Medtronic	
Study Title	Evaluation of Updated Continuous Glucose Monitoring (CGM) Form Factor in Adults, Adolescents and Pediatrics
NCT Number	NCT04436822
Document Description	Clinical Investigation Plan (Version D)
Document Date	31-MAR-2022

Medtronic **Clinical Investigation Plan (CIP)**	
Study Title	Evaluation of Updated Continuous Glucose Monitoring (CGM) Form Factor in Adults, Adolescents and Pediatrics
CIP Identifier	330

Study Product Name & Study Product Model	Investigational devices:
	• Disposable Sensor (DS5) – labeled as DS5 and referred to as DS5 throughout this protocol
	• Auxiliary Devices:
	  ○ Synergy Download Utility Software (part number M004060C001)
	  ○ Blue Bluetooth® Low Energy Adapter - referred to as the Blue Adapter in this protocol **(non-investigational and commercially available in US)**
	
	Non-Investigational devices:
	• Medtronic CareLink™ Personal Therapy Management Software for Diabetes For Clinical Research –referred to as CareLink™ Personal For Clinical Research software in this protocol **(commercially available in US only)**
	• Ascensia CONTOUR® NEXT LINK 2.4 Blood Glucose Meter -referred to as the CONTOUR® NEXT LINK 2.4 study meter in this protocol **(commercially available in US only)**
	• Ascensia CONTOUR® PLUS Blood Glucose Meter-referred to as the CONTOUR® PLUS study meter in this protocol **(commercially available in China only)**
	• Abbott™*/Medisense™*Precision Xtra™* meter to be used for blood ketone measurements only - referred to as the

	Precision Xtra™* ketone meter in this protocol **(commercially available in US only)** • Abbott™* FreeStyle Optium Neo Blood Glucose & Ketone Monitoring System to be used for blood ketone measurements only - referred to as the FreeStyle Optium Neo ketone meter throughout this protocol **(commercially available in China only)** • Over-the-counter (OTC) tape(s) if needed (e.g., Hypafix™* tape, etc.)
Category of investigational medical device (China Only)	Class III
Class III medical devices requiring clinical trial approval (China Only)	No
Similar product in China	Yes
Description of CIP	This global study will assess the use of Disposable Sensor (DS5) for the span of 170 hours (7 days) in an adult, adolescent, and pediatric population in US and China.
Sponsor	Medtronic MiniMed ("Medtronic") 18000 Devonshire St Northridge, CA 91325 866.948.6633
Local Sponsor (Agent)	Medtronic (Shanghai) Management Co., Ltd. Room 2106A, 2106F, 2106G, 2106H, Floor 21, Donghua Financial Building, No. 28 Maji Road, China (Shanghai) Pilot Free Trade Zone, 200120, Shanghai, P.R.China.
Document Version	D (Equivalent to FDA Version D.1)
Document Reference Number	10976639DOC

Version Date	17-FEB-2022

Confidentiality Statement

1. Investigator Statement (China Only)

Study Product Name	*Investigational Devices:*
	• Disposable Sensor (DS5) – labeled as DS5 and referred to as DS5 throughout this protocol
	• Auxiliary Devices:
	  ○ Synergy Download Utility Software (part number M004060C001)
	  ○ Blue Bluetooth® Low Energy Adapter - referred to as the Blue Adapter in this protocol
	
	Non-Investigational Devices:
	• Ascensia CONTOUR® PLUS Blood Glucose Meter- referred to as the CONTOUR® PLUS study meter in this protocol
	• Abbott™* FreeStyle Optium Neo Blood Glucose & Ketone Monitoring System to be used for blood ketone measurements only -referred to as the FreeStyle Optium Neo ketone meter throughout this protocol
	• Over-the-counter (OTC) tape(s) if needed

Sponsor	Medtronic MiniMed
Clinical Investigation Plan Identifier	330
Version Number/Date	D (Equivalent to FDA Version D.1)/17-FEB-2022

Investigator's statement

[redacted]

I agree that:

[redacted]

1. I will conduct this clinical trial in strict compliance with the Declaration of Helsinki, current laws and regulations of China, and the requirements of the protocol;

1.[redacted]

2. And record all required data accurately on the Case Report Form (CRF) and complete the final report of the clinical trial on time;

2.[redacted]（CRF）[redacted]，[redacted]

3. The investigational medical device will be used only for this clinical trial and the receipt and use of the investigational medical device will be recorded completely and accurately and the records will be retained during the process of the clinical trial;

3.[redacted]

4. The monitor and verifier authorized or designated by the Sponsor and the regulatory authorities are allowed to conduct monitoring, verification and inspection for the clinical trial;

4.[redacted]

5. The clinical trial should be conducted in strict compliance with contract/articles of agreement signed by all parties.

5. [redacted]

I have already read the clinical study protocol, including the above statement and I fully agree all the above requirements.

[redacted]

Comments of the sponsor:	Signature (Seal): Date:

Comments of the investigator:	Signature: Date:
Comments of the clinical investigational site:	Signature (Seal): Date:

Table of Contents

2. Glossary

Term	Definition
HbA1c	Glycosylated hemoglobin
AE	Adverse Event
ARE	Absolute Relative Error
AR1	Auto-regressive
BG	Blood Glucose
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CGMS	Continuous Glucose Monitoring System
CHF	Congestive Heart Failure
CI	Confidence Interval
CIP	Clinical Investigation Plan
CMDE	Center for Medical Device Evaluation
CVA	Cerebrovascular Accident
DKA	Diabetic Ketoacidosis
DS5	Disposable Sensor
EC	Ethics Committee

Term	Definition
eCRF	Electronic Case Report Form
EGA	Error Grid Analysis
ER	Emergency Room
EOS	End of Study
exch	Exchangeable
EtO	Ethylene Oxide
FDA	United States Food and Drug Administration
FST	Frequent Sample Testing
GEE	Generalized Estimating Equation
GST	Glucose Sensor Transmitter
Hct	Hematocrit
HIPAA	Health Insurance Portability and Accountability Act of 1996
IB	Investigator's Brochure
iCGM	Integrated Continuous Glucose Monitoring
ICF	Informed Consent Form
ID	Identification
IDE	Investigational Device Exemption
IFU	Instructions for Use
IND	Independence
IRB	Institutional Review Board
ISIG	Interstitial Signal
IV	Intravenous

Term	Definition
MC2	Medtronic Core Clinical Solutions
NGSP	National Glycohemoglobin Standardization Program
NMPA	National Medical Products Administration
NS	Normal Saline
OC-RDC	Oracle Clinical Remote Data Capture
OTC	Over-the-counter
PC	Personal Computer
POC	Point of Care
QC	Quality Control
QIC	Quasi-AIC
RF	Radio Frequency
SAE	Serious Adverse Event
SG	Sensor Glucose
SMBG	Self-Monitoring of Blood Glucose
SR	Significant Risk
SQ	Subcutaneous
TDD	Total Daily Dose
TS	Technical Support
TIA	Transient Ischemic Attack
TLS	Transport Layer Security
UADE	Unanticipated Adverse Device Effect
WHO	World Health Organization

Term	Definition
YSI™*	Yellow Springs Instrument

3. Synopsis

Title	Evaluation of Updated Continuous Glucose Monitoring (CGM) Form Factor in Adults, Adolescents and Pediatrics
Investigational Device Exemption (IDE) Number	**G200156**
Clinical Study Type	Pivotal study
Sponsor	Medtronic MiniMed, Inc. ("Medtronic") 18000 Devonshire St Northridge, CA 91325 866.948.6633
Local Sponsor (Agent)	Medtronic (Shanghai) Management Co., Ltd. Room 2106A, 2106F, 2106G, 2106H, Floor 21, Donghua Financial Building, No. 28 Maji Road, China (Shanghai) Pilot Free Trade Zone, 200120, Shanghai, P.R.China.
Indication Under Investigation	Type 1 diabetes, Type 2 diabetes

Devices	*Investigational Devices:*
	• Disposable Sensor (DS5) – labeled as DS5 and referred to as DS5 throughout this protocol
	• Auxiliary Devices:
	  ○ Synergy Download Utility Software (part number M004060C001)
	  ○ Blue Bluetooth® Low Energy Adapter - referred to as the Blue Adapter in this protocol **(non-investigational and commercially available in US)**
	
	Non-Investigational Devices:

	• Medtronic CareLink™ Personal Therapy Management Software for Diabetes For Clinical Research –referred to as CareLink™ Personal For Clinical Research software in this protocol **(commercially available in US only)** • Ascensia CONTOUR® NEXT LINK 2.4 Blood Glucose Meter -referred to as the CONTOUR® NEXT LINK 2.4 study meter in this protocol **(commercially available in US only)** • Ascensia CONTOUR® PLUS Blood Glucose Meter-referred to as the CONTOUR® PLUS study meter in this protocol **(commercially available in China only)** • Abbott™*/Medisense™*Precision Xtra™* meter to be used for blood ketone measurements only - referred to as the Precision Xtra™* ketone meter in this protocol **(commercially available in US only)** • Abbott™* FreeStyle Optium Neo Blood Glucose & Ketone Monitoring System to be used for blood ketone measurements only -referred to as the FreeStyle Optium Neo ketone meter throughout this protocol **(commercially available in China only)** • Over-the-counter (OTC) tape(s) if needed (e.g., Hypafix™* tape, etc.)
Category of investigational medical device (China Only)	Class III
Class III medical devices requiring Clinical Trial Approval (CTA) **(China Only)**	No
Purpose	The purpose of this study is to demonstrate the performance of the Disposable Sensor (DS5) 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 Disposable Sensor (DS5) when used over a period of 7 days (i.e., 170 hours) in subjects 2-80 years of age.

<table>
<tr><td>Study Design</td><td>The study is a multi-center, prospective, single-arm study without controls, and random assignments of sensor location, frequent sample testing (FST) day, and FST time.

For the Study Design, refer to:
• Section 10.1 for Subjects 14-80 years Study Design
• Section 11.1 for Subjects 2-13 years Study Design

A total of up to 376 previously-diagnosed type 1 or type 2 diabetes subjects in the U.S. and China will be enrolled in order to have 260 subjects complete the study.

Up to 22 investigational centers in the US and China will be used during the study.</td></tr>
<tr><td>FST Timing</td><td>Subjects will be assigned to FST Timing (random assignment) according to their age:

FST Timing for 14-80 years old:
<table>
<tr><th>Group</th><th>Sensor Wear Day</th><th>Timing of FST 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 hours (±6), 138-146 hours (±6)</td></tr>
</table></td></tr>
</table>

FST Timing for 7-13 years old:

Group	Sensor Wear Day	Timing of FST 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 FST 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)

	The following is the FST schedule for the subjects according to their age: **Subjects 14 - 80 years** • 4 x 8 hours FST • Challenges ▪ Two Hyperglycemic Challenges ▪ Two Hypoglycemic Challenges ▪ If challenges are performed, the following are recommended: • **US only:** Investigator discretion may be used in selecting which challenge is to be performed for each FST as long as 2 hyperglycemic challenges and 2 hypoglycemic challenges are met. • **China only**: Whether performing recommended challenges or not will be based on Ethics Committee (EC) suggestion and investigator discretion. Absence of challenges during FST will not be considered a protocol deviation. **Subjects 7 - 13 years** • 2 x 6 hours FST **Subjects 2 - 6 years** • 2 x 4 hours FST • SMBG only

Sensor Location	Subjects will be assigned to sensor location (random assignment) according to their age: ○ **Subjects 14 - 80 years** ▪ 14-17 years • Arm/Arm/Buttock • Buttock/Buttock/Arm ▪ 18-80 years • Arm/Arm ○ **Subjects 7 - 13 years** ▪ Arm/Arm/Buttock ▪ Buttock/Buttock/Arm ○ **Subjects 2 - 6 years** ▪ Arm/Buttock ▪ Subjects 2-6 years old may have their parent, guardian, or legally authorized representative choose the area for their sensor placement.
Sample Size and Investigational Centers	A total of up to 376 previously-diagnosed type 1 or type 2 diabetes subjects in the U.S. and China will be enrolled in order to have 260 subjects complete the study. Up to 22 investigational centers in the US and China will be used during the study. **US:** A total of up to 300 previously-diagnosed type 1 or type 2 diabetes subjects in the U.S. will be enrolled in order to have 200 subjects complete study.

