

Exercise Cohort:

- Subjects in exercise cohort will be asked to exercise for at least 30 minutes during YSI™* FST

- Only subjects who have been previously established for participation in Exercise Cohort during Visit 1 can participate in the Exercise Cohort activities during YSI™* FST.
- A subject who qualified at Visit 1 for participation in Exercise cohort is expected to exercise during hyperglycemic challenge at YSI™* FST days.

- Exercise will take place at the Investigator's discretion during the YSI™* FST visit. Subjects may exercise during the observation period based on Investigator's discretion.
- See Hyperglycemic Challenge Guidelines for exercise guidelines. Exercises will not occur during the Hypoglycemic challenges.
- Procedures:
  - Exercise will consist of treadmill or stationary bicycle. Others forms of exercise may be allowed with sponsor permission.
  - Subjects who normally exercise more than 30 minutes at home will be allowed to exercise longer than 30 minutes during the study as long as the subject does not become hypoglycemic.
  - Exercise will be terminated if subjects develop chest pain.
  - Exercise is not being performed to induce hypoglycemia but rather to collect data on the Guardian™ Sensor (3) performance under stress conditions.

Compression procedure:

Subjects will be asked to lay on their sensors for at least one hour for each YSI™* FST. Time, duration, and activity will be collected based on sensor location on an eCRF for subjects 18-80 years old (See Table 4) and subjects 14-17 years old (See Table 5):

Table 4. Age 18-80 years, Compression Procedure Based on Sensor Wear Location

Sensor	Guardian™ Sensor (3)		
Location	Arm	Arm	Abdomen
Compression Procedure	Subject will be instructed to lay on the arm/ lean on a chair where sensors are inserted.		
OR			
Sensor	Guardian™ Sensor (3)		
Location	Abdomen	Abdomen	Arm
Compression Procedure	Subject will be instructed to lay on the abdomen where sensors are inserted.		

Table 5. Age 14-17 years, Compression Procedure Based on Sensor Wear Location

Sensor	Guardian™ Sensor (3)		
Location	Arm	Arm	Buttock
Compression Procedure	Subject will be instructed to lay on the arm/ lean on a chair where sensors are inserted.		
OR			
Sensor	Guardian™ Sensor (3)		
Location	Buttock	Buttock	Arm
Compression Procedure	Subject will be instructed to lay on their buttocks where sensors are inserted.		

8.2.2.7. Visit 6, 8, and 10: 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 blood glucose reading, ketone testing (as applicable), and assessing for AE) to determine how the subject has been doing. In addition, subjects should be reminded to bring medication, syringes, insulin, and infusion sets that might be needed for their personal pumps during the YSI™* FST visit. If subject is unable to be reached, then this should be documented and at least one second attempt to reach subject be performed.

8.2.2.8. Visit 12: End of Study

- Visit 11 and Visit 12 may be combined. (e.g., FST occurs on day 7 and end of the sensor wear).
- 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 Guardian™ Sensor (3)(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 Transmitter) following instructions provided
- Perform a Skin assessment on the area of each of the Guardian™ Sensor (3) insertion sites and document in subject source and complete the Skin Assessment eCRFs

- Return all study sensors, devices, unused supplies and study guides from subjects (refer to Section 6.4)
- An Exit eCRF will be completed at this visit.

9. Subjects 2-13 Years Study Design and Study Procedures

This section is presented as below:

- **Section 9.1:** Study Design
- **Section 9.2:** Study Procedures (Subjects 2-13 years)

Commercially available devices used outside their approved intended use include subjects 2-13 years

9.1. Study Design

The study is a multi-center, randomly assigned, prospective, single-sample correlational design without controls. Subjects will be randomly assigned to sensor location, FST day, and FST time.

It is expected that subjects 7 - 13 years will complete 2 days of YSI™* FST with the Guardian™ Sensor (3) and subjects 2 - 6 years will complete 2 days of SMBG FST with the Guardian™ Sensor (3). Subjects ages 2 – 6 years will only do SMBG during their FST.

Subjects will wear Guardian™ Sensor (3)s in the following configurations outlined in Table 6 and Table 7:

Table 6. Age 7 - 13 years; Sensor Wear Location

Sensor	Guardian™ Sensor (3)		
Location*	Arm	Arm	Buttock
Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter
Pairing	Function as Glucose Recorder	Function as Glucose Recorder	Function as Glucose Recorder
OR			
Sensor	Guardian™ Sensor (3)		
Location*	Buttock	Buttock	Arm
Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter
Pairing	Function as Glucose Recorder	Function as Glucose Recorder	Function as Glucose Recorder

Sensor wear location will be randomly assigned.

*Sensors worn this combination may be inserted on same side or opposite sides. Sensors may be inserted with the assistance of a caretaker.

Table 7. Age 2 - 6 years; Sensor Wear Location

Sensor	Guardian™ Sensor (3)	
Location*	Arm	Arm
Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter
Pairing	Function as Glucose Recorder	Function as Glucose Recorder
OR		
Sensor	Guardian™ Sensor (3)	
Location*	Buttock	Buttock
Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter
Pairing	Function as Glucose Recorder	Function as Glucose Recorder
OR		
Sensor	Guardian™ Sensor (3)	
Location*	Arm	Buttock
Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter
Pairing	Function as Glucose Recorder	Function as Glucose Recorder

*Sensors worn this combination may be inserted on same side or opposite sides. Sensors may be inserted with the assistance of a caretaker.

Subjects will wear the devices (with sensors) up to 7-day training period, 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 early sensor removal occurs during the training period, the subject can continue to study period based on PI discretion.

During the YSI™* FST, IV blood samples will be drawn every 5-15 minutes and analyzed using the YSI™*. For subject's ages 2 – 6 years, the frequency of blood draws with SMBG is every 5 – 30 minutes.

The YSI™* FST will be approximately 6 hours during the in-clinic visit for subjects 7- 13 years. The SMBG FST will be approximately 4 hours during the in-clinic visit for subjects 2-6 years. For details on maximum amount of blood drawn refer to Synopsis and Stopping Rules (section 10.10).

FST Timing for 7-13 years old:

Group	Sensor Wear Day	Timing of YSI™* FST & Start of Challenge (if applicable) from Sensor Insertion T=0
A1	Day 1, 7	2-8 hours (+2), 146-152 hours (±6)
A2	Day 1, 7	20- 26 hours (±2), 164-170 hours (-6, +2)
B1	Day 2, 5	26-32 hours (±2), 116-122 hours (±6)
B2	Day 2, 5	44-50 hours (±2), 98-104 hours (±6)
C1	Day 3, 5	50-56 hours (±6), 116-122 hours (±6)
C2	Day 3, 5	68-74 hours (±6), 98-104 hours (±6)
D1	Day 4, 6	74 -80 hours (±6), 140-146 hours (±6)
D2	Day 4, 6	92-98 hours (±6), 122-128 hours (±6)

FST Timing for 2-6 years old:

Group	Sensor Wear Day	Timing of SMBG FST & Start of Challenge (if applicable) from Sensor Insertion T=0
A1	Day 1, 7	2-6 hours (+2), 148-152 hours (±6)
A2	Day 1, 7	20- 24 hours (±2), 166-170 hours (-6, +2)
B1	Day 2, 5	26-30 hours (±2), 118-122 hours (±6)
B2	Day 2, 5	44-48 hours (±2), 100-104 hours (±6)
C1	Day 3, 5	50-54 hours (±6), 118-122 hours (±6)
C2	Day 3, 5	68-72 hours (±6), 100-104 hours (±6)
D1	Day 4, 6	74 -78 hours (±6), 142-146 hours (±6)
D2	Day 4, 6	92-96 hours (±6), 124-128 hours (±6)

Subjects 7 - 13 years

Subjects will be assigned to the following according to their age:

- Sensor Location - **Random Assignment**
  - Arm/Arm/Buttock
    - N=10 minimum
  - Buttock/Buttock/Arm
    - N=10 minimum
- FST Schedule - **Random Assignment**
  - 2x 6 hours FST

Subjects 2 - 6 years

- Sensor Location
  - Arm/Arm
    - N=3 minimum
  - Buttock/Buttock
    - N=3 minimum
  - Arm/Buttock
    - N=6 minimum
  - Subjects 2-6 years old may have their parents/guardians choose the area for their sensor placement.
- FST Schedule - **Random Assignment**
  - 2 x 4 hours FST

    SMBG only

Subjects and/or Sites are to call the 24-Hour TS for device troubleshooting and device complaints (See Section 14.

Hypoglycemic and Hyperglycemic Challenges

Subjects 2 - 13 years:
During the day of YSI™*/SMBG FST, subjects (2 - 13 years) will not participate in hypoglycemic and hyperglycemic challenges.

9.2. Study Procedures (Subjects 2-13 years)

9.2.1. Study Timeline

The subject's maximum participation from study start to completion is 90 days (including replacement sensor wear and repeat in clinic procedures).

9.2.2. Schedule of Events

In this section, "subject (s)" refers to both subject and/or parent/guardian (if applicable).

9.2.2.1. Visit Schedule

9.2.2.1.1. Visit Schedule for Subjects 7-13 Years

Subjects 7 - 13 years will have the following schedule:

Each subject's participation will include the following visits below. The intent is for subjects to wear the study Guardian™ Sensor (3)s and devices and perform 2 YSI™* FSTs.

One rescheduled visit can occur if Guardian™ Sensor (3) primary sensors dislodge and new Guardian™ Sensor (3)s must be re-inserted (See Replacement Sensors Section 10.2 and 10.3).

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

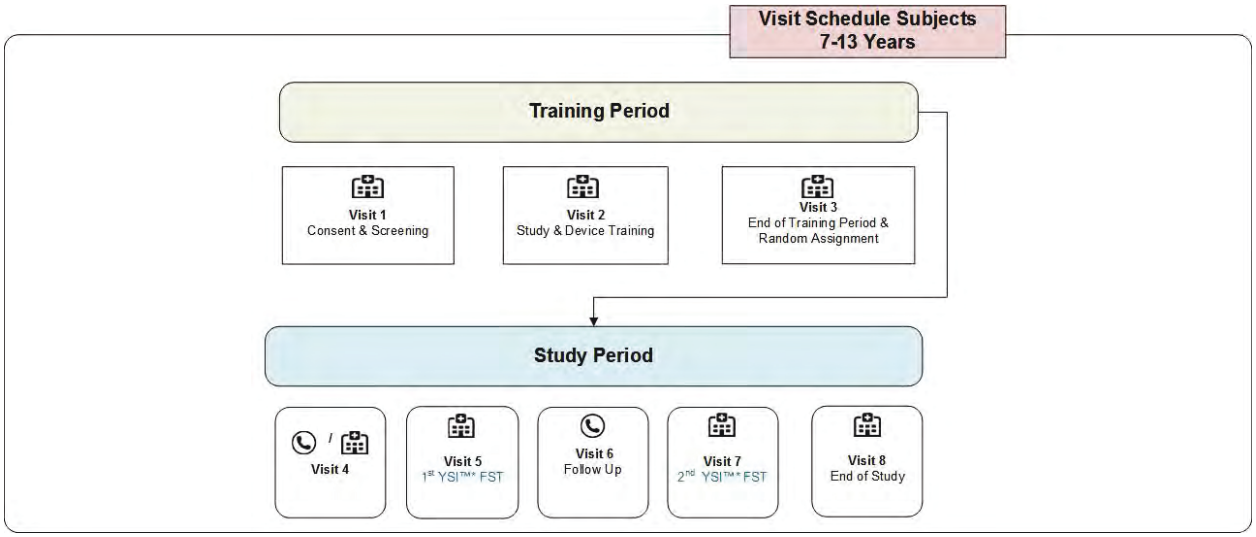
- Visit 1: Consent and Screening
- Visit 2: Study and Device Training
  - Confirm eligibility. Please note that Hct eligibility criteria may be confirmed prior to FST.
  - Visit 1 and 2 can be combined if eligibility criteria are met (see note above on Hct).
- Visit 3: End of Training Period and Random Assignment- Investigational center Visit

Start of Study Period: To be completed in 60 days from Visit 4 to Visit 8; Additional 15 days for sensor replacements (e.g. 75 days)

- Visit 4– Phone Visit or Optional Office Visit
  - **Group A1**- May be combined with Visit 5 (e.g., if sensor insertion for Day 1 is done at Visit 5)
  - **Group A2, B1, B2, C1, C2, D1 and D2 -**Investigational center must confirm either via phone or in person that the Guardian™ Sensor (3) insertion was performed at the appropriate insertion time, location, and SMBG reminder.
- Visit 5: YSI™* 1st FST

- Visit 6: Follow Up Phone Call
- Visit 7: YSI™* 2nd FST
- Visit 8: End of Study Visit
    - Subject has worn sensors for T= 176-188 hours.
    - Visit 7 and Visit 8 may be combined. (e.g. FST occurs on day 7 and end of the sensor wear)

Figure 4. Visit Schedule Subjects 7-13 Years



9.2.2.1.2. Visit Schedule for Subjects 2-6 Years

Subjects 2 - 6 years will have the following schedule:

Each subject's participation will include the following visits below (depending on randomly assigned group). The intent is for subjects to wear the study Guardian™ Sensor (3)s and devices and perform 2 SMBG FSTs based on the subjects' random assignment.