	Up to 17 investigational centers in the US will be used during the study. Number of subjects to complete study: • N= 100 subjects 18-80 years old • N= 100 subjects 2-17 years old The US investigational centers will be encouraged to include subjects of different ethnicities including Hispanic, Native American, Asian, and African-American. **China:** A total of up to 76 previously-diagnosed type 1 or type 2 diabetes subjects in China will be enrolled in order to have 60 subjects complete study. Up to 5 investigational centers in China will be used during the study. Number of subjects to complete study: • N= 40 subjects 18-80 years old • N= 20 subjects 2-17 years old A minimum of 6 subjects and a maximum of 24 subjects is expected to be enrolled at each investigational center.
Duration	The study is anticipated to last approximately 14 months from investigational center initiation to finalization of all data entry and monitoring procedures in US and China regions, respectively. The subject's maximum participation from study enrollment to study exit is approximately 90 days (including replacement sensor wear and repeat in clinic procedures if needed).
Inclusion/Exclusion Criteria	**Inclusion Criteria:** 1. Individual is 2 - 80 years of age at time of enrollment. 2. Subject has a clinical diagnosis of type 1 or type 2 diabetes: a. If subject is 14-80 years of age, subject has a clinical diagnosis of type 1 or type 2 diabetes for a minimum of 6 months

	duration as determined via medical record/ source documentation by an individual qualified to make a medical diagnosis. b. If subject is 2-13 years of age, subject has a clinical diagnosis of type 1 or type 2 diabetes as determined via medical record/ source documentation by an individual qualified to make a medical diagnosis. 3. If subject is participating in YSI™* FST , subject has 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 factor(s). Subjects without ratios may participate under observation only. **Exclusion Criteria:** 1. Subject will not tolerate tape adhesive in the area of sensor 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 (e.g., drug or device) wherein he/she has received treatment from an investigational study (drug or device) in the last 2 weeks prior to Visit 1. (Please note participation in an observational study is acceptable.) 4. Subject is female of child-bearing potential and has a pregnancy screening test that is positive. 5. Subject is a sexually active female of child-bearing potential and 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. If subject is 7-80 years of age, subject has a hematocrit (Hct) more than 10% below the lower limit of normal reference range (please note that patients may use prior blood draw from routine care as long as done within 6 months of screening and report of lab placed with subject source documents). 14. Subject has a history of adrenal insufficiency. 15. Subject is a member of the research staff involved with the study.
Study Visit Schedules:	See Section 10.2.1.1 for Subjects 14-80 years Visit Schedule. See Section 11.2.1.1 for Subjects 2-13 years Visit Schedule
Device Deficiencies	**US:** 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 deficiencies. **CHINA:** Subject and investigational center reports of device deficiencies will be collected by electronic Case Report Forms (eCRF) for device troubleshooting and device deficiencies. For additional information, see Section 24.
Starting Rules for Subjects for FST	**<u>Challenges</u>** Subjects may start the challenge when 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, intravenous (IV) or oral hydration may be provided to subject to bring the ketone level down to less than or equal to (≤) 0.6 mmol/L.

	Observation • No specific criteria to start the FST

Stopping Rules for Subjects for FST :	• 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 3 mL/kg of blood volume in a 24-hour period is to be drawn.
	  ○ 4 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 during the study. However, no more than 1 mL/kg of blood volume in a 24-hour period is to be drawn.
	
	Please note that the time of the 24-hour blood draw limit would begin at the start of the first blood draw of an FST and end 24 hours after that. Because patients may have FSTs on two consecutive days (Day 3 and Day 4 or Day 4 and Day 5), please be careful not to exceed the 24-hour blood draw volume maximum. For example, when FSTs occur on two consecutive days it may be preferable to have a hyperglycemic challenge on one day and then a hypoglycemic challenge on the subsequent day, or vice versa, in subjects who may be more likely to reach the maximum 24-hour blood draw volume.
	• Severe hypoglycemia (see severe hypoglycemia definition Section 22.1). Subject may continue in study (including observational FST) but not participate in any more challenges.
	• Glucose greater than (>) 500 mg/dL (27.8 mmol/L) during challenge. Subject may continue in study (including observational FST) but not participate in any more challenges.
	• Ketone greater than or equal (≥) to 3 mmol/L regardless of BG during challenge. Subject may continue in study (including observational FST) but not participate in any more challenges.

Subject Stopping Rules for Study	Refer to Section 19 on "Subject Exit, Withdrawal or Discontinuation ".

Study Stopping Rules for Entire Study	During a hypoglycemic or hyperglycemic challenge, if a subject experiences DKA, severe hypoglycemia with seizures or severe hypoglycemia requiring glucagon, the following actions will be taken: 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. The Clinical Events Committee (CEC) will review the event within 10 days from the time that the sponsor is notified and provide one of the following recommendations: • enrollment and study procedures may continue • stop enrollment, previously enrolled subjects are still allowed to continue in study • stop entire study, withdraw previously enrolled subjects
Repeat Rules for In-Clinic Procedures	• Concurrent failure of both the primary and back-up YSI™* instruments during YSI™* FST. • If subject experiences unresolved IV occlusions during YSI™* FST requiring fingerstick measurements, the in-clinic procedures may be repeated per sponsor recommendation. • If primary sensor dislodges and FST cannot be completed. Subject should replace all sensors and repeat any FSTs not completed.
Statistical Analysis for Datasets, Endpoints and Hypothesis:	*Primary Endpoints – Will Be Performed on Primary and Secondary Datasets* Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 20% mean agreement rate (±20 mg/dL [1.1 mmol/L] when SG less than (<) 80 mg/dL [4.4 mmol/L]), μ, between sensor 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 (GEE) 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, Exchangeable (exch) or Auto-regressive (AR1) or Independence (IND) correlation structure will be used, based on quasi-AIC (QIC). Site effect will be evaluated. If it is not significant (p-value greater than (>) 0.1), site will not be included in the model. The primary endpoint will be independently evaluated for each of the 18 datasets, as described below: **Datasets** **Primary Datasets** Athena Plus algorithm • Dataset 1: Adult (18 – 80 years), arm insertion location and 0 Calibration • Dataset 2: Peds (2 to 17 years), buttock insertion location and 0 Calibration • Dataset 3: Peds (2 to 17 years), arm insertion location and 0 Calibration **Secondary Datasets** Athena algorithm • Dataset 4: Adult (18 – 80 years), arm insertion location and 0 Calibration • Dataset 5: Adult (18 – 80 years), arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration) • Dataset 6: Peds (2 to 17 years), buttock insertion location and 0 Calibration • Dataset 7: Peds (2 to 17 years), buttock insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration) • Dataset 8: Peds (2 to 17 years), arm insertion location and 0 Calibration • Dataset 9: Peds (2 to 17 years), arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration) Athena Plus algorithm

	• Dataset 10: Adult (18 – 80 years), arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration) • Dataset 11: Adult (18 – 80 years), arm insertion location and three Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration) • Dataset 12: Adult (18 – 80 years), arm insertion location and daily Calibrations (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) • Dataset 13: Peds (2 to 17 years), buttock insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration) • Dataset 14: Peds (2 to 17 years), buttock insertion location and three Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration • Dataset 15: Peds (2 to 17 years), buttock insertion location and daily Calibrations (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) • Dataset 16: Peds (2 to 17 years), arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration) • Dataset 17: Peds (2 to 17 years), arm insertion location and three Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration) • Dataset 18: Peds (2 to 17 years), arm insertion location and daily Calibrations (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) *Secondary Endpoints– Will Be Performed on Primary and Secondary Datasets* **National Medical Products Administration (NMPA) CGM for DS5**

	The four secondary endpoints will be evaluated in a fixed sequence of testing for adjustment of multiplicity. The results will be compared to the NMPA CGM criteria for sensor accuracy (SG limit of 50-400 mg/dL [2.8-22.2 mmol/L]): • Sensor values from primary sensor will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 20% agreement rate (±20 mg/dL [1.1 mmol/L] when Reference BG less than or equal to (≤) 80 mg/dL [4.4 mmol/L]) between sensor values and YSI™* plasma glucose values during YSI™* FST days defined as p will be evaluated against the null Hypothesis: H0: $p \leq 60\%$ H1: $p > 60\%$ • Sensor values from primary sensor will be compared to YSI™* plasma glucose values during YSI™* FSTs. A mean rate in Zone A+B of Consensus Error Grid between sensor values and YSI™* plasma glucose values during YSI™* FST days defined as p will be evaluated against the null Hypothesis: H0: $p \leq 90\%$ H1: $p > 90\%$ • Sensor values from primary sensor will be compared to YSI™* plasma glucose values during YSI™* FSTs. A mean rate in Zone A+B of Clarke Error Grid between sensor values and YSI™* plasma glucose values during YSI™* FST days defined as p will be evaluated against the null Hypothesis. H0: $p \leq 90\%$ H1: $p > 90\%$ • Sensor values from primary sensor will be compared to YSI™* plasma glucose values during YSI™* FSTs. A mean absolute relative difference (MARD) between sensor values and YSI™* plasma glucose values during YSI™* FST days defined as μ will be evaluated against the null Hypothesis. H0: $\mu \geq 20\%$ H1: $\mu < 20\%$

- Statistical testing

  One proportion Z test will be used to obtain 97.5% lower confidence limit of the agreement rate, the mean rate in Zone A+B of Consensus Error Grid, and the mean rate in Zone A+B of Clarke Error Grid, which will be tested against corresponding threshold, respectively.

  One sample T test will be used to obtain the 97.5% upper confidence limit of the MARD, which will be tested against corresponding threshold.

The secondary endpoints will be independently evaluated for each of the 12 datasets, as described below:

Datasets

Primary Datasets

Athena Plus algorithm

- Dataset 1: Arm insertion location and 0 Calibration
- Dataset 2: Buttock insertion location and 0 Calibration

Secondary Datasets

Athena algorithm

- Dataset 3: Arm insertion location and 0 Calibration
- Dataset 4: Arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Dataset 5: Buttock insertion location and 0 Calibration
- Dataset 6: Buttock insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)

Athena Plus algorithm

- Dataset 7: Arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Dataset 8: Arm insertion location and three Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Dataset 9: Arm insertion location and daily Calibrations (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) • Dataset 10: Buttock insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration) • Dataset 11: Buttock insertion location and three Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration) • Dataset 12: Buttock insertion location and daily Calibrations (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) **Integrated Continuous Glucose Monitoring (iCGM) for DS5** The 11 secondary endpoints 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 [2.8-22.2 mmol/L]). 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 • Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 20% mean agreement rate between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated.

	• Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 15% mean agreement rate when SG >180 mg/dL (10.0 mmol/L) between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated. • Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 40% mean agreement rate when SG >180 mg/dL (10.0 mmol/L) between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated. • When iCGM values are greater than 180 mg/dL (10.0 mmol/L), the number of corresponding blood glucose values that read less than 70 mg/dL (3.9 mmol/L). • Sensor 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 (3.9 and 10.0 mmol/L) between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated. • Sensor 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 (3.9 and 10.0 mmol/L) between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated. • When iCGM values are less than 70 mg/dL (3.9 mmol/L), the number of corresponding blood glucose values that read above 180 mg/dL (10.0 mmol/L). • Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±15 mg/dL (0.8 mmol/L) mean agreement rate when SG less than (<) 70 mg/dL (3.9 mmol/L) between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated. • Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±40mg/dL (2.2 mmol/L) mean agreement rate when SG less than (<) 70 mg/dL (3.9 mmol/L) between sensor values

	and YSI™* plasma glucose values during YSI™* FST days will be evaluated. The iCGM secondary endpoints will be independently evaluated for each of the 6 datasets as described for primary endpoints on the Athena algorithm, and 12 datasets as described for primary endpoints on the Athena Plus algorithm. *Safety* Descriptive summary will be used to characterize adverse events: • Skin assessment at sensor insertion sites • All adverse events *Device Deficiencies* Descriptive device deficiencies will include all reports of sensor damage, breakage or fracture. *Subject Feedback* Descriptive summary will be used to characterize study survey results.

4. Introduction

4.1. Background

Current methods of continuous glucose monitoring (CGM) include the use of subcutaneous (SQ) glucose sensors worn by the user, which convert glucose from the subject's interstitial fluid into an electronic signal, the strength of which is proportional to the amount of glucose present in the fluid. A CGM sensor is attached to a transmitter, which typically sends interstitial glucose information to a monitor (e.g., the Guardian™ Connect App) as radio frequency (RF) signals. The sensor is composed of a microelectrode with a thin coating of glucose oxidase beneath several layers of biocompatible membrane. 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 the Disposable Sensor (DS5), which is a single-use integrated disposable device, integrating the sensor and transmitter. The DS5 is packaged into the single-use insertion device, minimizing the number of components. The DS5 CGM reduces user burden by minimizing the form factor of the device and simplifying the insertion process.

The portion of the DS5 sensor flex that is implanted beneath the skin is the same design as the Guardian™ Sensor (3) sensor flex. As a result of the integration of sensor and the electronic components, the DS5 will require a new sterilization method, ethylene oxide (EtO) sterilization, as opposed to ebeam sterilization used on Guardian™ Sensor (3). The Zeus Algorithm, which is the algorithm platform developed for Guardian Sensor (3) and housed in GST5G transmitter, has been modified to benefit performance with the DS5. This modified version of Zeus is called the Athena algorithm.

The Athena Plus algorithm is a further refinement of the Athena algorithm. The only design difference between Athena and Athena Plus is the sensor glucose model coefficients resulting from the utilization of YSI intravenous blood glucose reference data to train part of the sensor glucose model instead of SMBG reference data. The expected benefit is to improve overall sensor accuracy.

In this study, sensor data will be collected in a blinded approach, where the DS5 sensor will be used as a recorder for the purposes of data collection. There will not be any real-time receiver used during the study as no mobile application or pump display will be used. At the end of the study, raw sensor data collected by the DS5 sensor will be processed using the Athena and Athena Plus algorithms and various calibration schemes through the post-processing tool. The Athena and Athena Plus algorithms will be implemented in the final code format which will be included in the post-processing analysis tools to support this study. The values used for these calibration schemes will be collected using the commercially available CONTOUR® NEXT LINK 2.4 study meter (**US only**) and CONTOUR® PLUS study meter (**China only**).

Testing on human subjects is necessary to characterize the accuracy of DS5 with the Athena and Athena Plus algorithms. For purposes of this study, subjects will wear the DS5 sensors. Subjects will manage their diabetes independent of the DS5 sensor values. During YSI™*/ Self-Monitoring of Blood Glucose (SMBG) frequent sample testing (FST), venous blood glucose concentrations or SMBG (subjects 2-6 years only) will be measured periodically; these values will be compared to sensor glucose (SG) values 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™* 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. Accuracy data will be calculated based on comparing calibrated glucose sensor values to SMBG during SMBG FST in the 2-6 age group.

4.2. Purpose

The purpose of this study is to demonstrate the performance of the Disposable Sensor (DS5) in subjects age 2 – 80 years, for the span of 170 hours (7 days).

5. Objectives and Endpoints

5.1. Objectives

5.1.1. Primary Objective(s)

The primary objective of the study is to demonstrate the accuracy of Disposable Sensor (DS5) when used over a period of 7 days (i.e., 170 hours) in subjects 2-80 years of age.

5.2. Endpoints

5.2.1. Primary Endpoints– Will Be Performed on Primary and Secondary Datasets

Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 20% mean agreement rate (±20 mg/dL [1.1 mmol/L] when SG less than (<) 80 mg/dL [4.4 mmol/L]), μ, between sensor 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 (GEE) 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, Exchangeable (exch) or Auto-regressive (AR1) or Independence (IND) correlation structure will be used, based on quasi-AIC (QIC).

Site effect will be evaluated. If it is not significant (p-value greater than (>) 0.1), site will not be included in the model.

The primary endpoint will be independently evaluated for each of the 18 datasets, as described below:

Datasets

Primary Datasets

Athena Plus algorithm

- Dataset 1: Adult (18 – 80 years), arm insertion location and 0 Calibration
- Dataset 2: Peds (2 to 17 years), buttock insertion location and 0 Calibration
- Dataset 3: Peds (2 to 17 years), arm insertion location and 0 Calibration

Secondary Datasets

Athena algorithm

- Dataset 4: Adult (18 – 80 years), arm insertion location and 0 Calibration
- Dataset 5: Adult (18 – 80 years), arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Dataset 6: Peds (2 to 17 years), buttock insertion location and 0 Calibration
- Dataset 7: Peds (2 to 17 years), buttock insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Dataset 8: Peds (2 to 17 years), arm insertion location and 0 Calibration
- Dataset 9: Peds (2 to 17 years), arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)

Athena Plus algorithm

- Dataset 10: Adult (18 – 80 years), arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Dataset 11: Adult (18 – 80 years), arm insertion location and three Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Dataset 12: Adult (18 – 80 years), arm insertion location and daily Calibrations (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)
- Dataset 13: Peds (2 to 17 years), buttock insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Dataset 14: Peds (2 to 17 years), buttock insertion location and three Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration

- Dataset 15: Peds (2 to 17 years), buttock insertion location and daily Calibrations (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)
- Dataset 16: Peds (2 to 17 years), arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Dataset 17: Peds (2 to 17 years), arm insertion location and three Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Dataset 18: Peds (2 to 17 years), arm insertion location and daily Calibrations (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)

5.2.2. Secondary Endpoints– Will Be Performed on Primary and Secondary Datasets

5.2.2.1. National Medical Products Administration (NMPA) CGM for DS5

The four secondary endpoints will be evaluated in a fixed sequence of testing for adjustment of multiplicity. The results will be compared to the NMPA CGM criteria for sensor accuracy (SG limit of 50-400 mg/dL [2.8-22.2 mmol/L]):

- Sensor values from primary sensor will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 20% agreement rate (±20 mg/dL [1.1 mmol/L] when Reference BG less than or equal to (≤) 80 mg/dL [4.4 mmol/L]) between sensor values and YSI™* plasma glucose values during YSI™* FST days defined as p will be evaluated against the null Hypothesis:

  H0: $p \leq 60\%$

  H1: $p > 60\%$

- Sensor values from primary sensor will be compared to YSI™* plasma glucose values during YSI™* FSTs. A mean rate in Zone A+B of Consensus Error Grid between sensor values and YSI™* plasma glucose values during YSI™* FST days defined as p will be evaluated against the null Hypothesis:

  H0: $p \leq 90\%$

  H1: $p > 90\%$

- Sensor values from primary sensor will be compared to YSI™* plasma glucose values during YSI™* FSTs. A mean rate in Zone A+B of Clarke Error Grid between sensor values and YSI™* plasma glucose values during YSI™* FST days defined as p will be evaluated against the null Hypothesis.

  H0: $p \leq 90\%$

  H1: $p > 90\%$

- Sensor values from primary sensor will be compared to YSI™* plasma glucose values during YSI™* FSTs. A mean absolute relative difference (MARD) between sensor values and YSI™* plasma glucose values during YSI™* FST days defined as μ will be evaluated against the null Hypothesis.

  H0: $\mu \geq 20\%$

  H1: $\mu < 20\%$

- Statistical testing

  One proportion Z test will be used to obtain 97.5% lower confidence limit of the agreement rate, the mean rate in Zone A+B of Consensus Error Grid, and the mean rate in Zone A+B of Clarke Error Grid, which will be tested against corresponding threshold, respectively.

  One sample T test will be used to obtain the 97.5% upper confidence limit of the MARD, which will be tested against corresponding threshold.

The secondary endpoints will be independently evaluated for each of the 12 datasets, as described below:

Datasets

Primary Datasets

Athena Plus algorithm

- Dataset 1: Arm insertion location and 0 Calibration
- Dataset 2: Buttock insertion location and 0 Calibration

Secondary Datasets

Athena algorithm

- Dataset 3: Arm insertion location and 0 Calibration
- Dataset 4: Arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Dataset 5: Buttock insertion location and 0 Calibration

- Dataset 6: Buttock insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)

Athena Plus algorithm

- Dataset 7: Arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Dataset 8: Arm insertion location and three Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Dataset 9: Arm insertion location and daily Calibrations (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)
- Dataset 10: Buttock insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Dataset 11: Buttock insertion location and three Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Dataset 12: Buttock insertion location and daily Calibrations (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)

5.2.2.2. Integrated Continuous Glucose Monitoring (iCGM) for DS5

The 11 secondary endpoints 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 [2.8-22.2 mmol/L]). 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

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

- Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 15% mean agreement rate when SG >180 mg/dL (10.0 mmol/L) between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated.

- Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 40% mean agreement rate when SG >180 mg/dL (10.0 mmol/L) between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated.

- When iCGM values are greater than 180 mg/dL (10.0 mmol/L), the number of corresponding blood glucose values that read less than 70 mg/dL (3.9 mmol/L).

- Sensor 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 (3.9 and 10.0 mmol/L) between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated.

- Sensor 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 (3.9 and 10.0 mmol/L) between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated.

- When iCGM values are less than 70 mg/dL (3.9 mmol/L), the number of corresponding blood glucose values that read above 180 mg/dL (10.0 mmol/L).

- Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±15 mg/dL (0.8 mmol/L) mean agreement rate when SG less than (<) 70 mg/dL (3.9 mmol/L) between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated.

- Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±40mg/dL (2.2 mmol/L) mean agreement rate when SG less than (<) 70 mg/dL (3.9 mmol/L) between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated.

The iCGM secondary endpoints will be independently evaluated for each of the 6 datasets as described for primary endpoints on the Athena algorithm, and 12 datasets as described for primary endpoints on the Athena Plus algorithm.

5.2.3. Safety

Descriptive summary will be used to characterize adverse events:

- Skin assessment at sensor insertion sites
- All adverse events

5.2.4. Device Deficiencies

Descriptive device deficiencies will include all reports of sensor damage, breakage or fracture.

5.2.5. Subject Feedback

Descriptive summary will be used to characterize study survey results.

6. Study Design

The study is a multi-center, prospective, single-arm study without controls, and random assignments of sensor location, frequent sample testing (FST) day, and FST time.

For the Study Design, refer to:

- Section 10.1 for Subjects 14-80 years Study Design
- Section 11.1 for Subjects 2-13 years Study Design

6.1. Duration

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

6.2. Rationale

The clinical study is being conducted in subjects with type 1 or type 2 diabetes to demonstrate Disposable Sensor (DS5) performance during in-clinic and at home testing. The study will demonstrate the use of DS5 when used over a period of 7 days in subjects 2-80 years of age.

7. Product Description

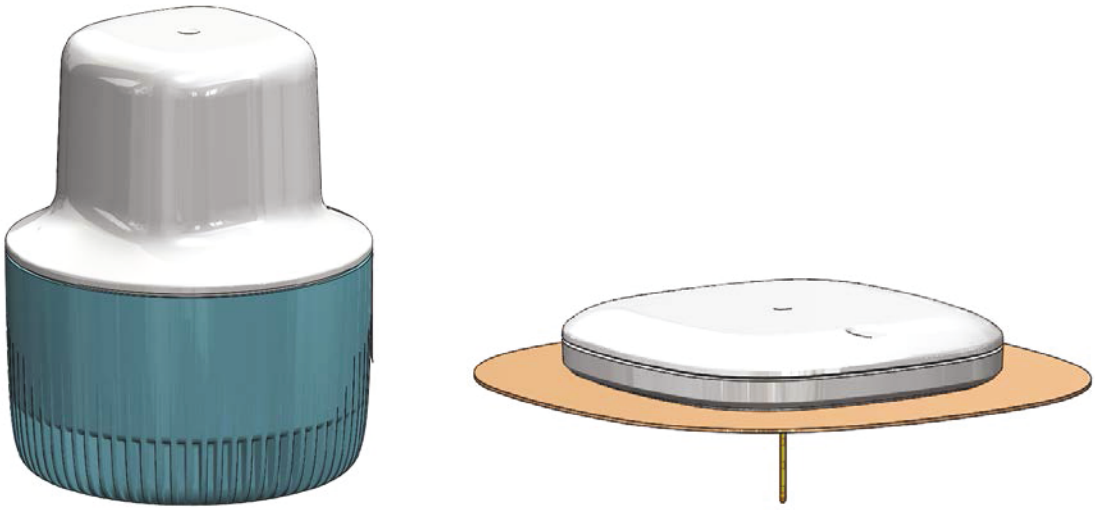
7.1. Investigational Devices

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

7.1.1. Disposable Sensor (DS5)

The Disposable Sensor, referred to as DS5 in this protocol, is a disposable integrated sensor-transmitter platform. The sensor is packaged into a single-use insertion device called the inserter, resulting in an all-in-one device out of the box. The inserter is designed to simplify the insertion process. The sensor flex is inserted subcutaneously with an introducer needle, which is retracted by the inserter upon removal. In this study, the DS5 sensor will function as a recorder and not transmit to a display device.

Figure 1. DS5



7.1.2. Auxiliary Devices

7.1.2.1. Synergy Download Utility Software

The Synergy Download Utility Software (part number M004060C001), version 2.0a, is an investigational personal computer (PC) based program used to download and time sync data from the DS5. DS5 data is downloaded via the Blue Adapter.

7.1.2.2. Blue Bluetooth® Low Energy Adapter

The Blue Bluetooth® Low Energy Adapter is an investigational device in China but non-investigational device in US. It is used in conjunction with the study laptop and the Synergy Download Utility Software to communicate to the DS5 sensors via Bluetooth® for purposes of data download and time syncing.

7.2. Non-Investigational Devices

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

7.2.1. Medtronic CareLink™ Personal Therapy Management Software for Diabetes For Clinical Research

Medtronic CareLink™ Personal Therapy Management Software for Diabetes For Clinical Research is a web-based system, commercially available in US only, 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.

7.2.2. Ascensia CONTOUR® NEXT LINK 2.4 Blood Glucose Meter (US Only)

Ascensia CONTOUR® NEXT LINK 2.4 blood glucose meter, referred to as the CONTOUR® NEXT LINK 2.4 study meter, is a commercially available blood glucose meter in US only and will be provided to subjects for use. The meter determines the subject's capillary blood glucose level using the Ascensia CONTOUR®NEXT Strips, and this value may be post-processed and 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 the CareLink™ Personal For Clinical Research software.