One rescheduled visits can occur if Guardian™ Sensor (3) dislodge and new Guardian™ Sensor (3) must be re-inserted (See Replacement Sensors Section 10.2).

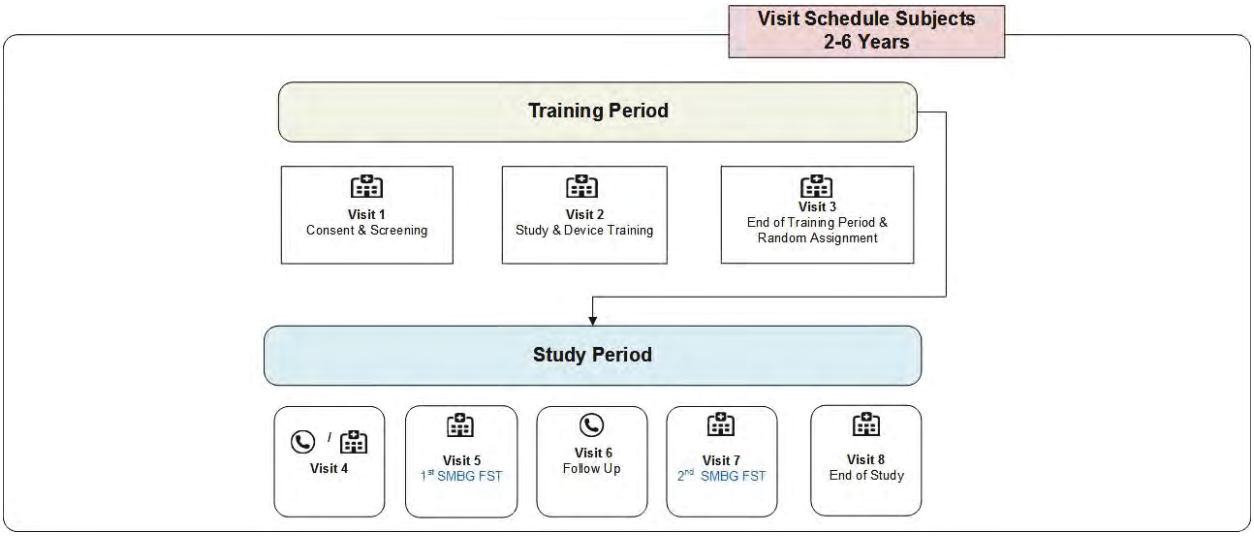
Screening and Training Period: To be completed in 30 days (Visit 1 to Visit 3)

- Visit 1: Consent and Screening
- Visit 2: Study and Device Training
    - Confirm eligibility. Please note that Hct eligibility criteria may be confirmed prior to FST.
    - Visit 1 and 2 can be combined if eligibility criteria are met (see note above on Hct).
- Visit 3: End of Training Period and Random Assignment- Investigational center Visit

Start of Study Period: To be completed in 60 days from Visit 4 to Visit 8; Additional 15 days for sensor replacements (e.g. 75 days)

- Visit 4– Phone Visit or Optional Office Visit
    - **Group A1**- May be combined with Visit 5 (e.g., if sensor insertion for Day 1 is done at Visit 5)
    - **Group A2, B1,B2,C1, C2, D1 and D2 -**Investigational center must confirm either via phone or in person that the Guardian™ Sensor (3) insertion was performed at the appropriate insertion time, location, and SMBG reminder.
- Visit 5: 1st SMBG FST
- Visit 6: Follow Up Phone Call
- Visit 7: 2nd SMBG FST
- Visit 8: End of Study Visit
    - Subject has worn sensors for T= 176-188 hours.
    - Visit 7 and Visit 8 may be combined. (e.g. FST occurs on day 7 and end of the sensor wear)

Figure 5. Visit Schedule Subjects 2-6 Years



9.2.2.2. Visit 1: Consent and Screening

Overview General

Investigational center staff will:

- Obtain California Experimental Subject's Bill of Rights (if applicable), Informed Consent Form (ICF) /Assent form, 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
  - Height and Weight

    Note: BMI will be calculated automatically in the study database, based on height and weight measurements entered.
  - Concomitant medications (Screening Only)
  - Date of diabetes diagnosis
  - Insulin carbohydrate ratio and insulin sensitivity for subject's insulin requiring, if applicable
- 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 needs to be done.
      - HbA1c (not an eligibility criteria)
    - Send to Central Laboratory
    - Note: For all out of range lab results, a single re-test is permitted
- Per Investigator's discretion, subjects may participate in the exercise cohort. Exercise cohort subjects will be asked to exercise for a minimum of 60 minutes during SMBG FSTs.

- Enter electronic Case Report Forms (eCRF)s into the study database 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/Assent form, 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.

9.2.2.3. Visit 2: Study and Device Training

Visit 2 can be done the same day as Visit 1 as long as eligibility is confirmed, including having an eligible Hct value.

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 meter need to be synchronized with a 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 a 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 meter (see Investigator Site Binder for details).

Any instructions or training to subjects referenced in the study procedures may be perform by the study participant's parent/guardian (e.g., performing a sensor insertion, adhesive taping, etc.). If assistance for sensor insertion is required, the Investigational center staff will collect on an eCRF.

Guardian™ Connect Transmitter setup instructions

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

- Refer to Section 9.2.2.3.1 for Procedures including YSI™*/SMBG FST Timing and SMBG Requirements

Overview general study procedures

Investigational center staff will:

- Confirm eligibility
- Synchronize time on Guardian™ Connect Transmitters and CONTOUR®NEXT LINK 2.4 study meter using 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
- Confirm Guardian™ Sensor (3) sensor locations according to subject's age (see Sensor Wear Location Table)
- Enter eCRFs into the study database as appropriate
- Schedule the next visit date and time

Overview study devices and supplies

Investigational center staff will disburse the following to the subject:

- 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 device accountability section (see Section 6.4) on the appropriate eCRF.

Overview training and instructions

Investigational center staff will:

- Train each subject on Guardian™ Sensor (3) insertions, taping and removal, study devices, and study procedures
- 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 blood glucose
    - 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 Guardian™ Sensor (3) calibrations
- 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 Guardian™ Sensor (3)s in the sensor locations according to their age (Investigational center staff may choose from either combination of sensor wear location based on tables below):

Age 7 - 13 years; Sensor Wear Location

Sensor	Guardian™ Sensor (3)		
Location*	Arm	Arm	Buttock
Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter
Pairing	Function as Glucose Recorder	Function as Glucose Recorder	Function as Glucose Recorder
OR			
Sensor	Guardian™ Sensor (3)		
Location*	Buttock	Buttock	Arm

Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter
Pairing	Function as Glucose Recorder	Function as Glucose Recorder	Function as Glucose Recorder

*Sensors worn this combination may be inserted on same side or opposite sides. Sensors may be inserted with the assistance of a caretaker.

Age 2 - 6 years; Sensor Wear Location

Sensor	Guardian™ Sensor (3)	
Location*	Arm	Arm
Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter
Pairing	Function as Glucose Recorder	Function as Glucose Recorder
OR		
Sensor	Guardian™ Sensor (3)	
Location*	Buttock	Buttock
Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter
Pairing	Function as Glucose Recorder	Function as Glucose Recorder
OR		

Sensor	Guardian™ Sensor (3)	
Location*	Arm	Buttock
Transmitter	Guardian™ Connect Transmitter	Guardian™ Connect Transmitter
Pairing	Function as Glucose Recorder	Function as Glucose Recorder

*Sensors worn this combination may be inserted on same side or opposite sides. Sensors may be inserted with the assistance of a caretaker. The area of sensor placement can be chosen by the subjects' parent/guardian.

- 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, 10 hours, and 24 hours 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 remove the Guardian™ Sensor (3)s (at end of training period or at investigational center) after 7 days.
- 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 14 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 12 and 14 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 Guardian™ Sensor (3) 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.

Guardian™ Sensor (3) wear duration during training period:

All subjects should spend time bending and twisting even if they don't undergo aerobic exercise. Subjects will be told to remove the Guardian™ Sensor (3)s (at home or at the investigational center) after 7 days.

9.2.2.3.1. Procedures including YSI™*/SMBG FST Timing and SMBG Requirements

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

SMBG Requirements

- One SMBG should be taken approximately at the same time of the day of insertion (e.g., 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

- Time = 0 hour
  - Guardian™ Sensor (3) insertions will be performed
  - The 0 hour represents the time after sensors have been connected to the last of the Guardian™ Connect Transmitter(s)
- Time = 2 hours
  - YSI™*/SMBG FST period begins.
  - T = 2 hours after the Guardian™ Sensor (3)s have been connected to the Guardian™ Connect Transmitter(s).
- Time = 10 hours
  - T = 10 hours after the Guardian™ Sensor (3)s have been connected to the Guardian™ Connect Transmitter(s).
- Time = 24 hours
  - T = 24 hours after the Guardian™ Sensor (3)s have been connected to the Guardian™ Connect Transmitter(s).
  - Approximately 4 fingerstick glucose readings (SMBG) per day will be requested with target of 7 fingerstick glucose readings (with fingersticks at 2 hours, 10 hours, and 24 hours after the Guardian™ Sensor (3) have been connected to the Guardian™ Connect Transmitter(s)).
- 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.
- At the end of YSI™*/SMBG FST, take one fingerstick glucose reading.

9.2.2.4. Visit 3: End of Training Period and Random Assignment -Investigational Center Visit

Overview general study procedures
Investigational center staff will:

- Instruct subject to self-remove the Guardian™ Sensor (3)s that he/she is still wearing at this visit
- Perform a Skin Assessment on the area of each of the Guardian™ Sensor (3) insertion sites and document in subject source and complete the Skin Assessment eCRFs
- Upload study devices via:
  - CareLink™ Personal For Clinical Research software (CONTOUR®NEXT LINK 2.4 study meter)
  - GST Download Utility Software (Guardian™ Connect Transmitter) following instructions provided

- Determine if additional training is needed (e.g., if the subject is following finger-stick monitoring requirements). If additional training is required, subjects will be retrained using training materials supplied during training visit and research staff may focus on specific areas of opportunity for improvement (Visit 2).
- Randomly assign eligible subjects
- Enter eCRFs into the study database 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)
- Schedule the next visit date and time (first YSI™*/SMBG FST)
- The subject will be instructed to insert Guardian™ Sensor (3)s. Note that the subject will use the same insertion device and 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 Accountability Requirements)

This study will involve random assignment and 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 assignment

FST Timing for 7-13 years old:

Group	Sensor Wear Day	Timing of YSI™* FST & Start of Challenge (if applicable) from Sensor Insertion T=0
A1	Day 1, 7	2-8 hours (+2), 146-152 hours (±6)
A2	Day 1, 7	20- 26 hours (±2), 164-170 hours (-6, +2)
B1	Day 2, 5	26-32 hours (±2), 116-122 hours (±6)

Group	Sensor Wear Day	Timing of YSI™* FST & Start of Challenge (if applicable) from Sensor Insertion T=0
B2	Day 2, 5	44-50 hours (±2), 98-104 hours (±6)
C1	Day 3, 5	50-56 hours (±6), 116-122 hours (±6)
C2	Day 3, 5	68-74 hours (±6), 98-104 hours (±6)
D1	Day 4, 6	74 -80 hours (±6), 140-146 hours (±6)
D2	Day 4, 6	92-98 hours (±6), 122-128 hours (±6)

FST Timing for 2-6 years old:

Group	Sensor Wear Day	Timing of SMBG FST & Start of Challenge (if applicable) from Sensor Insertion T=0
A1	Day 1, 7	2-6 hours (+2), 148-152 hours (±6)
A2	Day 1, 7	20- 24 hours (±2), 166-170 hours (-6, +2)
B1	Day 2, 5	26-30 hours (±2), 118-122 hours (±6)
B2	Day 2, 5	44-48 hours (±2), 100-104 hours (±6)
C1	Day 3, 5	50-54 hours (±6), 118-122 hours (±6)
C2	Day 3, 5	68-72 hours (±6), 100-104 hours (±6)
D1	Day 4, 6	74 -78 hours (±6), 142-146 hours (±6)
D2	Day 4, 6	92-96 hours (±6), 124-128 hours (±6)

Subjects 7 - 13 years

Subjects will be assigned to to the following according to their age.

- Sensor Location - **Random Assignment**
  - Arm/Arm/Buttock
    - N=10 minimum
  - Buttock/Buttock/Arm
    - N=10 minimum
- FST Schedule - **Random Assignment**
  - 2x 6 hours FST

Subjects 2 - 6 years

Subjects will be assigned to the following according to their age.

- Sensor Location
  - Arm/Arm
    - N=3 minimum
  - Buttock/Buttock
    - N=3 minimum
  - Arm/Buttock
    - N=6 minimum
  - Subjects 2-6 years old may have their parents/guardians choose the area for their sensor placement.
- FST Schedule - **Random Assignment**
  - 2 x 4 hours FST

    SMBG only

The YSI™*/SMBG FST visits should be scheduled at this visit by the investigational center staff. The visits will be scheduled so that YSI™*/SMBG FST Timing and fingerstick glucose reading requirements are conducted as displayed in FST Timing Table (Section 9.2.2.3).

The study coordinator will enter all necessary device return information on the appropriate eCRF and any additional subject visits (unscheduled) on the appropriate eCRF.

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.

9.2.2.5. Visit 4 :Phone Call or Optional Office Visit

The purpose of the visit 4 (phone/clinic visit) is to verify that the Guardian™ Sensor (3) insertion was performed at the appropriate insertion time insertion location, and SMBG reminder.

For Group A1 subjects, this visit may be combined with Visit 5.

For Group A2,B1, B2, C1, C2, D1 and D2 subjects: During the phone call or at the investigational center, the investigational center will confirm subject has inserted, connected, and taped the Guardian™ Sensor (3)s at the appropriate time and sensor location. Once the study period Guardian™ Sensor (3)s are inserted, the subject should follow the YSI™*/SMBG FST Timing and SMBG requirements (Section 9.2.2.3.1).

In addition, subjects should be reminded to bring medication, syringes, insulin, and infusion sets that might be needed for their personal pumps during the YSI™*/SMBG FST visit.

9.2.2.6. Visit 5 and 7 : YSI™* FSTs (Subjects 7-13 years)/ SMBG FSTs (Subjects 2-6 years)

For subjects 7-13 years, the YSI™* FST is a 6 hour frequent blood glucose sampling session using IV samples and a laboratory blood glucose analyzer, YSI™*. The investigational center staff will set up the YSI™*.

For subjects 2-6 years, the SMBG FST is a 4 hour frequent blood glucose sampling session using SMBG.

Meals will be provided to the subjects.

Additionally, on Visit 7 please give reminder that subject should keep the sensor in for at least 176 hours.

9.2.2.6.1. At Home, Prior to Arrival at the Clinic for the YSI™/SMBG FST

Subjects will be recommended to take their normal basal insulin the night before the YSI™*/SMBG FST and on the day of their YSI™*/SMBG FST (long acting insulin once or twice a day or continuous insulin infusion with an insulin pump).

Subjects will be recommended to take all other medications at their usual times both prior to arrival at clinic and during the YSI™*/SMBG FST. Subjects will be recommended to bring all medications they are taking with them to the clinic, even if they aren't scheduled to take that medication that day.

9.2.2.6.2. In-Clinic Procedures

Overview general study procedures

Investigational center staff will:

- Set up the YSI™* instrument (subjects 7-13 years only; see Investigator Site Binder for details)
- Perform applicable QC testing (CONTOUR®NEXT LINK 2.4 study meter and Precision Xtra™* ketone meter)
- Synchronize YSI™* devices at the investigational center with the designated study clock (subjects 7-13 years only)
- Verify that Guardian™ Sensor (3) insertion was performed at the appropriate insertion time and, insertion location, and SMBG reminder.
- Conduct ketone testing upon subject arrival, when YSI™*/SMBG blood glucose is above 300 mg/dL, and prior to discharge
- Conduct SMBG testing upon subject arrival
- Refer to Section 9.2.2.3.1 for instructions on Procedures including YSI™*/SMBG FST Timing and SMBG Requirements.
- Conduct YSI™*/SMBG FST procedures. Subjects ages 2 – 6 years will only do SMBG during their FST.
- Upload study devices following completion of each YSI™*/SMBG FST:
    - CONTOUR®NEXT LINK 2.4 study meter via CareLink™ Personal For Clinical Research software
- Upload YSI™* data to sponsor's secure site (subjects 7-13 years only)
- 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 (**Visit 7 only**)
- Subjects will continue to wear Guardian™ Sensor (3)s past the end of this visit

- Review requirements of next study visit (phone visit) with subjects
- Review the next visit date and time for YSI™*/SMBG FST
- Enter eCRFs into the study database as appropriate
- Subjects should be reminded to bring extra infusion sets for their personal pump to next YSI™*/SMBG FST in case they are asked to change them due to occlusion or suspicion of occlusion.
- Remind subject to bring medication, syringes, insulin, infusion sets that might be needed during the YSI™*/SMBG FST visit.
- Remind subjects on Guardian™ Sensor (3)s return (see Table 1 Device Accountability Requirements)
- Record all sensor taping information on appropriate eCRF

Overview study devices and supplies

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

- Guardian™ Sensor (3)(s)
- 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.

Investigational center staff will:

- Remind subjects to perform fingersticks (capillary SMBG)
- Remind subjects to contact the 24-Hour TS for technical issues and support
- Will follow the Discharge Criteria Guidelines
- Fingerstick will be performed at home as stated in 9.2.2.3.1.

Hydration:

- In order to avoid ketosis, subjects will be encouraged to ingest unlimited sugar free fluids to maintain hydration.

Meals/Medication:

- During the in-clinic YSI™*/SMBG FST, subjects should continue to eat and take diabetes medications and meals as per their usual diabetes management and investigator discretion.

Insulin Administration:

- During the in-clinic YSI™*/SMBG FST, subjects should take their insulin as per their usual diabetes management and investigator discretion

Exercise:

Subjects are required to begin exercise at start of YSI™*/SMBG FST if their glucose is between 100-300 mg/dL mg/dL. They should continue exercise for at least 60 minutes. This exercise can be in the form of playing or moving around. We recommend the sites provide toys and games for young subjects to use during the exercise period. However, exercise should be stopped, and meal administered and/or glucose given when:

- Glucose is less than or equal to 70 mg/dL for subjects 2-6 years of age
- Glucose is less than or equal to 65 mg/dL for subjects 7-13 years of age

Compression procedure:

Subjects will be asked to lay on their sensors for at least one hour for each YSI™*/SMBG FST. Time, duration, and activity will be collected based on sensor location on an eCRF for subjects 7-13 years old (See Table 8) and subjects 2-6 years old (See Table 9) :

Table 8. Age 7-13 years, Compression Procedure Based on Sensor Wear Location

Sensor	Guardian™ Sensor (3)		
Location	Arm	Arm	Buttock
Compression Procedure	Subject will be instructed to lay on the arm/ lean on a chair where sensors are inserted.		
OR			
Sensor	Guardian™ Sensor (3)		
Location	Buttock	Buttock	Arm
Compression Procedure	Subject will be instructed to lay on their buttocks where sensors are inserted.		

Table 9. Age 2-6 years, Compression Procedure Based on Sensor Wear Location

Sensor	Guardian™ Sensor (3)	
Location	Arm	Arm
Compression Procedure	Subject will be instructed to lay on the arm/ lean on a chair where sensors are inserted.	
OR		
Sensor	Guardian™ Sensor (3)	
Location	Buttock	Buttock
Compression Procedure	Subject will be instructed to lay on their buttocks where sensors are inserted.	
OR		
Sensor	Guardian™ Sensor (3)	
Location	Arm	Buttock
Compression Procedure	Subject will be instructed to lay on the arm/ lean on a chair where sensors are inserted. **OR** Subject will be instructed to lay on their buttocks where sensors are inserted.	

9.2.2.7. Visit 6: Follow-up Phone Call

The investigational center staff will follow-up with the subject after the YSI™*/SMBG FST within 24 hours from discharge to address any questions, concerns and ask questions (e.g. most recent blood glucose reading, ketone testing (as applicable), and assessing for AE) to determine how the subject has been doing. In addition, subjects should be reminded to bring medication, syringes, insulin, and infusion sets that might be needed for their personal pumps during the YSI™*/SMBG FST visit. If subject is unable to be reached, then this should be documented and at least one second attempt to reach subject be performed.

9.2.2.8. Visit 8: End of Study

- Visit 7 and Visit 8 may be combined. (e.g., FST occurs on day 7 and end of the sensor wear).
- 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 Guardian™ Sensor (3)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 Transmitter) following instructions provided
- Perform a Skin assessment on the area of each of the Guardian™ Sensor (3) insertion sites and document in subject source and complete the Skin Assessment eCRFs
- Return all study sensors, devices, unused supplies and study guides from subjects
- An Exit eCRF will be completed at this visit.

10. Combined Adult and Pediatric Study Protocol

10.1. Assessment of Safety

Adverse Event information is collected in this study. See Section 12 for further information on the collection of AEs and safety information.

10.2. Replacement Sensors

10.2.1. Training Period Sensor Wear Rules

During the training period, if a Guardian™ Sensor (3) dislodges prior to completing, the subject may continue with the remaining sensor(s) until the end of the training period.

10.2.2. Study Period Sensor Wear Repeat Rules

A subject can replace their ***primary*** sensor(s) (See Section 15.8.1) once.

Subject will wear the replaced sensors for 7 days and attempt to complete the required YSI™*/SMBG FST visits.

Please note: It is important for sites to clearly identify the location of the ***primary*** sensor so that if it falls out, the site does not confuse the ***primary*** sensor with a companion sensor that may be located close to the primary sensor.

For example, if a primary sensor dislodges the subject should replace all sensors and repeat any FSTs not completed.

- 20 year old subject loses a primary sensor on day 4 and has completed 2 FSTs. Subject should replace **all** sensors and complete the remaining 2 FSTs. Subject does not have to repeat FSTs already completed

For example, if a companion sensor dislodges but the primary sensor is still inserted, the subject should continue with his/her FST schedule.

Scheduling should be performed so that subjects remain in the 90-day window period (i.e. between Visit 1 – Visit 12 for subjects 14-80 years or Visit 1-Visit 8 for subjects 2-13 years).

Subjects will have their YSI™*/SMBG FST visit rescheduled per the original randomly assigned FST Group.

10.3. 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 for a prolonged time period, the in-clinic procedures may be re-scheduled per sponsor recommendation.
- If primary sensor dislodges and FST cannot be completed. Subject should replace all sensors and repeat any FSTs not completed.

10.4. Medical Oversight

In order to conduct the glucose challenges, 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 diabetes patients must be available during the entire hypoglycemic and hyperglycemic challenge.
- The Investigator (or designee) will need to have one of the following qualifications; endocrinology fellowship, management in patients with diabetes in a clinical practice or experience running prior studies performing hypoglycemic induction or rescue. The provider must be qualified to treat diabetic emergencies.
- It is assumed that not every subject will meet the desired range or desired time per Hyperglycemic and Hypoglycemic Challenge guidelines. If a subject is unable to meet the desired range for the desired time for either challenge, the challenge still may be viewed as complete.