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

7.2.3. Ascensia CONTOUR® PLUS Blood Glucose Meter (China Only)

Ascensia CONTOUR® PLUS blood glucose meter, referred to as the CONTOUR® PLUS study meter, is a commercially available blood glucose meter in China only and will be provided to subjects for use. The meter determines the subject's capillary blood glucose level using the Ascensia CONTOUR® Strips, and this value may be post-processed and used to calibrate the CGM systems.

In this study, the BG measurements from the CONTOUR® PLUS study meter will be uploaded only by the investigational center staff or sponsor designee.

The Ascensia CONTOUR® PLUS blood glucose test strips, lancet devices, USB connector cables, and Ascensia CONTOUR® PLUS Control Solutions will be used in conjunction with the CONTOUR® PLUS study meter.

7.2.4. Abbott™*/MediSense Precision Xtra™* Meter (US Only)

The Abbott™*/Medisense™* Precision Xtra™* meter, referred to as Precision Xtra™* ketone meter, is commercially available blood glucose meter in US only. It 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 File 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 a preferred patient method of testing over urine testing.

7.2.5. Abbott™* FreeStyle Optium Neo Blood Glucose & Ketone Monitoring System (China Only)

The Abbott™* FreeStyle Optium Neo Blood Glucose& Ketone Monitoring System, referred to as FreeStyle Optium Neo ketone meter throughout this protocol, is commercially available blood glucose meter in China only. It 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 File 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 the preferred patient method of testing over urine testing.

7.3. Anticipated Device Changes

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

7.4. Product Accountability

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

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

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

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices. Additional details regarding device accountability and device disposition requirements are provided in Table 1 and Table 2.

China only: All study devices will be labeled as per local regulations in China. Investigational devices will be labeled "Clinical trial use only" in accordance with NMPA Order No. 25.

Table 1. US Device Accountability Requirements

Device	Record on Site Received eCRF	Record Disbursement, Returned or Not Returned from Subject on Subject Device Identification eCRF	Subject Return Device to Investigational Center	Record Returned or Not Returned to Sponsor on Site Returned eCRF	Site Return Device to Sponsor at Conclusion of Study
DS5 (MMT-5100)	Yes	Yes	Yes	Yes	Return used and unused device (all components) to sponsor
CONTOUR® NEXT LINK 2.4 study meter (MMT-1152/1352)	Yes	Yes	No	Yes	Return unused to sponsor

Table 2. China Device Accountability Requirements

Device	Record on Site Received eCRF	Record Disbursement, Returned or Not Returned from Subject on Subject Device Identification eCRF	Subject Return Device to Investigational Center	Record Returned or Not Returned to Sponsor on Site Returned eCRF	Site Return Device to Sponsor at Conclusion of Study
DS5 (MMT-5100)	Yes	Yes	Yes	Yes	Return unused device to sponsor Investigational center will destroy used device
Blue Bluetooth® Low Energy Adapter (part number ACC-1003911)	Yes	N/A	N/A	Yes	Yes
CONTOUR® PLUS study meter (Model number 7600P)	Yes	Yes	Yes	Yes	Yes

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.

7.4.1. 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 Address
    - Reference Number
    - Device Type
    - Quantity
    - Quantity per package
    - Lot number (where applicable)
    - Serial number (where applicable)
- Ensure that devices and supplies received have not reached or exceeded their expiration date
- Sign and date the packing slips/invoices, noting any discrepancies, and file in appropriate study binder
- Notify the study monitor of any discrepancies
- Enter or acknowledge the study device information on the appropriate electronic Case Report Forms (eCRF) in the study database, if applicable as described in Table 1 US Device Accountability Requirements and Table 2 China Device Accountability Requirements.

7.4.2. 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.

7.4.3. Disbursement of Study Devices

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

- Date of disbursement
- Subject ID
- Lot number(s)

- Serial Number
- Device Type
- Amount dispensed

7.4.4. 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 US Device Accountability Requirements and Table 2 China Device Accountability Requirements and store them in a secure environment. If containers/units/devices are missing, the reasons should be documented in the applicable eCRF and/or source document. If discrepancies between the amounts used by subjects and the amounts expected to be returned exist, the reasons should be documented in the applicable eCRF and/or source document.

Requirements for return of devices by subjects to the investigational center and return of device by the investigational center to the sponsor are listed in Table 1 US Device Accountability Requirements and Table 2 China Device Accountability Requirements. The devices that are being returned to the investigational center may be returned to the sponsor as subjects complete the study, at the end of study (EOS) or upon sponsor request.

Other consumable devices (i.e., alcohol wipes, CONTOUR® NEXT LINK 2.4 (**US only**)/CONTOUR® PLUS (**China only**) study meter supplies, tape, etc.), ketone meters and accessories shipped in kits, supplies or materials may be returned to the sponsor, they may be retained by investigational centers for educational purposes only, or they may be disposed of properly by the investigational center staff. **US only:** The used commercial study meter can be retained by the subject.

Disposable devices and supplies that have been ***used*** by a subject (except the DS5) will be disposed properly by the subject or the investigational center staff during the conduct of the study.

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

8. Study Site Requirements

8.1. Study Site Activation

During the activation process (prior to subject enrollment), Medtronic will train investigational center staff. If new members join the study investigational center team, they will receive training on the applicable study requirements relevant to their role before contributing to the study.
Prior to performing study related activities, all regulatory requirements shall be fulfilled.

9. Selection of Subjects

9.1. Study Population

US:

A total of up to 300 previously-diagnosed type 1 or type 2 diabetes subjects in the U.S. will be enrolled in order to have 200 subjects complete study.

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

Number of subjects to complete study:

- N= 100 subjects 18-80 years old
- N= 100 subjects 2-17 years old

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

China:

A total of up to 76 previously-diagnosed type 1 or type 2 diabetes subjects in China will be enrolled in order to have 60 subjects complete study.

Up to 5 investigational centers in China will be used during the study.

Number of subjects to complete study:

- N= 40 subjects 18-80 years old
- N= 20 subjects 2-17 years old

A minimum of 6 subjects and a maximum of 24 subjects is expected to be enrolled at each investigational center.

9.2. Subject Enrollment

Subjects will be considered enrolled in the study upon signing the Informed Consent Form (ICF) and assent form (if applicable). A subject will be assigned a unique study subject identification (ID) via the eCRF, which is a 9-digit code (330XXXXXX). The first three numbers refer to the clinical investigation plan (CIP) number (330), 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., 330002001 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.

9.3. Inclusion Criteria

1. Individual is 2 - 80 years of age at time of enrollment.
2. Subject has a clinical diagnosis of type 1 or type 2 diabetes:
    a. If subject is 14-80 years of age, subject has a clinical diagnosis of type 1 or type 2 diabetes for a minimum of 6 months duration as determined via medical record/ source documentation by an individual qualified to make a medical diagnosis.
    b. If subject is 2-13 years of age, subject has a clinical diagnosis of type 1 or type 2 diabetes as determined via medical record/ source documentation by an individual qualified to make a medical diagnosis.
3. If subject is participating in YSI™* FST , subject has 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 factor(s). Subjects without ratios may participate under observation only.

9.4. Exclusion Criteria

1. Subject will not tolerate tape adhesive in the area of sensor 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 (e.g., drug or device) wherein he/she has received treatment from an investigational study (drug or device) in the last 2 weeks prior to Visit 1. (Please note participation in an observational study is acceptable.)
4. Subject is female of child-bearing potential and result of pregnancy screening test is positive.
5. Subject is female of child-bearing potential and who is sexually active should be excluded if she is not using a form of contraception deemed reliable by investigator.

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. If subject is 7-80 years of age, subject has a hematocrit (Hct) more than 10% below the lower limit of normal reference range (please note that patients may use prior blood draw from routine care as long as done within 6 months of screening and report of lab placed with subject source documents).
14. Subject has a history of adrenal insufficiency.
15. Subject is a member of the research staff involved with the study.

9.5. Subject Consent

US only:
Informed Consent and assent will be obtained in accordance with the Code of Federal Regulations (CFR) Title 21, Part 50. Prior to entry into the study the California Experimental Subject's Bill of Rights (if applicable), the IRB and Medtronic-approved ICF and assent form, and an Authorization Form required by the Health Insurance Portability and Accountability Act (HIPAA) Authorization Form will be presented to each subject and their parent, guardian, or legally authorized representative (as applicable) to review and sign as applicable.

China only:
Informed consent and assent will be obtained in accordance with the NMPA Order No. 25. Prior to entry into the study, the EC and Medtronic-approved ICF and assent form will be presented to each subject and their parent, guardian, or legally authorized representative (as applicable) to review and sign as applicable.

All regions:
The subject and their parent, guardian, or legally authorized representative will be offered the opportunity to review these documents away from the investigational center.

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

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

US only:
Subjects will complete California Experimental Subject's Bill of Rights (if applicable), the HIPAA Form, and the ICF and assent form.

China only:
The ICF and assent form will include a dated signature of the subject or their parent, guardian, or legally authorized representative acknowledging their participation in the study is voluntary. In addition, it will include a dated signature of the principal investigator or an authorized designee responsible for conducting the informed consent process.

All regions:
The consenting process must be documented in the subject's source documents. The subject and their parent, guardian, or legally authorized representative will receive copies of the fully executed documents. A subject's participation in study procedures cannot begin before the consent process has been properly executed.

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

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

If the ICF and assent form is amended during the course of the study, the IRB/EC will determine

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

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

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

- Failure to obtain informed consent and assent from subject and their parent, guardian, or legally authorized representative.
- Failure to obtain informed consent and assent prior to performing one or more study procedures.

- Failure to maintain ICFs and assent forms on file for all subjects who have provided informed consent and assent.
- Use of an ICF and assent form that has not received approval from the IRB/EC.
- Use of an incorrect version of the ICF and assent form.

9.6. FST Timing

Subjects will be assigned to FST Timing (random assignment) according to their age:

FST Timing for 14-80 years old:

Group	Sensor Wear Day	Timing of FST 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 hours (±6), 138-146 hours (±6)

FST Timing for 7-13 years old:

Group	Sensor Wear Day	Timing of FST 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)

Group	Sensor Wear Day	Timing of FST from Sensor Insertion T=0
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 FST 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)

The following is the FST schedule for the subjects according to their age:

Subjects 14 - 80 years

- 4 x 8 hours FST
- Challenges
    - Two Hyperglycemic Challenges

- Two Hypoglycemic Challenges
- If challenges are performed, the following are recommended:
    - **US only:** Investigator discretion may be used in selecting which challenge is to be performed for each FST as long as 2 hyperglycemic challenges and 2 hypoglycemic challenges are met.
    - **China only**: Whether performing recommended challenges or not will be based on Ethics Committee (EC) suggestion and investigator discretion. Absence of challenges during FST will not be considered a protocol deviation.

Subjects 7 - 13 years

- 2 x 6 hours FST

Subjects 2 - 6 years

- 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.

9.7. Treatment Assignment

Investigational centers will receive random assignment (sensor location) from Medtronic.

Subjects will be assigned to sensor location (random assignment) according to their age:

- **Subjects 14 - 80 years**
    - 14-17 years
        - Arm/Arm/Buttock
        - Buttock/Buttock/Arm
    - 18-80 years
        - Arm/Arm
- **Subjects 7 - 13 years**
    - Arm/Arm/Buttock
    - Buttock/Buttock/Arm

- **Subjects 2 - 6 years**
  - Arm/Buttock
  - Subjects 2-6 years old may have their parent, guardian, or legally authorized representative choose the area for their sensor placement.

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

This section is presented as below:

- **Section 10.1:** Study Design
- **Section 10.2:** Study Procedures (Subjects 14-80 years)

10.1. Study Design

The study is a multi-center, prospective, single-arm study without controls, and random assignments of sensor location, frequent sample testing (FST) day, and FST time.

Subjects will wear sensors in the following configurations and follow the FST schedule:

- Sensor Location
  - 14-17 years
    - Arm/Arm/Buttock
    - Buttock/Buttock/Arm
  - 18-80 years
    - Arm/Arm
- FST Schedule
  - 4 x 8 hours FST
  - Challenges
    - Two Hyperglycemic Challenges
    - Two Hypoglycemic Challenges
    - If challenges are performed, the following are recommended:

- **US only:** Investigator discretion may be used in selecting which challenge is to be performed for each FST as long as 2 hyperglycemic challenges and 2 hypoglycemic challenges are met.
- **China only**: Whether performing recommended challenges or not will be based on Ethics Committee (EC) suggestion and investigator discretion. Absence of challenges during FST will not be considered a protocol deviation.

Subjects will be assigned to FST Timing (random assignment) according to their age:

FST Timing for 14-80 years old:

Group	Sensor Wear Day	Timing of FST 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 hours (±6), 138-146 hours (±6)

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.

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.

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 Stopping Rules for Subjects for FST (section 20.1.1).

For device troubleshooting and device complaints (See Section 24):

- **US only:** Subjects and/or Sites are to call the 24-Hour Technical Support (TS)
- **China only:** Subjects are to call Investigational Center staff

Hypoglycemic and Hyperglycemic Challenges:

US only: During the YSI™* FST, subjects with a known insulin sensitivity factor and insulin carbohydrate ratio will undergo hypoglycemic and hyperglycemic challenges.

China only: Whether performing recommended challenges or not will be based on EC suggestion and investigator discretion. Absence of challenges during FST will not be considered a protocol deviation.

10.2. Study Procedures (Subjects 14-80 years)

10.2.1. Schedule of Events

10.2.1.1. Visit Schedule & Scheduled Follow-up Visit Windows

Each subject's participation will include the following visits (depending on randomly assigned group). The intent is for subjects to wear the study sensors and perform 4 YSI™* FSTs.

One rescheduled visit can occur during the study period if primary sensors dislodges and new sensors must be re-inserted (See Replacement Sensors Sections 13 and 14).

If subject exits the study early (i.e. before their last scheduled visit), all requirements that apply to the final visit should be completed if possible.

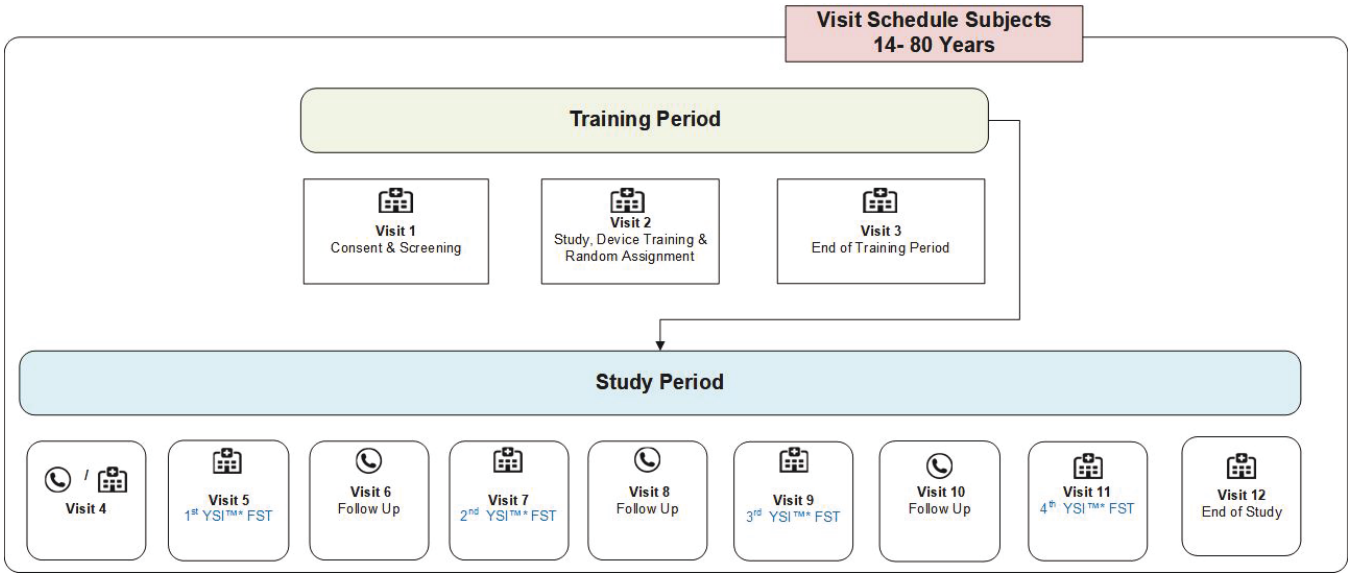
Screening and Training Period: To be completed in 30 days (Visit 1 to Visit 3)

- Visit 1: Consent and Screening
- Visit 2: Study, Device Training and Random Assignment
    - Confirm eligibility. 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 - Investigational center Visit

Start of Study Period: To be completed in 60 days from Visit 4 to Visit 12

- 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 sensor 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 Period 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)
  - Subjects who have new or unresolved adverse event(s) from device-related skin reactions should schedule a follow up visit 3-7 days after Visit 12.
- Unscheduled Visit: For AE Follow Up, if Required (3-7 days after Visit 12)
  - Assess for adverse events, including adverse event from device-related skin reaction ongoing at Visit 12.
  - Update adverse event form or fill in new adverse event form, as applicable.

Figure 2. Visit Schedule Subjects 14-80 years



10.2.1.2. Visit 1: Consent and Screening

Overview General

Investigational center staff will:

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

    Note: Body mass index (BMI) will be calculated automatically in the study database, based on height and weight measurements entered.
  - Concomitant medications (Screening Only)
  - CGM experience
  - Pump experience
  - Total Daily Dose (TDD), if applicable
  - Daily basal amount, if applicable
  - Time of day basal/long acting insulin is delivered, if applicable
  - Insulin carbohydrate ratio and insulin sensitivity factor for subject's insulin requirement, if applicable
- Complete required screening tests, if all eligibility criteria are met:
  - **US only:** Perform urine test for pregnancy, female subjects of child-bearing age or capability
  - Obtain blood sample:
    - Pregnancy **(China only):** Perform blood test for pregnancy, female subjects of child-bearing age or capability. Send to investigational center's lab for required screening tests.
    - Hct

- If patient has prior Hct from routine care done within 6 months of enrollment and the report of lab placed with subject source documents, then no blood test needs to be done.
- **Note:** For all out of range lab results, a single re-test is permitted
- **US only:** Send to Central Laboratory or local lab for required screening tests. There is no point of care (POC) testing for Hct.
- **China only:** Send to investigational center's lab for required screening tests.

- Obtain blood sample for Glycosylated hemoglobin (HbA1c) (not an eligibility criteria)
  - **US only:** Send to Central Laboratory
  - **China only:** Send to investigational's center lab
- Per Investigator's discretion, subjects may exercise . Subjects will be asked to exercise for a minimum of 30 minutes a day during the YSI™* FSTs.
- Enter data into electronic Case Report Forms (eCRF)s as appropriate
- Schedule next visit date and time

The study is open to all individuals who meet the eligibility criteria of the study. The investigational center will be responsible for determining adequate source documents to verify subject eligibility. Subjects who do not meet the eligibility requirements for participation in the study will be entered into the database as screen failures. Applicable eCRF(s) will be completed for all subjects and their parent, guardian, or legally authorized representative who signed an ICF and assent form (if applicable), 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.

10.2.1.3. Visit 2: Study and Device Training

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 CONTOUR® NEXT LINK 2.4 study meters (**US only**)/ CONTOUR® PLUS study meters (**China only**) need to be synchronized with the time on the laptop at the investigational center. Subjects will be instructed not to change the time in these devices. Subjects will be provided a CONTOUR® NEXT LINK 2.4 study

meter (**US only**)/ CONTOUR® PLUS study meter (**China only**) to be used to perform fingerstick (capillary SMBG).

US only: The investigational center staff will also have to create an account for the subject in CareLink™ Personal For Clinical Research software (see Investigator Site File for details).

Overview of general study procedures

Investigational center staff will:

- Confirm eligibility
- Randomly assign eligible subjects
- Synchronize time of the CONTOUR® NEXT LINK 2.4 study meter(**US only**)/ CONTOUR® PLUS study meters (**China only)** with the time on the investigational center's laptop
- **US only:** Create an account for the study subjects in CareLink™ Personal For Clinical Research software
- Train subjects on study devices
- Confirm sensor locations according to subject's age (see Sensor Wear Location Table)
- Enter data into eCRFs as appropriate
- Schedule the next visit date and time

Overview of study devices and supplies

Investigational center staff will disburse the following to subjects:

- DS5(s)
- CONTOUR® NEXT LINK 2.4 study meter(s) (**US only**)/ CONTOUR® PLUS study meters (**China only)**
- BG supplies (e.g. control solution, batteries, meter strips, and lancets)
- Other study materials (e.g., study reference card, device user guides, and training materials)
- Other study supplies (e.g., DS5 return materials and alcohol swabs)

Investigational center staff will record and track all study devices outlined in the device accountability section (see Section 7.4) on the appropriate eCRF.

Overview of training and instructions

Investigational center staff will:

- Train each subject on sensor insertions, removal, study devices, and study procedures
    - Subject will be instructed to wash hands thoroughly with soap and water.
    - Subject will be instructed to clean the insertion site with alcohol and let the insertion site air dry prior to sensor insertion.
- Instruct subjects that additional OTC tape(s) (e.g. Hypafix™* tape, etc.) may be used if needed
- Train subjects on use of CONTOUR® NEXT LINK 2.4 study meter(**US only**)/ CONTOUR® PLUS study meter (**China only)**
    - 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 (**US only**)/ CONTOUR® PLUS study meter (**China only)** during the course of the study to perform study defined SMBG measurements
    - Subjects will be instructed to perform a quality control (QC) testing when a new vial of test strips is used
- Perform applicable QC testing (CONTOUR® NEXT LINK 2.4 study meter [**US only**]/ CONTOUR® PLUS study meter [**China only]**). Shake control solution bottle well prior to use.
- Instruct subjects to insert sensors in the locations according to their age. 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:
    - 14-17 years
        - Arm/Arm/Buttock
        - Buttock/Buttock/Arm
    - 18-80 years
        - Arm/Arm

- Synchronize time on each Disposable Sensor (DS5) worn in-clinic by the subject using the Synergy Download Utility
- 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 after insertion on Day 1 and also one approximately at the same time every day as time of the insertion
- Have subject perform the first SMBG at the investigational center or a follow up call will be required to confirm this
- Instruct subjects to wear the devices up to 7-day training period. Instruct subjects to remove the sensors (at end of training period or at investigational center) after 7 days (T= 176-188 hours).
- Instruct subjects during training period that they should spend time bending and twisting even if they don't undergo aerobic exercise.
- Instruct subjects on Disposable Sensor (including the inserter component) 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 24 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 for technical issues and support:
    - **US only:** Subjects and/or Sites are to call the 24-Hour Technical Support (TS)
    - **China only:** Subjects are to call Investigational Center staff
- Remind subjects to bring in the CONTOUR® NEXT LINK 2.4 study meter (**US only**)/ CONTOUR® PLUS study meter (**China only)** 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 22 and 24 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 perform random assignment and provide the subjects with study device training that would be comparable to training provided to patients in the actual clinical use. The subjects will receive training on the study requirements before completing the training visit. All subjects will be trained on the device(s) to be used in the study prior to leaving the investigational center. Investigational center staff will train the subjects on the appropriate use of the study devices. Each subject will receive training on sensor

insertion and removal, other study devices, and study procedures. This training includes SMBG. The training is expected to last 15 minutes to 2 hours in duration on average, depending on the subject's experience. Training materials provided to the subject may include instructions for use (IFU)s, 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.

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 of assignment

Subjects will be assigned to FST Timing (random assignment) according to their age:

FST Timing for 14-80 years old:

Group	Sensor Wear Day	Timing of FST 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 hours (±6), 138-146 hours (±6)

The following is the FST schedule for the subjects according to their age:

The following is the FST schedule for the subjects according to their age:

Subjects 14 - 80 years

- 4 x 8 hours FST
- Challenges
  - Two Hyperglycemic Challenges
  - Two Hypoglycemic Challenges
  - If challenges are performed, the following are recommended:
    - **US only:** Investigator discretion may be used in selecting which challenge is to be performed for each FST as long as 2 hyperglycemic challenges and 2 hypoglycemic challenges are met.
    - **China only**: Whether performing recommended challenges or not will be based on Ethics Committee (EC) suggestion and investigator discretion. Absence of challenges during FST will not be considered a protocol deviation.

Subjects will be assigned to sensor location (random assignment) according to their age:

- 14-17 years
  - Arm/Arm/Buttock
  - Buttock/Buttock/Arm
- 18-80 years
  - Arm/Arm

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

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

SMBG Requirements

- On Day 1, a minimum of 4 fingerstick glucose readings (SMBG) at the times below will be requested with target of 7 total fingerstick glucose readings:
    - Time = 0 hour
        - Sensor insertions will be performed
        - The 0 hour represents the time after the last sensor has been inserted
    - Time = 2 hours
        - T = 2 hours after the last sensor has been inserted
    - Time = 10 hours
        - T = 10 hours after the last sensor has been inserted
    - Time = 24 hours
        - T = 24 hours after the last sensor has been inserted
- On Day 2-7, a minimum of 4 fingerstick glucose readings (SMBG) per day will be requested with target of 7 fingerstick glucose readings (with one of them occurring at the same time of day as initial sensor insertion [±1 hour]). For example, if sensor was inserted at 8 am, then each day after that one SMBG will done at this same time.
- One SMBG should be taken upon arrival for each FST
- At the end of each FST, take one SMBG.
- 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.