- Deviation from pre-specified protocol requirements defined in Section 10.5.3 may occur for subject safety per investigator discretion.
- Detailed guidelines for the protocol requirements defined in Section 10.5.3 have been provided to account for diabetes management during study. However, these are guidelines only and investigator discretion may be used.

10.5. YSI™*/SMBG FST Instructions

10.5.1. Monitoring During the YSI™*/SMBG FST

Ages 7 - 80 years

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

- less than (<) 75 mg/dL; every 5 minutes (3-8 minutes)
- greater than or equal to (≥) 75 mg/dL; every 15 minutes (7 - 23 minutes)

Ages 2 - 6 years

The frequency of blood draws for SMBG FST sampling is dependent on the value of the previous sample, according to the following ranges:

- less than (<) 70 mg/dL; every 5 minutes (3-8 minutes)
- 70-80 mg/dL; every 15 minutes (7 -23 minutes)
- greater than (>) 80 mg/dL; every 30 minutes (maximum of 45 minutes)

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

Ages 7 – 80 years

In the event that YSI™* blood glucose 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.

Ages 2 - 6 years

Subjects ages 2 – 6 years will only do SMBG during their FST. The fingerstick glucose values will be recorded on the appropriate eCRF and will be used for analysis.

10.5.3. Ketone Monitoring

Arrival at the Clinic:
The start of the YSI™*/SMBG FST with challenge can occur if subject's ketone level is less than or equal to (≤) 0.6 mmol/L.

For example, should a subject arrive with ketone levels greater than (>) 0.6 mmol/L, per investigator discretion, IV or oral hydration may be provided to subject to bring ketone level less than or equal to (≤) 0.6 mmol/L.

Once ketone level is less than or equal to (≤) 0.6 mmol/L, per investigator discretion, subject may start YSI™*/SMBG FST.

During Challenge:

- Glucose greater than (>) 300 mg/dL every 60 minutes
- Nausea, abdominal pain or vomiting regardless of glucose level
- Within 30 minutes before the start of any exercise

Note: Should be performed with fingerstick only

At Discharge:

Refer to Discharge guidelines for ketone monitoring in a separate cover.

10.5.4. Treatment Guidelines Based on Ketones (Investigator Discretion May Be Used for Medical Management)

a) Ketone level greater than or equal to (≥) 0.6 mmol/L and less than (<) 3.0 mmol/L with no symptoms of ketoacidosis (nausea, vomiting, or abdominal pain) and for glucose less than or equal to (≤) 500 mg/dL the following should occur:

For Ketones greater than or equal to (≥) 0.6 mmol/L and less than or equal to (≤ 1.5) mmol/L

- In-clinic procedures may continue
- Administer oral hydration with sugar free, caffeine free liquids (if subject is able to drink) or IV fluid hydration (if needed):
  - 22 years and older: 100 cc/hour of 0.9 normal saline (NS) for 2 hours
  - 2-21 years rate for IV fluid hydration is 10 cc/kg given over 2 hours.
- If no nausea, vomiting, or abdominal pain, subjects may continue with hydration for a maximum of 2 hours with glucose greater than (>) 250 mg/dL with ketones greater than or equal to (≥) 0.6 mmol/L and less than or equal to (≤) 1.5 mmol/L before insulin is administered
- The maximum amount of saline to be infused per kg during the YSI™* FST is:
  - 60 ml/kg, however it is preferred to have no more than 50 ml/kg for (7 – 80 years).
  - 20 ml/kg for (2 – 6 years).
- For subjects treated with CSII, the catheter should be changed if glucose is greater than or equal to (≥) 250 mg/dL for 2 hours and insulin should be administered with a syringe
- If subjects develop nausea, vomiting, or abdominal pain, the study should be stopped.
- If subject shows signs of fluid overload (i.e., congestive heart failure (CHF), lower extremity edema, crackles on lung auscultation of S3 heart sound) then rate of IV hydration will be decreased to half the current rate

For Ketones greater than (>) 1.5 mmol/L and less than (<) 3 mmol/L

- In-clinic procedures may continue
- Administer oral hydration with sugar free, caffeine free liquids (if subject is able to drink) or IV fluid hydration (if needed):
  - 22 years and older: 100 cc/hour of 0.9 NS for 2 hours
  - 2-21 years rate for IV fluid hydration is 10 cc/kg given over 2 hours.
- The maximum amount of saline to be infused per kg during the YSI™* FST is:
  - 60 ml/kg, however it is preferred to have no more than 50 ml/kg for (7 – 80 years).
  - 20 ml/kg for (2 – 6 years).
- Insulin should be administered for ketones with blood glucose greater than or equal to (≥) 250 mg/dL
- For subjects treated with CSII, the catheter should be changed and the correction dose of insulin should be administered subcutaneously.
- If ketones do not decrease to less than or equal to (≤) 1.5 mmol/L after 2 hours of hydration, the study should be stopped
- The study should be stopped if the subject develops nausea, vomiting, or abdominal pain.
- If subject shows signs of fluid overload (i.e., CHF, lower extremity edema, crackles on lung auscultation of S3 heart sound) then rate of IV hydration will be decreased to half the current rate

b) Ketone level greater than or equal (≥) to 3 mmol/L and with no symptoms of ketoacidosis (nausea, vomiting, or abdominal pain) regardless of glucose level.
    - The in-clinic procedures will be stopped
    - Subjects will be instructed to replace their current infusion set with new infusion set and give subcutaneous dose of correction insulin with syringe or pen if needed. Patients on insulin injections should give correction insulin.
    - Administer oral hydration with sugar free, caffeine free liquids (if subject is able to drink) or IV fluid hydration (if needed):
        - 22 years and older: 100 cc/hour of 0.9 NS for 2 hours
        - 2-21 years rate for IV fluid hydration is 10 cc/kg given over 2 hours.
    - The maximum amount of saline to be infused per kg during the YSI™* FST is:
        - 60 ml/kg, however it is preferred to have no more than 50 ml/kg for 7 – 80 years.
        - 20 ml/kg for 2 – 6 years.
    - If ketone levels do not return to less than (<) 1.5 mmol/L after 2 hours of oral hydration or IV fluids the subject will be referred to an emergency department and clinic procedures are stopped
    - If subject shows signs of fluid overload (i.e., CHF, lower extremity edema, crackles on lung auscultation of S3 heart sound) then rate of IV hydration will be decreased to 50 cc/hour

c) Subject is exhibiting signs and symptoms of DKA. The following guidelines to determine the signs of DKA requiring insulin administration are the following:
    - Glucose greater than or equal to (≥) 250 mg/dL
    - Ketone levels above 1.5 mmol/L
    - With symptoms of nausea, vomiting and/or abdominal pain
    - If ketone levels do not return to less than or equal to (≤)1.5 mmol/L after 2 hours of oral hydration or IV fluids the subject will be referred to an emergency department and clinic procedures are stopped
    - Administer oral hydration with sugar free, caffeine free liquids (if subject is able to drink) or IV fluid hydration (if needed):
        - 22 years and older: 100 cc/hour of 0.9 NS for 2 hours
        - 2-21 years: rate for IV fluid hydration is 10 cc/kg given over 2 hours
        - The maximum saline infusion rate is 30 cc/kg for 2-6 year olds

10.5.5. Rescue Therapy/Low Glucose Guidelines for Subjects "Undergoing Observation Only":

Glucose less than (<) 50 mg/dL

- Severe hypoglycemia - see definition Section 12.1
- Subject had seizure, loss of consciousness, or altered mental status so uncooperative with food or liquid orally. Subject will be withdrawn from study (stop the challenge, stop the YSI™*/SMBG FST and DO NOT continue with any future scheduled frequent sampling days).
    - Dextrose: 25 grams of dextrose using an ampule (50 ml/25 grams of dextrose) of Dextrose 50% IV push over 3 minutes. Repeat administration

may be given again after 15 minutes if glucose is not above 100 mg/dL. This dose may be adjusted according to investigator discretion based on subject age and other clinical considerations.
    - Glucagon emergency kit (glucagon for injection [ribosomal DNA, rDNA origin] 1 mg, with 1 mL of diluting solution administered intramuscular (IM): only given if Dextrose was not able to be given due to IV access.
- Target glucose 100 mg/dL

- Low Glucose without altered level of consciousness
    - Replacement simple carbohydrate may be administered per investigator discretion to a target of above 75 mg/dL (e.g. 15 grams/every 15 minutes).

Glucose 50-75 mg/dL

- Replacement carbohydrate may be administered per investigator discretion to a target of above 75 mg/dL. (e.g. 15 grams/every 15 minutes).
- Please see the Hypoglycemic and Hyperglycemic Challenge Guidelines for instructions on treating hypoglycemia for the hypoglycemic challenge.
- In this range, insulin should not be given until glucose is at least above 100 mg/dL.

10.5.6. Instructions for Guidelines on Approach to Low and High Glucose for Subjects Undergoing Challenge:

See Hypoglycemic and Hyperglycemic Challenge Guidelines.

If the subject has taken insulin at home, the following guidelines must be followed:

- Subject must wait 3 hours from last bolus dose of home insulin before a challenge is started.
- Subject will only perform one challenge that day, if the insulin bolus at home was within 3 hours from the start of YSI™* FST.

10.5.7. End of Challenges and Discharge

Please refer to the Discharge Criteria Guidelines.

10.5.8. 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.

10.6. Glucose and Glycemia Measurements

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

- **Daily blood glucose-** 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 blood glucose values -**During the YSI™* FSTs at the investigational center, blood plasma glucose will be determined using the laboratory blood glucose analyzer (YSI™*).
- **Blood ketone values** – During the YSI™*/SMBG FSTs at the investigational center, blood ketones will be determined by all subjects using the Precision Xtra™* ketone meter. A QC test will be performed on the meter assigned to each subject before each YSI™*/SMBG 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. Study staff will be trained on the use of the Precision Xtra™* ketone meter per the manufacturer's IFU. All ketone measurements will be logged in the subject records, and recorded on the appropriate eCRF.
- **SGVs** - Assessed using the following methods:
    - SGVs collected by subject's Guardian™ Connect Transmitter
- **HbA1c** - Collected at baseline (Visit 1) and will be used as demographic information.
- **Alternate POC blood glucose values**- During the YSI™*/SMBG FST at the investigational center, alternate POC blood glucose 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™*/SMBG 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.

10.7. Recording Data

All data required for analysis will be captured on eCRFs using OC-RDC's module. Original eCRFs will not be used to capture raw/source data and supporting documentation will be required.

Electronic device data will be collected from the CONTOUR®NEXT LINK 2.4 study meter using Medtronic 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™ Connect Transmitter 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. Only authorized study personnel are permitted to enter data and sign eCRFs. These tasks may be delegated by the Investigator as desired and noted on the delegation of authority log. Information on eCRFs must conform to the information in the source documents. Medtronic will provide detailed instructions to assist with eCRF completion. In the event of data discrepancies, investigational centers will be asked to resolve queries electronically in the 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 OC-RDC system will be consistent with Medtronic standard procedures.

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

10.8. Deviation Handling

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

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

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

Deviations related to:

<u>Blood glucose range and duration targets:</u>

Blood glucose range and duration targets listed for the hypoglycemic and hyperglycemic challenges are targets. It is expected that the investigational centers participating in the study will make their best efforts to reach these targets with the subjects who participate in these challenges, but the sponsor understands that managing diabetes itself is a challenge and meeting these target values and durations for all subjects may not always be possible.

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.

FST timing:
Out of window protocol deviations related to start of FST time will be given if the patient does not come on the scheduled day of FST only.

FST Sample:

It is noted that collecting YSI™*/SMBG FST every 5 – 30 minutes may be challenging. Deviations for missing YSI™*/SMBG FST samples will be issued for the following reasons:

- If there are 2 consecutive YSI™*/SMBG FST samples missing (unless they were missed for safety issues, IV or YSI™* FST device issues). Example of 1 missing YSI™*/SMBG FST:
    - YSI™*/SMBG FST at 8 A.M. which is 65 mg/dL
    - YSI™*/SMBG FST at 8:15 A.M. which is 60 mg/dL

  Since the 1st sample is less than (<) 75 mg/dl, the next draw should be in 5 mins (+ 3 - 8 minutes); but the 2nd sample is at 8:15 AM, so there is at least 1 missing sample which could have occurred at latest 8:08 AM

- If there are 3 or more total YSI™*/SMBG FST samples missing per subject per YSI™*/SMBG FST (unless they were missed for safety issues, IV or YSI™* FST device issues).