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

Overview of general study procedures
Investigational center staff will:

- Instruct subject to self-remove the sensors that he/she is still wearing at this visit
- Perform a Skin Assessment on the area of each of the sensor insertion sites and document in subject source and complete Skin Assessment eCRFs for each inserted sensor.
- **US only**:
    - Upload CONTOUR® NEXT LINK 2.4 study meter into CareLink™ Personal For Clinical Research software
    - Upload Disposable Sensor using Synergy Download Utility Software (following instructions provided)
- **China only:**
    - Download CONTOUR® PLUS study meter and provide to sponsor
    - Upload Disposable Sensor using Synergy Download Utility Software (following instructions provided)
- Determine if additional training is needed (e.g., if the subject is not following finger-stick monitoring requirements). If additional training is required, subjects will be retrained using training materials supplied during training visit 2 and research staff may focus on specific areas of opportunity for improvement.
- Enter data into the eCRFs as appropriate
- Review requirements of next study visit with subjects
- Disburse Disposable Sensor to subjects who will insert at home
- Schedule the next visit dates and times (including the first YSI™* FST)
- The subject will be instructed to insert sensors. Note: the subject will use the CONTOUR® NEXT LINK 2.4 study meter (**US only**)/ CONTOUR® PLUS study meter (**China only)** provided by the Investigational center staff.
- Remind subjects on Disposable Sensor(s) (including the inserter component) return (see Table 1 US Device Accountability Requirements and Table 2 China Device Accountability Requirements)

Overview of study devices and supplies

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

- DS5(s)
- BG supplies (e.g. control solution, batteries, meter strips, and lancets)
- Other study supplies (e.g. DS5 return materials and alcohol swabs)

Investigational center staff will record and track all study devices outlined in the device accountability section (see Section 7.4) on the appropriate eCRF.

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 Section 10.1.

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.

10.2.1.5. Visit 4: Phone Call or Optional Office Visit

The purpose of visit 4 (phone/clinic visit) is to verify that the sensor 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 the sensors at the appropriate time and sensor location. Once the study period sensors are inserted, the subject should follow the YSI™* FST Timing and SMBG requirements (Section 10.2.1.3.1).

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. Also, subjects will be reminded on Disposable Sensor (including the inserter component) return.

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

The YSI™* FST is an 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.

10.2.1.6.1. Procedure Guidelines For Subjects Undergoing Observation Only (Visit 5, 7, 9, and 11)

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. There are no specific criteria to start the FST.

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 at home and in clinic. Subjects should bring all medications they are taking with them to the clinic, even if they are not scheduled to take that medication that day.

Subjects may exercise during the observation period if their glucose is between 100-300 mg/dL (5-6-16.7 mmol/L).

Insulin (if applicable), medication (if applicable), diet, diabetes monitoring/management and ketone monitoring/management may be performed per Investigator discretion.

10.2.1.6.2. Prior to Arrival at the Clinic (Visit 5, 7, 9, and 11) for the Subject Undergoing Challenges

For subjects who undergo hyperglycemic or hypoglycemic challenges, the investigator will provide recommendations for ***the night before*** and ***during*** the YSI™* FST visit in the following areas:

- Food intake
- Medication management
- Glucose target

China only: Whether performing recommended challenges or not will be based on EC suggestion and investigator discretion. This section is only applicable if subject undergoes challenge(s).

10.2.1.6.3. Upon Arrival to the Clinic (Visit 5, 7, 9, and 11) for the Subject Undergoing Challenges

Ketones should be in the following range *for those who undergo hypoglycemic or hyperglycemic challenge* as described below:

Subjects may start the challenge when 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, intravenous (IV) or oral hydration may be provided to subject to bring the ketone level down to less than or equal to (≤) 0.6 mmol/L.

Site should also have available during hypoglycemic and hyperglycemic challenge the following:

- IV catheter for IV access of subject
- At least 1000 ml of normal saline for IV fluid hydration
- At least 1000 ml of 5% dextrose for IV use
- 1 mg of Glucagon
- Two 50 ml Ampules of 50% dextrose
- Regular insulin for IV administration

China only: Whether performing recommended challenges or not will be based on EC suggestion and investigator discretion. This section is only applicable if subject undergoes challenge(s).

10.2.1.6.4. In-Clinic Procedures

Overview of general study procedures

Investigational center staff will:

- Set up the YSI™* instruments (see Investigator Site File for details)
- Perform applicable QC testing:
    - **US only:**CONTOUR® NEXT LINK 2.4 study meter and Precision Xtra™* ketone meter
    - **China only:** CONTOUR® PLUS study meter and FreeStyle Optium Neo ketone meter
- Synchronize YSI™* devices at the investigational center with the designated study clock

- Verify that sensor insertion was performed at the appropriate insertion time, insertion location and SMBG reminders.
- Synchronize time on each Disposable Sensor (DS5) worn in-clinic and at home by the subject using the Synergy Download Utility (Visit 5 only)
- Conduct SMBG testing upon subject arrival
- Refer to Section 10.2.1.3.1 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 factor and insulin carbohydrate ratio.
    - **China only:** Whether performing recommended challenges or not will be based on EC suggestion and investigator discretion.
- Following completion of each YSI™* FST:
    - **US only**: Upload CONTOUR® NEXT LINK 2.4 study meter into CareLink™ Personal For Clinical Research software
    - **China only:** Download CONTOUR® PLUS study meter and provide to sponsor
- 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 sensors past the end of this visit to achieve sensor wear for T=176-188 hours
- Review requirements of next study visit (phone or EOS visit) with subjects
- Review the next visit date and time for YSI™* FST **(Visits 5, 7 and 9 only)**
- Enter data into eCRFs 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 and infusion sets that might be needed during the YSI™* FST visit.
- Remind subjects on Disposable Sensor(s) (including the inserter component) return (see Table 1 US Device Accountability Requirements and Table 2 China Device Accountability Requirements)

Overview of study devices and supplies

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

- DS5(s)
- BG supplies (e.g., batteries, meter strips, and lancets)

- Other study supplies (e.g., alcohol swabs)

Investigational center staff will record and track all study devices outlined in device accountability section (see Section 7.4) on the appropriate eCRF.

Overview training and instructions

Investigational center staff will:

- Remind subjects to perform fingersticks (capillary SMBG)
- Remind subjects to contact for technical issues and support:
  - **US only:** Subjects and/or Sites are to call the 24-Hour Technical Support (TS)
  - **China only:** Subjects are to call Investigational Center staff
- Fingerstick will be performed at home as stated in Section 10.2.1.3.1.

10.2.1.6.4.1 Blood Glucose Monitoring During the YSI™* FST

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

- less than (<) 75 mg/dL (4.2 mmol/L); every 5 minutes (window of 3-8 minutes)
- greater than or equal to (≥) 75 mg/dL (4.2 mmol/L); every 15 minutes (window of 7-23 minutes)

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

In the event that YSI™* blood glucose values are not immediately available, for safety purposes, the investigational center may use the subject's CONTOUR® NEXT LINK 2.4 study meter (**US only**)/ CONTOUR® PLUS study meter (**China only)** 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.

10.2.1.6.4.3 Ketone Monitoring

During Challenge:

- Glucose greater than (>) 300 mg/dL (16.7 mmol/L) every 60 minutes
- Nausea, abdominal pain or vomiting regardless of glucose level

Note: Should be performed with fingerstick only.

Ketone management should be per investigator discretion. This may include oral or IV hydration and insulin management.

10.2.1.6.4.4 Procedure Guidelines For Subjects Undergoing Hypoglycemic and Hyperglycemic Challenges

Subject Criteria

- Only subjects with a known insulin sensitivity factor 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 and can be refined and fine-tuned by investigator
- Subjects without a known insulin sensitivity factor 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:

The goal for the challenge is to maintain the subject within a hypoglycemic range of <70 mg/dL (3.9 mmol/L) for approximately 2 hours and within those 2 hours, target 15 minutes in the 50-60 mg/dL (2.8-3.3 mmol/L) range.

Investigator may manage insulin, medication, diabetes management, meal, activity including exercise and PO intake as per his/her discretion to achieve these targets.

After challenge completion, observation target glucose should be 100-150 mg/dL (5.6 -8.3 mmol/L). Subject may eat and take insulin per Investigator discretion.

Blood glucose range and duration targets

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.

Hypoglycemic Treatment Guidelines

The following are specific hypoglycemic treatment guidelines during the challenges:

Subjects who have glucose less than (<) 70 mg/dL (3.9 mmol/L) and accompanied by seizure, loss of consciousness, or altered mental status (i.e., uncooperative with food or liquid orally so that subject is unable to take carbohydrate to raise glucose) will no longer be allowed to continue in challenges (stop the challenge and DO NOT continue with any future challenges) and the following should be considered:

- 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 (5.6 mmol/L). 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 origin] 1 mg, with 1 mL of diluting solution administered intramuscular): may be given if Dextrose was not able to be given due to IV access or per investigator discretion.

HYPERGLYCEMIC CHALLENGE:

The goal for the challenge is to maintain the subject within a hyperglycemic range of 180 mg/dL (10.0 mmol/L) to 400 mg/dL (22.2 mmol/L) for approximately 2.5 hours and within those 2.5 hours, target 30 minutes in the 350-400 mg/dL (19.4-22.2 mmol/L) range.

Investigator may manage insulin, medication, diabetes management, meal, activity including exercise and PO intake as per his/her discretion to achieve these targets.

After challenge completion, observation target glucose should be 100-150 mg/dL (5.6 -8.3 mmol/L). Subject may eat and take insulin per Investigator discretion.

Blood glucose range and duration targets

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.

Hyperglycemic Treatment Guidelines

The following are specific hyperglycemic treatment guidelines during the challenges:

- Subjects who have all of the following criteria:
    - Glucose greater than (>) 250 mg/dL or greater than (>) 13.9 mmol/L
    - Ketone levels above 1.5 mmol/L
    - Symptoms of nausea, vomiting and/or abdominal pain
- Subject will no longer be allowed to continue in challenges (stop the challenge and DO NOT continue with any future challenges) and the following should be considered:
    - Insulin administration per investigator discretion
    - 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
        - 14-21 years: rate for IV fluid hydration is 10 cc/kg given over 2 hours

Subject Stopping Criteria for Hypoglycemic and Hyperglycemic Challenges

The subject will stop the challenge if the subject develops chest pain, shortness of breath or any other symptoms that could represent a safety concern as per investigator discretion.

China only: Whether performing recommended challenges or not will be based on EC suggestion and investigator discretion. This section is only applicable if subject undergoes challenge(s).

10.2.1.6.4.5 Exercise

- Only subjects who have been previously established for participation in exercise during Visit 1 can participate in the exercise activities during YSI™* FST.
- Subjects may exercise during FST if their glucose is between 100-300 mg/dL (5.6-16.7 mmol/L).
- Ketone testing should be per investigator discretion
- Subjects who exercise will be asked to exercise for at least 30 minutes during YSI™* FST
- Procedures:
    - Exercise will consist of treadmill or stationary bicycle. Other forms of exercise may be allowed with sponsor permission.
    - Exercise will be terminated if subjects develop chest pain, shortness of breath, dizziness or any other symptom as per investigator discretion.

10.2.1.6.4.6 Rescue Therapy

Rescue therapy is based on investigator discretion. The following are required to be available during challenges:

- Treatment with Glucagon and ampules of dextrose for hypoglycemia are required to be available.
- Treatment with IV saline hydration and regular insulin for IV for hyperglycemia are required to be available.
- IV catheter for IV access is required during challenges/FST (during Challenge procedures, if applicable).

10.2.1.6.4.7 End of FST and Discharge

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

- Investigator center staff will perform the following prior to or at discharge:
- For both hypoglycemic and hyperglycemic challenges, two blood glucose measurements will be performed at least 30 minutes apart. These measurements should be within a safe glycemic range of 70 mg/dL (3.9 mmol/L) – 200 mg/dL (11.1 mmol/L) prior to discharge. These two blood glucose measurements may include the last FST blood glucose measurements. However, if

criteria is not met with FST blood glucose measurements, additional fingerstick glucose measurement(s) may be performed with study meter.
- For hypoglycemic challenges, a snack should be provided to subject at discharge.
- For hypoglycemic challenges, subjects will be reminded at discharge to check SMBG prior to going to bed on the night of the challenge.
- 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.

10.2.1.7. 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. Also, subjects will be reminded on Disposable Sensor (including the inserter component) return. If subject is unable to be reached, then this should be documented and at least one second attempt to reach subject be performed.

10.2.1.8. Visit 12: End of Study Period

- Visit 11 and Visit 12 may be combined if 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 sensor(s), instruct subjects to remove them
- **US only:**
    - Upload CONTOUR®NEXT LINK 2.4 study meter into CareLink™ Personal For Clinical Research software
    - Upload Disposable Sensor using Synergy Download Utility Software (following instructions provided)

- **China only:**
    - Download CONTOUR® PLUS study meter and provide to sponsor
    - Upload Disposable Sensor using Synergy Download Utility Software (following instructions provided)
- Perform a Skin assessment on the area of each of the sensor insertion sites and document in subject source and complete the Skin Assessment eCRFs
- Collect study survey from subjects- Refer to "Subject Exit Market Survey"
    - Investigational center staff will have subject complete the survey which includes the following question, at a minimum:

      "The user guide and instructional materials provided the instructions I needed." (strong agreement or disagreement ranked using 7 point Likert scale)
- Return all used and unused Disposable Sensor (including inserter component), devices, unused supplies and study guides from subjects (refer to Section 7.4)
- Subjects who have new or unresolved adverse event(s) from device-related skin reactions should schedule a follow up visit 3-7 days after Visit 12.
- An Exit eCRF will be completed at this visit if no follow up visit is required.