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.

10.8.1. Documenting Requirements for Study Deviations

10.8.1.1. Unplanned CIP Deviations

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

All deviation 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 regulatory agency

10.8.1.2. Minor or Administrative CIP deviations

Minor or administrative deviations are those that do not "affect the scientific soundness of the research plan or the rights, safety, or welfare of human subjects."

Deviations that do not meet the criteria for expedited notification or prior regulatory/IRB approval, may be reported at the time of eCRF completion or separately upon discovery such as during monitoring visits.

If a CIP deviation occurs which meets this definition, the deviation should be reported to the IRB at the time the continuing review application is submitted.

10.8.1.3. 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, the deviation occurred under emergency situations that cannot be timely reported 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/assent, i.e., there is no documentation of informed consent/assent
- Informed consent/assent obtained after initiation of study procedures
- Continuation of a subject who did not meet all inclusion/exclusion criteria
- Performing study procedure not approved by the IRB
- Failure to inform IRB and sponsor of reportable AEs (see Section 12) per the requirements of the CIP
- 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 must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation. Reporting of

deviations must comply with IRB policies, local laws, and/or regulatory agency requirements. Refer to Investigator Reports, Table 10, for specific deviation reporting requirements and timeframes for reporting to Medtronic, IRB, and regulatory agency (if applicable).

10.8.2. 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.

10.9. 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 failure to meet the study requirements, the reason for termination must be documented both in source documents and Exit eCRF. All study devices and supplies must be returned 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

Subject will be withdrawn from the study if subject experiences diabetic ketoacidosis, unconsciousness or severe hypoglycemia.

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

10.10. Stopping Rules

10.10.1. Subject Stopping Rules

- Subject is exhibiting signs and symptoms of DKA (see DKA definition in Section 12.1)
- Severe hypoglycemia (see severe hypoglycemia definition Section 12.1)

- YSI™* glucose greater than (>) 500 mg/dL regardless of ketone level
    - For subjects 2-6 year olds, SMBG will be used. All applicable rules related to rescue therapy/low glucose guidelines, will be based on SMBG rather than YSI™*.
- Ketone greater than or equal (≥) to 3 mmol/L regardless of blood glucose
- Persistent ketone level greater than or equal to (≥) 1.5 mmol/L after hydration (see ketone management guidelines Section 10.5.4)
- Subject develops nausea, vomiting or abdominal pain
- Maximum blood volume drawn:
    - 4 mL/kg (inclusive of all YSI™* FST days) during this study or 400 cc whichever is more for subjects' age 14-80 years old. However, no more than 2 mL/kg of blood volume in a 24-hour period is to be drawn.
    - 3 mL/kg (inclusive of all YSI™* FST days) during this study for subjects' age 7-13 years old.
    - 50 mL will be maximum blood volume for subjects' age 2-6 years old. However, no more than 1 mL/kg of blood volume in a 24-hour period is to be drawn.

10.10.2. Stopping Rules for Entire Study

During the study, the following steps will be taken for:

- DKA during Hypoglycemic and Hyperglycemic Challenges
- Severe hypoglycemia with seizures or requiring glucagon during Challenges

1. Site will notify the sponsor within approximately 24 hours of receiving knowledge of the event.
2. Sponsor will notify Food and Drug Administration (FDA) within approximately 72 hours of knowledge of the event.
3. CEC is to review the event within 7 days from the time that the sponsor is notified.
4. CEC will act as DMC in this situation and will provide recommendation to the sponsor on the following:
    a) If enrollment and study may continue
    b) If enrollment should be stopped; enrolled subjects are still allowed to continue in study
    c) If the entire study must be stopped, including subjects who have already received study devices.

11. Risks and Benefits

11.1. 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 for insertions and care of sensors. • If a sensor site becomes infected or inflamed, the sensor should be removed and another placed in a new location
Risks with Transmitter	**Prevention and Mitigation**
Risks with Transmitter may include:	Prevention and mitigation include:

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

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 challenges • 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 should 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 presence during experiment • Constant observation and monitoring of the subject during challenges • Observation for redness at IV insertion site by qualified staff Treatment of these risks include: • Removal of IV catheter if infection develops and antibiotics should 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 presence during experiment • Constant observation and monitoring of the subject during challenges 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 hyperglycemic challenges	**Prevention and Mitigation**
Risks with hyperglycemia may include: • Diabetic ketoacidosis • Symptomatic ketosis • Cardiovascular event • Dehydration • Potassium and sodium imbalance • Shock • Altered mental status • Coma • Acidosis	Prevention and Mitigation include: • Follow frequent blood sampling per protocol (See Section 10.5.1) • Clear guidelines for management during hyperglycemic challenge • IV access to give immediate insulin • Qualified investigator presence during experiment • Stopping challenge procedures if ketones are elevated or subject is exhibiting signs and symptoms of DKA (Please refer to the ketone management guidelines in the protocol) • Limiting the time the subject is allowed to stay in the hyperglycemic ranges • The subject is under constant observation and monitoring at all times during the challenges • Preventing subjects who do not have a carb/insulin ratio and insulin sensitivity factor from participating in the challenge (observational only) • Investigational centers are to use glucose meter in the event a FST blood glucose value is not available at the required time interval. • Follow the Ketone management instructions per protocol Treatment of these risks include: • IV fluid administration with 0.9 NS will at a rate of 100 cc per hour if ketonemia develops • Rescue therapy management treatment guidelines are provided in the protocol for hyperglycemic events • IV insulin administration will be per the institutions DKA protocol if DKA is suspected • Immediate withdrawal from study if subject is exhibiting signs and symptoms of DKA (Stop the challenge, stop the FST and DO NOT continue with any future scheduled frequent sampling days).

	• Transfer to ER or follow DKA guidelines of the local institution for the disposition of subject if subject is exhibiting signs and symptoms of DKA
Risks with hypoglycemic challenges	**Prevention and Mitigation**
Risks for hypoglycemia may include: • Seizure • Coma • Altered mental status • Loss of consciousness • Cardiovascular event • Death • Risk of rebound hyperglycemia with ketosis	Prevention and Mitigation include: • Follow frequent blood sampling per protocol (See Section 10.5.1) • Clear guidelines for management during hypoglycemic challenge • IV access to give immediate dextrose or other emergency drugs • Qualified investigator presence during experiment. • Limiting the time the subject is allowed to stay in the hypoglycemic ranges • The subject is under constant observation and monitoring at all times during the challenges • Preventing subjects who do not have a carb/insulin ratio from participating in the challenge (observational only) • Investigational centers are to use glucose meter in the event a YSI blood glucose value is not available at the required time interval. Treatment of these risks include: • Rescue therapy treatment instructions are provided in the Hypoglycemic and Hyperglycemic Challenge Guidelines • IV administration of dextrose if uncooperative orally with food or liquid • Glucagon if subject does not respond to Dextrose • Immediate withdrawal from study if severe hypoglycemia (stop the challenge, stop the FST and DO NOT continue with any future scheduled frequent sampling days) Transfer to ER or follow severe hypoglycemia guidelines of the local institution for the disposition of subject.

Risks with exercise:	Prevention and Mitigation
Risks for exercise may include: • Hyperglycemia: DKA, symptomatic ketosis, cardiovascular event and dehydration. • Hypoglycemia: seizure, coma, altered mental status, loss of consciousness, cardiovascular event and death and risk of rebound hyperglycemia with ketosis. • Musculoskeletal injury: sprain and bone fracture. • Cardiovascular event	Prevention and Mitigation include: • Follow frequent blood sampling per protocol (See Section 10.5.1) • Clear guidelines for management during both hypoglycemic and hyperglycemic challenge • IV access to give immediate insulin or dextrose • Qualified Investigator presence during experiment • Stopping challenge procedures if ketones are elevated or if subject is exhibiting signs and symptoms of DKA (Please refer to the ketone management guidelines in the protocol) • Limiting the time the subject is allowed to stay in the hypoglycemic and hyperglycemic ranges • The subject is under constant observation and monitoring at all times during the challenges • Preventing subjects who do not have a carb/insulin ratio from participating in the challenge (observational only) • Investigational centers are to use glucose meter in the event a YSI blood glucose value is not available at the required time interval. Treatment of these risks include: • IV insulin for hyperglycemia if needed • IV dextrose for severe hypoglycemia • Rescue therapy treatment instructions are provided in the protocol or hypoglycemia and hyperglycemia • Immediate withdrawal from study if subject is exhibiting signs and symptoms of DKA or severe hypoglycemia (stop the challenge, stop the FST and DO NOT continue with any future scheduled frequent sampling days) • If there is a suspected sprain or bone fracture, the subject will be sent to the Urgent care or ER. • Calling 911 and then transfer to ER

11.2. 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.

11.3. 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.

11.4. Risk Determination

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

Although the devices used in the study do not present any significant risk to subjects, the study will involve hypo and hyperglycemic challenges that presents a potential serious risk to subjects.

Therefore, submission of an Investigational Device Exemption (IDE) application to the United States FDA is required (due to the risk associated with testing performed during the study).

11.5. Subject Compensation and Indemnification

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

12. 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.

12.1. 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.

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

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

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

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

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

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

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.

12.2. 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, FST exercise injuries). This includes study procedures such as FST and lab draws.

Examples of device or procedure related AEs include:

- **Device related** (ADE): insertion site infection
- Serious adverse device effect (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 on an AE eCRF as this is not considered an untoward event, but rather an expected occurrence. Any glycemic excursion that meets the protocol definition of Severe Hypoglycemia, Severe Hyperglycemia, or DKA is considered an untoward event and a worsening from the subject's baseline and would be reported to sponsor on an AE eCRF.

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

Adverse events will be documented in the subject source file and reported to sponsor on an eCRF. The investigational center is responsible for documentation of 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.

12.3. 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.

12.4. 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.

12.5. 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 the control arm utilize a non-medtronic device (such as a 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:

a) **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.

b) **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.

c) **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.

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

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

Example: A severe hyperglycemia AE with the following event description would have the following causality assessment for device relatedness:	
Improved glucose without an infusion set/site change	**Not related**
Changed infusion set with glucose improvement	**Possible**
Infusion set fell out, bent cannula, occlusion alarm	**Causal relationship**

12.6. 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.

12.7. Skin Assessment: Glucose Sensor Insertion Sites

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

It is expected that subjects will experience mild irritation, redness, bleeding or bruising associated with the insertion and or wear of the glucose sensor and devices. These events are to be documented and captured on the Skin Assessment eCRF. An AE eCRF will only be completed if the skin assessment observation meets the following criteria:

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

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

12.8. Documentation of Symptoms During Frequent Sample Testing

During FST it is expected that subjects may experience minor symptoms that are related to the procedure requirement of driving glucose levels high and low. All symptoms experienced by the subject 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:

- leg cramp or muscle discomfort related to exercise
- headache
- shakiness/tremors
- discomfort associated with IV insertion
- shortness of breath

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

13. Data Review Committees

13.1. Clinical Events Committee

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

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

The CEC will review the following events within 7 days from the time the sponsor is notified.

- DKA during Hypoglycemic and Hyperglycemic Challenges
- Severe hypoglycemia with seizures or requiring glucagon during Challenges

CEC will act as DMC in this situation and will provide recommendation to the sponsor on the following:

a) If enrollment and study may continue

b) If enrollment should be stopped; enrolled subjects are still allowed to continue in study

c) If the entire study must be stopped, including subjects who have already received study devices.

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.

14. 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**)

All device returns will follow the 24-Hour TS procedures. To return a study device as part of a device deficiency, the investigational center and or subject are to call the 24-Hour TS.

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

15. Statistical Design and Methods

15.1. 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. Data and analysis will be summarized in a Clinical Study Report.

15.2. 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.

15.3. Sensor Disposition

The number of Guardian™ Sensor (3) insertions and Guardian™ Sensor (3) removals for every subject enrolled in the study will be presented.