10.2.1.9. Unscheduled Visit: For AE Follow Up, if Required (3-7 Days after Visit 12)

Investigational center staff will:

- Assess for adverse events including adverse event from device-related skin reaction ongoing at Visit 12.
- Update adverse event form or fill in new adverse event form, as applicable.
- An Exit eCRF will be completed at this visit if applicable.

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

This section is presented as below:

- **Section 11.1:** Study Design
- **Section 11.2:** Study Procedures (Subjects 2-13 years)

11.1. Study Design

The study is a multi-center, prospective, single-arm study without controls, and random assignments of sensor location, FST day, and FST time.

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

Subjects will wear sensors in the following configurations and follow the FST schedule:

Subjects 7 - 13 years

- Sensor Location
  - Arm/Arm/Buttock
  - Buttock/Buttock/Arm
- FST Schedule
  - 2 x 6 hours FST

Subjects 2 - 6 years

- Sensor Location
  - Arm/Buttock
  - Subjects 2-6 years old may have their parent, guardian, or legally authorized representative choose the area for their sensor placement
- FST Schedule
  - 2 x 4 hours FST
  - SMBG only

FST Timing for 7-13 years old:

Group	Sensor Wear Day	Timing of FST 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 FST 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)

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.

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.

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 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 subjects 7-13 years. For subjects aged 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 for Subjects for FST (section 20.1.1).

For device troubleshooting and device complaints (See Section 24):

- **US only:** Subjects and/or Sites are to call the 24-Hour Technical Support (TS)
- **China only:** Subjects are to call Investigational Center staff

Hypoglycemic and Hyperglycemic Challenges

Subjects 2 - 13 years:
During the day of FST, subjects will not participate in hypoglycemic and hyperglycemic challenges.

11.2. Study Procedures (Subjects 2-13 years)

11.2.1. Schedule of Events

In this section, "subject (s)" refers to both subject and their parent, guardian, or legally authorized representative (if applicable).

11.2.1.1. Visit Schedule & Scheduled Follow-up Visit Windows

11.2.1.1.1. 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 (depending on randomly assigned group). The intent is for subjects to wear the study sensors and devices and perform 2 YSI™* FSTs.

One rescheduled visit can occur during the study period if primary sensors dislodge and new sensors must be re-inserted (See Replacement Sensors Sections 13 and 14).

If subject exits the study early (i.e. before their last scheduled visit), all requirements that apply to the final visit should be completed if possible.

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

- Visit 1: Consent and Screening
- Visit 2: Study, Device Training and Random Assignment
    - Confirm eligibility. 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 - Investigational center Visit

Start of Study Period: To be completed in 60 days from Visit 4 to Visit 8

- Visit 4– Phone Visit or Optional Office Visit
    - **Group A1**- May be combined with Visit 5
    - **Group A2, B1, B2, C1, C2, D1 and D2 -**Investigational center must confirm either via phone or in person that the sensor 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 Period 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).
    - Subjects who have new or unresolved adverse event(s) from device-related skin reactions should schedule a follow up visit 3-7 days after Visit 8.
- Unscheduled Visit: For AE Follow Up, if Required (3-7 Days after Visit 8)
    - Assess for adverse events including adverse event from device-related skin reaction ongoing at Visit 8.
    - Update adverse event form or fill in new adverse event form, as applicable.

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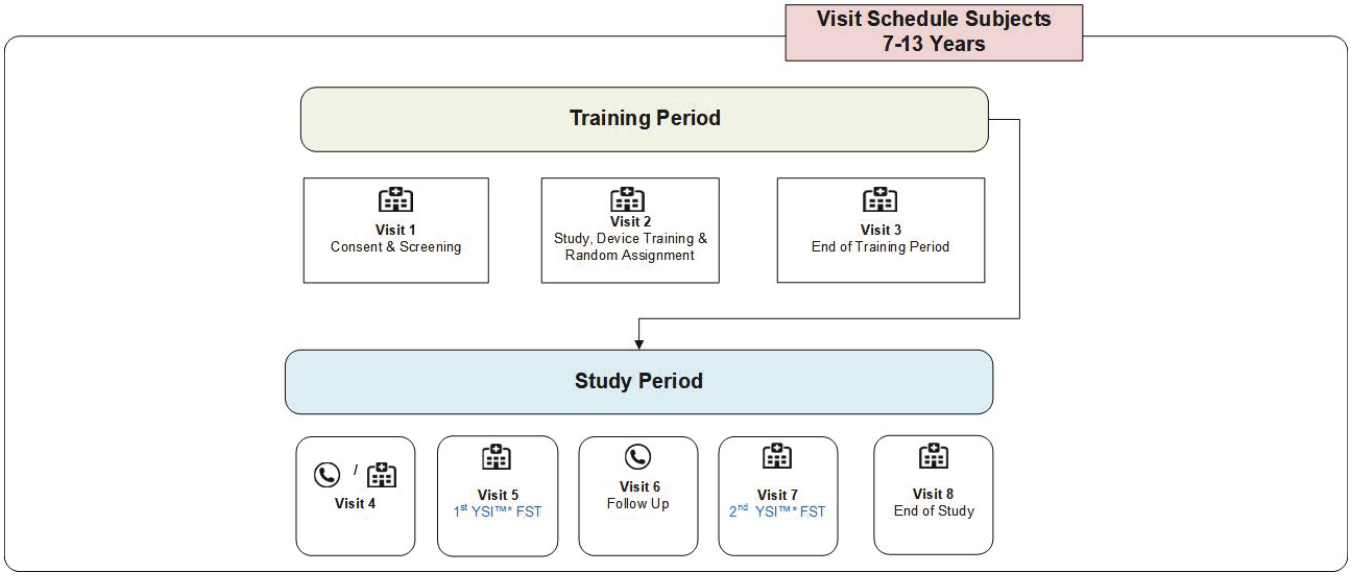
Figure 3. Visit Schedule Subjects 7-13 Years



11.2.1.1.2. 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 sensors and devices and perform 2 SMBG FSTs .

One rescheduled visit can occur during the study period if a primary sensor dislodge(s) and new sensor(s) must be re-inserted (See Replacement Sensors Section 13).

If subject exits the study early (i.e. before their last scheduled visit), all requirements that apply to the final visit should be completed if possible.

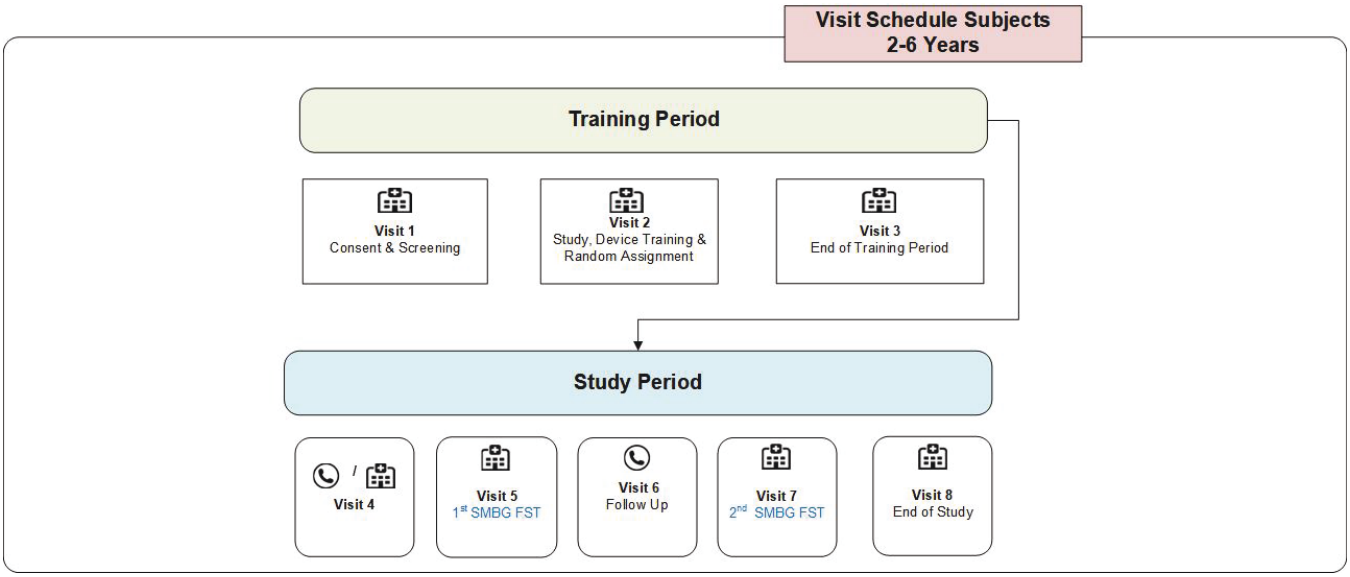
Screening and Training Period: To be completed in 30 days (Visit 1 to Visit 3)

- Visit 1: Consent and Screening
- Visit 2: Study, Device Training and Random Assignment
  - Confirm eligibility.
  - Visit 1 and 2 can be combined if eligibility criteria are met.
- Visit 3: End of Training Period - Investigational center Visit

Start of Study Period: To be completed in 60 days from Visit 4 to Visit 8

- 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 sensor 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 Period 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)
  - Subjects who have new or unresolved adverse event(s) from device-related skin reactions should schedule a follow up visit 3-7 days after Visit 8.
- Unscheduled Visit: For AE Follow Up, if Required (3-7 Days after Visit 8)
  - Assess for adverse events including adverse event from device-related skin reaction ongoing at Visit 8.
  - Update adverse event form or fill in new adverse event form, as applicable.

Figure 4. Visit Schedule Subjects 2-6 Years



11.2.1.2. Visit 1: Consent and Screening

Overview General

Investigational center staff will:

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

    Note: Body mass index (BMI) will be calculated automatically in the study database, based on height and weight measurements entered.
  - Concomitant medications (Screening Only)
  - CGM experience
  - Pump experience
  - Total Daily Dose (TDD), if applicable
  - Daily basal amount, if applicable
  - Time of day basal/long acting insulin is delivered, if applicable
- For subjects 7-13 years only: Complete required screening tests, if all eligibility criteria are met:
  - **US only:** Perform urine test for pregnancy, female subjects of child-bearing age or capability
  - Obtain blood sample:
    - Pregnancy **(China only):** Perform blood test for pregnancy, female subjects of child-bearing age or capability. Send to investigational center's lab for required screening tests.
    - Hct

- If patient has prior Hct from routine care done within 6 months of enrollment and the report of lab placed with subject source documents, then no blood test needs to be done.
- **Note:** For all out of range lab results, a single re-test is permitted
- **US only:** Send to Central Laboratory or local lab for required screening tests. There is no point of care (POC) testing for Hct.
- **China only:** Send to investigational center's lab for required screening tests.

- Obtain blood sample for Glycosylated hemoglobin (HbA1c) (not an eligibility criteria)
  - **US only:** Send to Central Laboratory
  - **China only:** Send to investigational center's lab
- Per Investigator's discretion, subjects may exercise. Subjects will be asked to exercise for a minimum of 30 minutes during YSI™/SMBG FSTs.
- Enter data into electronic Case Report Forms (eCRF)s as appropriate
- Schedule next visit date and time

The study is open to all individuals who meet the eligibility criteria of the study. The investigational center will be responsible for determining adequate source documents to verify subject eligibility. Subjects who do not meet the eligibility requirements for participation in the study will be entered into the database as screen failures. Applicable eCRF(s) will be completed for all subjects and their parent, guardian, or legally authorized representative who signed an ICF and assent form (if applicable), whether they are eligible or ineligible to participate. If a subject 7-13 years old 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.

For subjects 7-13 years old, 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. For subjects 2-6 years old, Visit 2 may be completed on the same day as Visit 1 if all eligibility criteria are met.

11.2.1.3. Visit 2: Study and Device Training

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 CONTOUR® NEXT LINK 2.4 study meters (**US only**)/ CONTOUR® PLUS study meters (**China only**) need to be synchronized with the time on the laptop at the investigational center. Subjects will be instructed not to change the time in these devices. Subjects will be provided a CONTOUR® NEXT LINK 2.4 study meter (**US only**)/ CONTOUR® PLUS study meter (**China only**) to be used to perform fingerstick (capillary SMBG).

US only: The investigational center staff will also have to create an account for the subject in CareLink™ Personal For Clinical Research software (see Investigator Site File for details).