A descriptive analysis of Guardian™ Sensor (3) disposition including Guardian™ Sensor (3) dislodgement and reasons why it dislodged will be included in the Final Report. Guardian™ Sensor (3) insertion and removals will be characterized by the following:

- Guardian™ Sensor (3) location
- Duration of Guardian™ Sensor (3) wear by investigational center subject report
- The number and percentage of Guardian™ Sensor (3)s remaining in place at study end.
- Duration of Guardian™ Sensor (3) wear (subject report) by insertion site.
- Reason for removal: for example, scheduled removal, adverse event, fell out.

The functional life of the Guardian™ Sensor (3) will also be characterized. The duration of Guardian™ Sensor (3) performance from the time of first valid Interstitial Signal (ISIG) to the last glucose reading (i.e., time to end of Guardian™ Sensor (3) life) will be described with Kaplan-Meier curves.

15.4. Subject Demographics and Baseline Characteristics

Subject characteristics, including age, gender, race, ethnicity, medical diagnosis, height, weight, 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.

15.5. Sample Size and Power

15.5.1. Guardian™ Sensor (3) accuracy, Threshold of 75%

The sample size selected is based on the primary effectiveness endpoint, which is the within 20% mean agreement rate (±20 mg/dL when Reference BG less than (<) 80 mg/dL) in comparative readings of paired Guardian™ Sensor (3) and YSI™* glucose readings in FST days. On those 4 days, 8 hours of paired testing will be recorded.

Data from CIP318 and ERP2018-11254 study was used for power estimation via simulation.

The simulation was performed 1000 times and the 95% lower confidence limit of 75%. The results of the simulation indicated that a sample size of 122 will yield greater than 80% power.

15.6. Analysis Populations

All enrolled subjects who have at least one paired Guardian™ Sensor (3) and YSI™* measurement will be included in the efficacy analysis population. All enrolled subjects who have a Guardian™ Sensor (3) inserted will be included in the safety analysis population.

15.7. Assignment to Day of YSI™* FST

Adult subjects and subjects with age of 14 - 80 will be required to attend four 8-hour sessions of frequent sampling in which agreement between YSI™* and Guardian™ Sensor (3)s connected to the Guardian™ Connect Transmitters will be evaluated.

Pediatric subjects with age of 7 – 13 will be required to attend two 6-hour sessions of frequent sampling in which agreement between YSI™* and Guardian™ Sensor (3)s connected to the Guardian™ Connect Transmitters will be evaluated.

Pediatric subjects with age of 2 – 6 will be required to attend two 4-hour sessions of frequent sampling in which agreement between SMBG and Guardian™ Sensor (3)s connected to the Guardian™ Connect Transmitters will be evaluated.

15.8. General Considerations for Data Analysis

15.8.1. Datasets Expected

The following datasets will be generated by the combination of:

- Primary sensors: For subjects 7 years and older and wearing 3 sensors, one primary sensor will be assigned to the sensor with lower serial number in the same location. The other primary sensor will be assigned to the sensor in the other location. For subjects 2 to 6 years old and wearing 2 sensors, primary sensor will be assigned to the sensor with lower serial number in the

same location. For the subjects 2 to 6 years old who are randomly assigned to the arm and buttock sensor location, both sensors will be considered primary sensors.

- Secondary sensor: For subjects 7 years and older and wearing 3 sensors, one secondary sensor will be assigned to the sensor with higher serial number in the same location. For subjects 2 to 6 years old and wearing 2 sensors, secondary sensor will be assigned to the sensor with higher serial number in the same location. Secondary sensor will only be included in the precision analysis.
- Algorithm:
    - 0 Calibration of Zeus algorithm
    - two Calibrations of Zeus algorithm (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
    - three Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
    - daily Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, 14 hours after second calibration and 24 hours after the previous calibration until end of wear)
- Age
    - Adult (18 – 80 years)
    - Pediatrics and adolescent (2 – 17 years)
- Location
    - Abdomen
    - Buttock
    - Arm

15.8.2. Pairing Scheme

All YSI™* and fingerstick values collected will be presented. However, primary endpoint analysis will only include Guardian™ Sensor (3) values of 50-400 mg/dL and paired YSI™*.

YSI™* values will be paired with the closest Guardian™ Sensor (3) value between [0, 5) minutes. Fingerstick values that were not used for calibration will be paired with the closest Guardian™ Sensor (3) value within [0, 5) minutes.

15.8.3. YSI™* Retention

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

15.9. Statistical Model and Analyses of Primary Endpoint(s)

15.9.1.1. Primary Endpoint for ZEUS Algorithm

A total of 16 primary endpoints will be independently evaluated in blocks of 16 in the study. Analysis will be done in the blocks of 16 as:

- Adult (18 – 80 years), abdomen insertion location and 0 Calibration of Zeus algorithm
- Adult (18 – 80 years), abdomen insertion location and two Calibrations of Zeus algorithm (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Adult (18 – 80 years), abdomen insertion location and three Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Adult (18 – 80 years), abdomen insertion location and daily Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, 14 hours after second calibration and 24 hours after the previous calibration until end of wear)
- Adult (18 – 80 years), arm insertion location and 0 Calibration of Zeus algorithm
- Adult (18 – 80 years), arm insertion location and two Calibrations of Zeus algorithm (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Adult (18 – 80 years), arm insertion location and three Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Adult (18 – 80 years), arm insertion location and daily Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, 14 hours after second calibration and 24 hours after the previous calibration until end of wear)
- Peds (2 to 17 years), buttock insertion location and 0 Calibration of Zeus algorithm
- Peds (2 to 17 years), buttock insertion location and two Calibrations of Zeus algorithm (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Peds (2 to 17 years), buttock insertion location and three Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Peds (2 to 17 years), buttock insertion location and daily Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, 14 hours after second calibration and 24 hours after the previous calibration until end of wear)
- Peds (2 to 17 years), arm insertion location and 0 Calibration of Zeus algorithm
- Peds (2 to 17 years), arm insertion location and two Calibrations of Zeus algorithm (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)

- Peds (2 to 17 years), arm insertion location and three Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Peds (2 to 17 years), arm insertion location and daily Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, 14 hours after second calibration and 24 hours after the previous calibration until end of wear)

Guardian™ Sensor (3) accuracy *for ZEUS Algorithms*

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 20% mean agreement rate (±20 mg/dL when SG less than (<) 80 mg/dL), μ, between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated against the null Hypothesis:

  H0: $\mu \leq 75\%$

  H1: $\mu > 75\%$

- Statistical testing

  A generalized estimating equation method model will be used. The one sided 95% lower confidence limit of the mean agreement rate will be tested against the threshold of 75%. For the GEE model, Exchangable (exch) or Auto-regressive (AR1) or Independence (IND) correlation structure will be used, based on quasi-AIC (QIC). Confidence intervals from bias-corrected and accelerated percentile bootstrap approaches will be provided, if applicable. In addition, the confidence intervals from GEE model and bootstrap approaches will be adjusted based on the proposed alpha level at the interim analyses.

  Site effect will be evaluated. If it is not significant (p-value greater than (>) 0.1), site will not be included in the model so as to obtain the adjusted confidence limit.

15.10. Statistical Model and Analyses of Secondary Endpoint(s)

15.10.1.1. Secondary Endpoint for ZEUS Algorithm

Within each block of 16, secondary endpoints (a total of 176) will be evaluated in a fixed sequence of testing for adjustment of multiplicity. The results will be compared to the iCGM Special Control criteria for sensor accuracy (SG limit of 50-400 mg/dL). For each of the endpoints, iCGM measurement refers to the sensor glucose value:

- % of iCGM measurements that indicate a positive glucose rate of change greater than 1 mg/dL/min when the corresponding true negative glucose rate of change is less than -2 mg/dL/min as determined by the corresponding blood glucose measurements

- % of iCGM measurements that indicate a negative glucose rate of change less than -1 mg/dL/min when the corresponding true positive glucose rate of change is greater than 2 mg/dL/min as determined by the corresponding blood glucose measurements

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 20% mean agreement rate between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 15% mean agreement rate when SG >180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 40% mean agreement rate when SG >180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

- When iCGM values are greater than 180 mg/dL, corresponding blood glucose value read less than 70 mg/dL.

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 15% mean agreement rate when SG between 70 and 180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 40% mean agreement rate when SG between 70 and 180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

- When iCGM values are less than 70 mg/dL, no corresponding blood glucose value shall read above 180 mg/dL.

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±15 mg/dL mean agreement rate when SG less than (<) 70 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±40mg/dL mean agreement rate when SG less than (<) 70 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

Within each block of 16, secondary endpoints (a total of 176) will be evaluated in a fixed sequence of testing for adjustment of multiplicity. The results will be compared to the iCGM Special Control criteria for sensor accuracy (SG limit of 40-400 mg/dL). For each of the endpoints, iCGM measurement refers to the sensor glucose value:

- % of iCGM measurements that indicate a positive glucose rate of change greater than 1 mg/dL/min when the corresponding true negative glucose rate of change is less than -2 mg/dL/min as determined by the corresponding blood glucose measurements

- % of iCGM measurements that indicate a negative glucose rate of change less than -1 mg/dL/min when the corresponding true positive glucose rate of change is greater than 2 mg/dL/min as determined by the corresponding blood glucose measurements

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 20% mean agreement rate between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 15% mean agreement rate when SG >180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 40% mean agreement rate when SG >180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

- When iCGM values are greater than 180 mg/dL, corresponding blood glucose value read less than 70 mg/dL.

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 15% mean agreement rate when SG between 70 and 180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 40% mean agreement rate when SG between 70 and 180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

- When iCGM values are less than 70 mg/dL, no corresponding blood glucose value shall read above 180 mg/dL.

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±15 mg/dL mean agreement rate when SG less than (<) 70 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±40mg/dL mean agreement rate when SG less than (<) 70 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

15.11. Numbers of Readings in the Low and High Ranges

Every effort to safely collect data in the low and high range via the hyperglycemic and hypoglycemic challenge will be made

15.11.1. Difference Tables Comparing Sensor and Reference Readings

Number and percentage of paired data points within 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% and 100% of the reference method (YSI™* for in-clinic portion and meter BG for home-use portion) will be summarized.

Number and percentage of paired data within 10 mg/dL, 15 mg/dL, 20 mg/dL, 30 mg/dL, 40 mg/dL, 50 mg/dL, 60 mg/dL, 70 mg/dL, 80 mg/dL, 90 mg/dL and 100 mg/dL of the reference method (YSI™* for in-clinic portion and meter BG for home-use portion) will be summarized.

15.11.2. Sensor Calibration

Characteristics of Guardian™ Sensor (3) calibration will be evaluated by:

- Rate of change (less than (<)-4.0 mg/dL/min, -4.0 to -2.5 mg/dL/min, -2.5 to -2.0 mg/dL/min, -2.0 to -1.5 mg/dL/min, -1.5 to -1.0 mg/dL/min, -1.0 to +1.0 mg/dL/min, +1 to +1.5 mg/dL/min, +1.5 to +2.0 mg/dL/min, +2.0 to +2.5 mg/dL/min, +2.5 to +4.0 mg/dL/min, and greater than (>) +4.0 mg/dL/min).
- Rate of change arrows that are displayed to users
- First calibration SMBG value ranges (40 - 70 mg/dL, 70 - 180mg/dL and 180 - 400 mg/dL): the numerical SGV accuracy will be evaluated against YSI™* stratified by the first calibration SMBG value up to the second calibration SMBG.

15.11.3. Clarke Error Grid Analysis (EGA) of Paired Sensor and YSI™* and Reference Values

1) Description

Clarke Error Grid Analysis (EGA) separates paired observations into five zones of clinical significance. The presence and severity of possible treatment error based on interstitial glucose assay evaluated by the sensor defines the five zones. Zone A represents the absence of treatment error, where the evaluation method and the reference method are within 20% of one another or in which both methods indicate hypoglycemia. Zone B represents cases where the two methods disagree by more than 20%, but do not lead to treatment error. Zones C, D, and E represent increasingly large and potentially harmful discrepancies between the evaluation and the reference method. If the method under evaluation has a high percentage (greater than (>)90%) of its pairs in Zones A and B, then it is considered clinically acceptable [Clarke et al, 1987].

2) Statistical analysis

Summary statistics (N, %) for each of the zones, as well as combined Zones A and B, will be calculated.

In order to evaluate differing levels of accuracy at various YSI™* defined glucose levels, the number and percentage of paired observations falling into Zones A, B, A+B, C, D, and E will be provided by YSI™* glucose ranges of 40-80 mg/dL, greater than (>) 80-120 mg/dL, greater than (>) 120-240 mg/dL, and greater than (>) 240 mg/dL.

All analysis performed using the Clarke Error Grid comparing the paired sensor and YSI™* reference glucose values will be duplicated using the Continuous Error Grid [Clarke et al, 1987] and the Consensus Error Grid [Parkes et al, 2000].

15.11.4. Precision Analysis

Precision analysis will be performed for the two sensors worn by the same subject in the same location.

15.11.5. Comparison of CGM Performance to Reference under conditions leadings to Alert

The alert will be triggered when the sensor BG value reaches the threshold glucose value. Predictive alerts will be evaluated by using the predicted sensor BG value based on current sensor BG and sensor BG readings within the previous 30 minutes.

In the in-clinic portion, the threshold and predictive alert analysis will be performed retrospectively with theoretical hypoglycemia threshold setting at 50 mg/dL, 60 mg/dL, 70 mg/dL, 80 mg/dL, 90 mg/dL and 100 mg/dL and theoretical hyperglycemia threshold setting at 180 mg/dL, 220 mg/dL, 250 mg/dL and 300 mg/dL.

The threshold alert performance will be evaluated for in-clinic portion by true alert rate, missed alert rate and false alert rate within 15 and 30 minute windows of the reference event. Predictive alert performance will only be evaluated for the in-clinic portion by true predictive alert rate, missed predictive alert rate and false predictive alert rate within 15 and 30 minute windows. All reference BG values will be used, including those less than (<) 40 mg/dL and greater than (>) 400 mg/dL.

The comparison of CGM performance to reference under conditions leading to alert will be evaluated by true alert rate, missed alert rate and false alert rate within 15 and 30 minutes window of the reference event.

The alert rates will be defined as follows:

Alert Rate Type	Column Label	Label Definition
Detection Rate	Hypo/Hyper Events Correctly Detected (%)	The device alarmed at the specified CGM settings within 30 minutes (or 15 minutes) before or after the reference blood glucose value (YSI™* or SMBG) goes below (for hypo) or above (for hyper) the specified CGM setting levels.

Alert Rate Type	Column Label	Label Definition
Missed Detection Rate	Hypo/Hyper Events Not Detected (%)	The device did not alarm at the specified CGM settings within 30 minutes (or 15 minutes) before or after the reference blood glucose value (YSI™* or SMBG) goes below (for hypo) or above (for hyper) the specified CGM setting levels.
True Alert	Alerts Verified by Hypo/Hyper Events (%)	There is at least one reference blood glucose value (YSI™* or SMBG) goes below (for hypo) or above (for hyper) the specified CGM setting levels within 30 minutes (or 15 minutes) before or after the sensor alarmed at the specified alert settings.
False Alert	False Alerts (%)	There is no reference blood glucose value (YSI™* or SMBG) goes below (for hypo) or above (for hyper) the specified CGM setting levels within 30 minutes (or 15 minutes) before or after the sensor alarmed at the specified alert settings.

15.11.6. Other Accuracy Analyses

The ARE, the absolute differences between the sensor and YSI™* relative to the YSI™* reference will be calculated for each day separately. Summary statistics will include its mean, standard deviation, min, median, and max.

The mean numerical bias, which is the difference between the sensor and YSI™* values, will be calculated for each day. Summary statistics will include its mean, standard deviation, min, median, and max.

A correlation between the sensor and YSI™* values will be performed. As this statistic ignores any data dependency, it will be used only as a descriptive measure of association.

A linear model, in which YSI™* is predicted by sensor values, using a repeated measures model, will be performed. The models solution will provide the intercept and slope, while adjusting for dependence in the data within day. An intercept of 0, along with a slope of 1, would indicate the absence of bias in predicting YSI™* from sensor readings. The residuals of the model will be inspected to determine if transformation of either variable is required.

Bland-Altman plots, with 95% CI, will be provided for each of the 3 study days. The paired differences between the sensor and YSI™* rating will be plotted against the X-axis reference of mean YSI™* and sensor values.

Descriptive subgroup analysis of Guardian™ Sensor (3) performance (20% mean agreement rate (±20 mg/dL when Reference BG less than (<) 70 mg/dL)) will be performed in the following cohorts:

- **Diabetes cohorts based on insulin requirement**
  - 18-80 years
    - Insulin requiring N = minimum 78 subjects
      - N= minimum of 52 type 1 insulin requiring
      - N= minimum of 26 type 2 insulin requiring
    - Non-Insulin requiring N = minimum 12 subjects
  - 14 - 17 years
    - Insulin requiring N = minimum 24 subjects
  - 2 - 13 years
    - Insulin requiring N = minimum 10 subjects

- **Diabetes cohorts based on Centers for Disease Control and Prevention (CDC) classification for 20 years old or younger**

  A description of the following 4 groups will be performed:
  - Underweight subjects (less than (<) 5th percentile): N=minimum of 1 subjects
  - Normal weight subjects (5th percentile to less than (<) 85th percentile): N= minimum of 40 subjects
  - Overweight (85th to less than (<) the 95th percentile): N= minimum of 8
  - Obese subjects (greater than or equal to (≥) the 95th percentile): N=minimum of 1 subjects

- **Diabetes cohorts based on BMI according to WHO criteria [World Health Organization, 2011] for subjects greater than 20 years old:**

A description of the following 5 groups will be performed:

- Underweight subjects (BMI less than (<)18.5 kg/m²): N=minimum of 1 subject
- Normal weight subjects (BMI 18.5 to 24.99 kg/m²): N= minimum of 28 subjects
- Overweight and obese subjects (BMI 25.00 to 40 kg/m²): N= minimum of 36 subjects
    - Overweight subjects (BMI 25.00 to 29.99 kg/m²)
    - Obese subjects (BMI 30.00 to 39.99 kg/m²)
- Morbidly obese subjects (BMI greater than or equal to (≥)40 kg/m²): N=minimum of 1 subject

- **Diabetes cohorts based on prior real-time CGM experience (by self report)**
    - CGM naïve: N= minimum of 40 subjects (2-80 years)
    - CGM experienced: N= minimum of 40 subjects (2-80 years)

- **Diabetes cohorts based on HbA1c:**
    - Baseline HbA1c (by certified National Glycohemoglobin Standardization Program, NGSP, method) will be collected:
        - A description of the following 3 groups will be performed: HbA1c less than (<) 7%, HbA1c 7-9%, HbA1c greater than (>) 9%
    - Quartile comparison (lowest to the highest) based on HbA1c

- **Diabetes cohort based on exercise activity:**
    - 18 – 80 years
        - N=minimum of 22 subjects
    - 14 - 17 years
        - N= minimum of 6 subjects
    - 2 - 13 years
        - N= minimum of 20 subjects
    - Sponsor may instruct site for exercise to be performed in order to obtain low glucose values
- **Diabetes cohort based on compression procedure:**
    - 18 – 80 years

- N=minimum of 22 subjects
- 14 - 17 years
  - N= minimum of 6 subjects
- 2 - 13 years
  - N= minimum of 10 subjects

All analysis follow the definitions provided in: Performance Metrics for Continuous Interstitial Glucose Monitoring: Approved Guideline, CLSI POCT05-A [Klonoff et al. 2008].

15.11.7. Home-Use Portion Data Analysis

Data from the home-use portion will be described. Analysis will include but not be limited to: 20% mean agreement rate (±20 mg/dL when Reference BG less than (<) 70 mg/dL) for all fingersticks (capillary SMBG) collected, Clark Error Grid, other accuracy analysis, ARE, bias, correlation between Guardian™ Sensor (3) and SMBG and Bland-Altman plots. In addition, 30% mean agreement rate (±20 mg/dL when Reference BG less than (<) 70 mg/dL) will be described by subgroups of: age, YSI™* FST, diabetes classification, BMI, CGM experience, HbA1c and exercise activity. The number of actual calibrations performed per day by study subjects will be tabulated and presented.

15.12. Exploratory Analysis

Additional adjustment to low SG values may be implemented to further assess the performance of Guardian™ Sensor (3) sensors.

15.13. Safety

Descriptive summary will be used to characterize safety events

- Skin assessment at Guardian™ Sensor (3) insertion sites
- All adverse events

15.14. Device Deficiencies

Descriptive device deficiencies will include all reports of Guardian™ Sensor (3) damage, breakage or fracture.

15.15. Interim Analysis

Interim Analysis will be performed for primary effectiveness endpoint to provide direction for continuing enrollment. If primary endpoint is met, secondary endpoints will also be evaluated. Two interim analyses will be conducted after there are 40 and 100 adult subjects complete the study, and separate two interim analyses will be conducted after there are 40 and 100 pediatric subjects complete the study.

The standard group sequential O'Brien-Fleming's approach will be used to estimate of significance level at interim analysis.

Number of Planned Analyses	Number of Interim Analyses	Number of Subjects	p-value threshold (Alpha)
3	1	40	N/A*
	2	100	0.031
	3 (final)	122	0.041

*N/A: No intention to stop for efficacy at the first interim analysis (N = 40). Therefore, p value threshold (Alpha) is Not Applicable (N/A)

For this three stage design, hypothesis testing (primary and secondary endpoints) will be conducted at p = 0.031 and p = 0.041 for the second (N = 100) and final analyses (N = 122), using O'Brien-Fleming's approach. If significance is found at the second interim analysis at N = 100 complete subject, Medtronic may request to stop the study because endpoints are met. Otherwise, the study will continue up to the planned enrollment.

16. Ethics

16.1. Statement(s) of Compliance

IRB

This protocol, any subsequent amendments to this protocol, the ICF/Assent form, subject material and any form of subject recruitment information (e.g. advertisements) relating to this study will be approved by the responsible IRB in accordance with 21 CFR Part 56. The study will not start until IRB approval has been granted, the sponsor has cleared the investigational center to begin the study, and the investigational clinical staff has been appropriately trained to conduct the study. Copies of all relevant correspondence between the investigational center and the IRB will be retained on-site with copies forwarded to the sponsor for their files.

Regulatory Compliance

This clinical study will be conducted in compliance with 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 (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 (or the subject's legally authorized representative) 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/assent process, IRB approval, study training, clinical trial registration, preclinical testing, risk benefit assessment, publication policy, etc.

If the subject is below 18 years of age, he/she should be informed about the study to the extent compatible with the subject's understanding. If the subject could give consent to decisions about participation in research, the investigator must obtain that consent in addition to the consent of their legally authorized representative or guardian.

Ethical Considerations

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

16.2. Investigator's Responsibilities

This study will be conducted at the investigational centers where all study-related activities will be performed and will be led by a principal Investigator. Per 21 CFR 56.102, an Investigator is "an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject) or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team."

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

- Conduct of the investigation in accordance with the protocol, the regulations as outlined in 21 CFR 812.2(b) that apply to significant risk studies and other applicable regulations, and any conditions of approval imposed by the reviewing IRB
- Conduct of investigation in accordance to draft guidance from FDA, "Protecting the Rights, Safety, and Welfare of Study Subjects - Supervisory Responsibilities of Investigators", to meet responsibilities with respect to protect human subjects and ensuring the integrity of the data from clinical investigations. This guidance is also intended to clarify FDA's expectations concerning the investigator's responsibility:

1) to supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other third parties, and
2) to protect the rights, safety, and welfare of study subjects.

- Supervision of all testing of the device involving human subjects
- Ensuring that the requirements for obtaining informed consent/assent are met in accordance with 21 CFR 50
- Allowing investigational devices to be used only with subjects under the Investigator's supervision and to supply investigational devices only to persons authorized to receive it
- Ensuring that investigational center staff are adequately trained to perform their assigned duties
- Maintenance of accurate, complete, and current records relating to the Investigator's part of an investigation, to include
    - all relevant correspondence with Medtronic and IRB
    - records of receipt, use, or disposition of a device
    - records of each subject's case history and exposure to the device
    - the protocol, with documents showing the dates of and reasons for each deviation from the protocol
- Preparation and submission to Medtronic and, when required, the reviewing IRB, the following complete, accurate, and timely reports:
    - any Unanticipated Adverse Device Effects and Serious Adverse Events occurring during an investigation
    - progress reports on the investigation as required by the IRB
    - any deviation from the investigational plan made to protect the life or physical well-being of a subject in an emergency
    - any use of the device without obtaining informed consent/assent
    - any further information requested by the IRB about any aspect of the investigation
- Meeting with the monitor to discuss study progress and findings
- Ensuring that investigational center resources are adequate to fulfill the obligations of the study
- Ensuring completion of eCRF to include: entry and addressing discrepancies in a timely fashion and approving selected eCRFs. It is expected that data is entered into OC-RDC. Failure to keep up with entry of study data may result in study payment delay.

Only authorized study personnel, as listed on the Delegation of Authority/Signature Log Form, 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 personnel are qualified and perform the tasks that have been delegated to them. In addition, the Investigator is responsible for the conduct of investigational center in the execution of the clinical trial.

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

17. Study Administration

17.1. Training of Clinical Staff

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

17.2. Monitoring

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

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

Investigational center Qualification and Initiation Visits will be completed prior to enrollment of the first subject. On-site monitoring activities will include an inspection of completed study documents, source document, and verification and reporting, verification of database accuracy and completeness. Any planned review of data by the monitor between on-site visits will be described in the Monitoring Plan. Following each monitoring visit, a report will be prepared and submitted to the sponsor. The principal investigator will be provided details of the monitor findings in writing in the form of a follow up visit letter. From initiation of study to close out visit, the Clinical Research Monitor(s) will assume primary responsibility for communications between the study investigators and the sponsor.

The principal investigator is responsible for ensuring that investigational center staff is appropriately trained to manage the protocol. Initial and ongoing investigational center staff training will be provided during the Investigational center Initiation Visit, subsequent monitoring visits, and regular investigational center staff contact. Prior to enrollment of the first subject, investigators and investigational center staff who will be participating in enrollment, eCRF completion, device insertion/application, device training, and consenting subjects must complete the sponsor-required training. Investigational center staff must complete and sign the Study Training Record(s) applicable to their delegated task as designated by the principal investigator and maintain the record(s) in the Investigator Site Binder. An investigational center staff who has been previously trained by sponsor can train additional site staff.

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

17.2.1. Accessibility of Investigational center Staff and Study Materials

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

17.2.2. Audits and Investigational center Inspections

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

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

17.2.3. Investigational Center Disqualification

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

- Unsatisfactory subject enrollment with regard to quality and quantity.
- Deviations from CIP, without prior notification and approval from Medtronic.
- 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 study devices.

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

17.3. Data Management

17.3.1. Data Collection

17.3.1.1. 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 must be consistent with the source documents and discrepancies need to be justified in a documented rationale, signed and dated by the (principal) investigator, and filed in the patient medical file.

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

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

Investigational center will be trained for use of the eCRF prior, or at latest during, investigational center initiation visit, on a training database. Access to final eCRFs for study conduct will be granted after training is performed and prior to patient's enrollment.

17.3.1.2. 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 SIDs to prevent patient identification by the sponsor.

17.3.1.3. 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.

17.3.2. Time Windows For Completion and Submission of eCRFs

It is expected that eCRFs are completed in a timely manner with the exception of reportable AEs (see Section 12.3). After data entry, eCRFs should be submitted (i.e. saved) so that Monitors can proceed with data verification without delay.

17.3.3. Data Preparation

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

17.3.4. Data Review and Processing

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

Collected data will be reviewed for completeness, correctness and consistency, 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.

17.4. Direct Access to Source Data/Documents

The patient's hospital/clinic file and laboratory reports are handled as source data.

In addition, investigational centers will receive visit requirement instructions that detail required activities and data to be collected during the patient visits. The objective of these instructions is to remind the investigational center of all study-related procedures to be performed and items to be recorded, before data is actually entered into the study database.

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

documents are retained, these shall be signed and dated by a member of the investigational center team with a statement that it is a true and complete reproduction of the original source document.

17.4.1. Quality Audits

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

17.5. Confidentiality

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. All correspondence between the investigational center and Medtronic that refers to individual study subjects will use unique identifiers that are specific to each subject in lieu of subject names. Furthermore, all subject names will be redacted from reports, safety updates, and source documents that are forwarded to the Medtronic.

17.6. CIP Amendments

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

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

17.7. Records and Reports

17.7.1. Investigator Records

An Investigator Site Binder will be provided by the sponsor and maintained by the investigational center. At a minimum, each Investigator Site Binder will include, but is not limited to:

- Study Contact Sheet
- Clinical Study Agreement(s)
- Signed/dated CV of Investigator(s)
- IRB Correspondence
- IRB-approved Protocol(s) and ICF(s)/Assent form(s), including all amendments
- 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 study protocol.
- Monitoring Visit Log
- Clinical Study Center Visit Sign-In Log
- Study Correspondence
- Delegation of Authority/Signature Log Form
- Training Records
- User Guide(s), IFU, and/or User Manual as applicable
- Quick Reference Guide
- Training materials
- Report of Prior(s)

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

- Signed and dated ICFs/Assent forms
- Source Document Requirement
- Protocol Deviation / Protocol Noncompliance, if any
- Adverse Event Notifications, if any

17.7.2. Investigator Reporting Responsibilities

Table 9. Investigator Reporting Requirements

Report	Submit to	Description/Constraints
AEs and Device Deficiencies	Sponsor, IRB, and local regulatory authority, where applicable	Refer to section 12 and 14 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.

Report	Submit to	Description/Constraints
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.
Final report	Sponsor IRBs Relevant Authorities	This report must be submitted within 6 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.

17.8. Record Retention

The sponsor and investigator will retain all records and documents pertaining to this study. They will be available for inspection by the appropriate regulatory agencies. In addition, the Investigator will retain the source documents from which the information entered on the eCRF was derived. These records are to be retained in a secure storage facility maintained by the investigational center until 2 years 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.

17.9. Suspension or Early Termination of Clinical Study

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.

17.9.1. 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.

17.9.2. 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.

17.10. Study Close Out

Upon completion of the study, when all subjects have completed the follow-up visits, all eCRFs have been entered and all related queries have been resolved, the sponsor and/or its designees will notify the investigational center of its intention to close out the study and a close-out visit will be performed. All study devices and all unused study materials will be accounted for through reconciliation with shipment logs and returned to the sponsor. The Monitor will ensure that the Investigator's regulatory files are up-to-date and complete and that any outstanding issues from previous visits have been resolved. Other issues that will be reviewed at this visit include discussing retention of study files, possibility of investigational center audits, and notifying the IRB of study closure.

17.11. Publication and Use of Information

This clinical study will be registered in a public clinical trials registry, ClinicalTrials.gov. Study information and study results will be posted. Furthermore, Medtronic may publish the results of the clinical study in a press release, abstract, scientific journal article, or public presentation.

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. However, participating investigational center(s) will have the right to publish, publicly disclose, present or discuss the results of information pertaining to the study once Medtronic releases or presents a multicenter publication.

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.

18. References

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

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World Health Organization, Global Database on Body Mass Index. Accessed May 11, 2011.

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19. Appendices

19.1. Appendix A: Names and addresses

19.1.1. Investigational Centers

At the time 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.

19.1.2. 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.

19.1.3. 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

At the time this CIP was finalized, the names and address of the monitors were not identified. The names and address of the monitors will be provided to the investigators under separate cover.

19.2. Appendix B: Labeling and IFUs of Devices

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

19.3. 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/Assent form, and the HIPAA Authorization.

20. Version History

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

B	○ Updated Version and date of CIP ○ Updated Table of Content and Glossary ○ Increased number of enrolled subjects and separated age groups of 2-6 years, 7-13 years, and 14-80 years old futher into subgroups ○ Updated FST Timing schedule for all age groups ○ FST schedule in 14-80 years of age updated to four 8-hour session. ○ Removed minimum number of subjects needed for each FST group. ○ Updated minimum for diabetes cohorts for insulin requiring subjects ○ Additional sensor wear location (arm/buttock) added to the 2-6 year old subjects to ensure adequate data can be collected for each insertion site. Based on this change, minimum number of subjects and the compression procedures is updated. ○ Updated Procedures Including YSI* FST Timing and SMBG Requirements ○ Updated study period sensor wear repeat rule section ○ Updated repeat rules for in-clinic procedures ○ Updated protocol and challenge guidelines on starting rules with respect to a subject's glucose level, to allow subjects to start the FST session between 60 mg/dL-300 mg/dL (updated from 50 mg/dL to 500 mg/dL). ○ Updated Hyperglycemic Challenge Guidelines to state that glucose time for glucose >300 mg/dL will be limited to	[redacted]

	60 minutes. ○ Updated Hypoglycemic Challenge Guidelines to state that glucose time for glucose <70 mg/dL will be limited to 2 hours. Additionally, we have stated that subjects should spend no more than 30 minutes between 50-60 mg/dL and require treatment for glucose below 50 mg/dL. ○ Reduced maximum blood draw volume for 2-6-year olds to 1ml/kg during the study. ○ Updated Stopping Rules for Entire Study ○ Added DMC section who will be overseeing interim analysis ○ Updated statement that commercially available devices used outside their approved intended use include subjects 2-to 13 years ○ Updated Sample Size and Power ○ Removed duplication description of Guardian™ Sensor 3 and Guardian™ Connect Transmitter	
C	○ Updated Version and date of CIP ○ Updated Table of Content ○ Updated FST Timing schedule ○ Extended windows for Start of study period to 60 days from Visit 4 to end of study under Visit Schedule for all subjects. ○ Removed duplicate entry description under Section 9.2.2.7 ○ Updated interim analysis section to perform one of 2 primary effectiveness endpoint within ±15 mg/dL mean agreement rate when SG less than (<) 70 mg/dL. ○ Updated YSI™*Retention section	[redacted]

D	○ Updated Version and date of CIP ○ Updated Table of Content ○ Updated Study Design and Study Procedures for 14-80 years: Added that the study procedures may be done in a camp/hotel setting, removed hyper/hypo challenges requirements for subjects 14-17 years old and clarified specific study procedures for subjects undergoing challenges. ○ Updated FST Timing schedule ○ Updated site to instruct subjects to wear 176-188 hours of sensor wear ○ Added site to recommend subjects to set alarm (e.g., on their phone) to check their fingersticks (SBMG) at insertion, 2 hours, 10 hours, and 24 hours on Day 1 and also one approximately at the same time every day as time of the insertion. ○ Updated Deviation Handling section ○ Updated Secondary Endpoint for ZEUS Algorithm ○ Updated Pairing Scheme ○ Added Exploratory Analysis ○ Updated Discharge Criteria Guidelines	

E	○ Updated Version and date of CIP ○ Updated Table of Content ○ Updated additional clarification regarding the hotel/camp study requirements. ○ Added back hyper/hypo challenges requirements for subjects 14-17 years old ○ Updated Treatment Assignment ○ Added back 40-400 mg/dL operating range from the Secondary Analysis ○ Updated Interim Analysis section ○ Updated Discharge Criteria Guidelines back to Version C	[redacted]
F	○ Updated Glossary ○ Updated Primary Endpoint and Guardian™ Sensor (3) accuracy for ZEUS Algorithms ○ Updated Stopping Rules for Entire Study ○ Removed DMC section as CEC will do the adjudication ○ Corrected Investigator Reporting requirements for Final Report ○ Updated Interim Analysis section ○ Updated IRB name and contact chairperson ○ Updated MC2 abbreviation ○ Updated References section ○ Updated Hyperglycemic and Hypoglycemic Challenge Guidelines	[redacted]

G	○ Updated Glossary ○ Updated statistical testing for Guardian™ Sensor (3) accuracy for ZEUS Algorithms ○ Removed Guardian™ Sensor (3) accuracy when SG less than 70 mg/dL, Threshold of 75% section (under Sample Size and Power) ○ Updated Interim Analysis section ○ Updated References section	[redacted]
H	○ Updated Interim Analysis section	[redacted]