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

Overview of general study procedures

Investigational center staff will:

- Confirm eligibility
- Randomly assign eligible subjects
- Synchronize time of the CONTOUR® NEXT LINK 2.4 study meter(**US only**)/ CONTOUR® PLUS study meters (**China only)** with the time on the investigational center's laptop
- **US only:** Create an account for the study subjects in CareLink™ Personal For Clinical Research software
- Train subjects on study devices
- Confirm sensor locations according to subject's age (see Sensor Wear Location Table)
- Enter data into eCRFs as appropriate
- Schedule the next visit date and time

Overview of study devices and supplies

Investigational center staff will disburse the following to subjects:

- DS5(s)
- CONTOUR® NEXT LINK 2.4 study meter(s) (**US only**)/ CONTOUR® PLUS study meters (**China only)**
- BG supplies (e.g. control solution, batteries, meter strips, and lancets)
- Other study materials (e.g., study reference card, device user guides, and training materials)
- Other study supplies (e.g., DS5 return materials and alcohol swabs)

Investigational center staff will record and track all study devices outlined in the device accountability section (see Section 7.4) on the appropriate eCRF.

Overview of training and instructions

Investigational center staff will:

- Train each subject on sensor insertions, removal, study devices, and study procedures
    - Subject will be instructed to wash hands thoroughly with soap and water.
    - Subject will be instructed to clean the insertion site with alcohol and let the insertion site air dry prior to sensor insertion.
- Instruct subjects that additional OTC tape(s) (e.g. Hypafix™* tape, etc.) may be used if needed
- Train subjects on use of CONTOUR® NEXT LINK 2.4 study meter(**US only**)/ CONTOUR® PLUS study meter (**China only)**
    - 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 (**US only**)/ CONTOUR® PLUS study meter (**China only)** during the course of the study to perform study defined SMBG measurements
    - Subjects will be instructed to perform a quality control (QC) testing when a new vial of test strips is used
- Perform applicable QC testing (CONTOUR® NEXT LINK 2.4 study meter [**US only**]/ CONTOUR® PLUS study meter [**China only]**). Shake control solution bottle well prior to use.
- Instruct subjects to insert sensors in the locations according to their age. 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.
    - 7 - 13 years
        - Arm/Arm/Buttock
        - Buttock/Buttock/Arm
    - 2 - 6 years
        - Arm/Buttock
        - Subjects 2-6 years old may have their parent, guardian, or legally authorized representative choose the area for their sensor placement
- Synchronize time on each Disposable Sensor (DS5) worn in-clinic by the subject using the Synergy Download Utility
- 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 after insertion on Day 1 and also one approximately at the same time every day as time of the insertion
- Have subject perform the first SMBG at the investigational center or a follow up call will be required to confirm this
- Instruct subjects to wear the devices up to 7-day training period. Instruct subjects to remove the sensors (at end of training period or at investigational center) after 7 days (T= 176-188 hours).
- Instruct subjects during training period that they should spend time bending and twisting even if they don't undergo aerobic exercise.
- Instruct subjects on Disposable Sensor (including the inserter component) 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 24 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 for technical issues and support:
    - **US only:** Subjects and/or Sites are to call the 24-Hour Technical Support (TS)
    - **China only:** Subjects are to call Investigational Center staff
- Remind subjects to bring in the CONTOUR® NEXT LINK 2.4 study meter (**US only**)/ CONTOUR® PLUS study meter (**China only)** 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 22 and 24 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 perform random assignment and provide the subjects with study device training that would be comparable to training provided to patients in the actual clinical use. The subjects will receive training on the study requirements before completing the training visit. All subjects will be trained on the device(s) to be used in the study prior to leaving the investigational center. Investigational center staff will train the subjects on the appropriate use of the study devices. Each subject will receive training on sensor insertion and removal, other study devices, and study procedures. This training includes SMBG. The training is expected to last 15 minutes to 2 hours in duration on average, depending on the subject's experience. Training materials provided to the subject may include instructions for use

(IFU)s, 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.

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 FST 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 FST 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)

The following is the FST schedule for the subjects according to their age:

- 7 - 13 years
  - 2 x 6 hours FST
- 2 - 6 years
  - 2 x 4 hours FST
  - SMBG only

Subjects will be assigned to sensor location (random assignment) according to their age:

- 7 - 13 years
  - Arm/Arm/Buttock
  - Buttock/Buttock/Arm
- 2 - 6 years
  - Arm/Buttock
  - Subjects 2-6 years old may have their parent, guardian, or legally authorized representative choose the area for their sensor placement

11.2.1.3.1. 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

- On Day 1, a minimum of 4 fingerstick glucose readings (SMBG) at the times below will be requested with target of 7 total fingerstick glucose readings:
    - Time = 0 hour
        - Sensor insertions will be performed
        - The 0 hour represents the time after the last sensor has been inserted
    - Time = 2 hours
        - T = 2 hours after the last sensor has been inserted
    - Time = 10 hours
        - T = 10 hours after the last sensor has been inserted
    - Time = 24 hours
        - T = 24 hours after the last sensor has been inserted
- On Day 2-7, a minimum of 4 fingerstick glucose readings (SMBG) per day will be requested with target of 7 fingerstick glucose readings (with one of them occurring at the same time of day as initial sensor insertion [±1 hour]). For example, if sensor was inserted at 8 am, then each day after that one SMBG will done at this same time.
- One SMBG should be taken upon arrival for each FST
- At the end of each FST, take one SMBG.
- 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.

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

Overview of general study procedures
Investigational center staff will:

- Instruct subject to self-remove the sensors that he/she is still wearing at this visit
- Perform a Skin Assessment on the area of each of the sensor insertion sites and document in subject source and complete Skin Assessment eCRFs for each inserted sensor.
- **US only**:
    - Upload CONTOUR® NEXT LINK 2.4 study meter into CareLink™ Personal For Clinical Research software
    - Upload Disposable Sensor using Synergy Download Utility Software (following instructions provided)
- **China only:**
    - Download CONTOUR® PLUS study meter and provide to sponsor
    - Upload Disposable Sensor using Synergy Download Utility Software (following instructions provided)
- Determine if additional training is needed (e.g., if the subject is not following finger-stick monitoring requirements). If additional training is required, subjects will be retrained using training materials supplied during training visit 2 and research staff may focus on specific areas of opportunity for improvement.
- Enter data into the eCRFs as appropriate
- Review requirements of next study visit with subjects
- Disburse Disposable Sensor to subjects who will insert at home
- Schedule the next visit dates and times (including the first YSI™*/SMBG FST)
- The subject will be instructed to insert sensors. Note: the subject will use the CONTOUR® NEXT LINK 2.4 study meter (**US only**)/ CONTOUR® PLUS study meter (**China only)** provided by the Investigational center staff.
- Remind subjects on Disposable Sensor(s) (including the inserter component) return (see Table 1 US Device Accountability Requirements and Table 2 China Device Accountability Requirements)

Overview of study devices and supplies

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

- DS5(s)
- BG supplies (e.g. control solution, batteries, meter strips, and lancets)
- Other study supplies (e.g. DS5 return materials and alcohol swabs)

Investigational center staff will record and track all study devices outlined in the device accountability section (see Section 7.4) on the appropriate eCRF.

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 11.1).

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.

11.2.1.5. Visit 4 :Phone Call or Optional Office Visit

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

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 the sensors at the appropriate time and sensor location. Once the study period sensors are inserted, the subject should follow the YSI™*/SMBG FST Timing and SMBG requirements (Section 11.2.1.3.1).

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. Also, subjects will be reminded on Disposable Sensor (including the inserter component) return.

11.2.1.6. Visit 5 and 7 : YSI™* FSTs / SMBG FSTs

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.

11.2.1.6.1. Procedure Guidelines For Subjects (Visit 5 and 7)

There are no specific criteria to start the FST.

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 at home and in clinic. Subjects should bring all medications they are taking with them to the clinic, even if they are not scheduled to take that medication that day.

Subjects may exercise during the observation period if their glucose is between 100-300 mg/dL (5.6-16.7 mmol/L).

Insulin (if applicable), medication (if applicable), diet, diabetes monitoring/management and ketone monitoring/management may be performed per Investigator discretion.

11.2.1.6.2. In-Clinic Procedures

Overview of general study procedures

Investigational center staff will:

- Set up the YSI™* instrument (subjects 7-13 years only; see Investigator Site Fiile for details)
- Perform applicable QC testing:
  - **US only**: CONTOUR® NEXT LINK 2.4 study meter and Precision Xtra™* ketone meter
  - **China only:** CONTOUR® PLUS study meter and FreeStyle Optium Neo ketone meter
- Synchronize YSI™* devices at the investigational center with the designated study clock (subjects 7-13 years only)
- Verify that sensor insertion was performed at the appropriate insertion time, insertion location and SMBG reminders.
- Synchronize time on each Disposable Sensor (DS5) worn in-clinic and at home by the subject using the Synergy Download Utility (Visit 5 only)
- Conduct SMBG testing upon subject arrival
- Refer to Section 11.2.1.3.1 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. For SMBG FST, will record the fingerstick glucose values on the appropriate eCRF and these will be used for analysis.
- Following completion of each YSI™*/SMBG FST:
  - **US only**: Upload CONTOUR® NEXT LINK 2.4 study meter into CareLink™ Personal For Clinical Research software
  - **China only:** Download CONTOUR® PLUS study meter and provide to sponsor
- 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 sensors past the end of this visit to achieve sensor wear for T=176-188 hours
- Review requirements of next study visit (phone or EOS visit) with subjects
- Review the next visit date and time for YSI™*/SMBG FST **(Visit 7 only)**
- Enter data into eCRFs 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 and infusion sets that might be needed during the YSI™*/SMBG FST visit.
- Remind subjects on Disposable Sensor (including the inserter component) return (see Table 1 US Device Accountability Requirements and Table 2 China Device Accountability Requirements)

Overview of study devices and supplies

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

- DS5(s)
- BG supplies (e.g. batteries, meter strips, and lancets)
- Other study supplies (e.g. alcohol swabs)

Investigational center staff will record and track all study devices outlined in device accountability section (see Section 7.4) on the appropriate eCRF.

Investigational center staff will:

- Remind subjects to perform fingersticks (capillary SMBG)

- Remind subjects to contact for technical issues and support:
  - **US only:** Subjects and/or Sites are to call the 24-Hour Technical Support (TS)
  - **China only:** Subjects are to call Investigational Center staff
- Fingerstick will be performed at home as stated in Section 11.2.1.3.1.

11.2.1.6.2.1 Blood Glucose Monitoring During the YSI™* /SMBG FST

Ages 7 – 13 years
The frequency of blood draws for YSI™* FST sampling is dependent on the average value of YSI-B and YSI-W probes of the previous sample, according to the following ranges:

- less than (<) 75 mg/dL (4.2 mmol/L); every 5 minutes (window of 3-8 minutes)
- greater than or equal to (≥) 75 mg/dL (4.2 mmol/L); every 15 minutes (window of 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 (3.9 mmol/L); every 5 minutes (window of 3-8 minutes)
- 70-80 mg/dL (3.9-4.4 mmol/L); every 15 minutes (window of 7 -23 minutes)
- greater than (>) 80 mg/dL (4.4 mmol/L); every 30 minutes (maximum of 45 minutes)

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

Ages 7 – 13 years

In the event that YSI™* blood glucose values are not immediately available, for safety purposes, the investigational center may use the subject's CONTOUR® NEXT LINK 2.4 study meter (**US only**)/ CONTOUR® PLUS study meter (**China only**) 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.

11.2.1.6.2.3 Exercise

- Only subjects who have been previously established for participation in exercise during Visit 1 can participate in the exercise activities during YSI™*/ SMBG FST.
- Subjects may exercise during FST if their glucose is between 100-300 mg/dL (5.6-16.7 mmol/L).
- Ketone testing should be per investigator discretion
- Subjects who exercise will be asked to exercise for at least 30 minutes during YSI/ SMBG FST
- Procedures:
    - 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 (3.9 mmol/L) for subjects 2-6 years of age
        - Glucose is less than or equal to 65 mg/dL (3.6 mmol/L) for subjects 7-13 years of age
    - Exercise will be terminated if subjects develop chest pain, shortness of breath, dizziness or any other symptom as per investigator discretion.

11.2.1.6.2.4 End of FST and Discharge

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

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

11.2.1.7. 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. Also, subjects will be reminded on Disposable Sensor (including the inserter component) return. If subject is unable to be reached, then this should be documented and at least one second attempt to reach subject be performed.

11.2.1.8. Visit 8: End of Study Period

- Visit 7 and Visit 8 may be combined if 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 sensors, instruct subjects to remove them
- **US only**:
    - Upload CONTOUR® NEXT LINK 2.4 study meter into CareLink™ Personal For Clinical Research software
    - Upload Disposable Sensor using Synergy Download Utility Software (following instructions provided)
- **China only:**
    - Download CONTOUR® PLUS study meter and provide to sponsor
    - Upload Disposable Sensor using Synergy Download Utility Software (following instructions provided)
- Perform a Skin assessment on the area of each of the sensor insertion sites and document in subject source and complete the Skin Assessment eCRFs
- Collect study survey from subjects- Refer to the "Subject Exit Market Survey"
    - Investigational center staff will have subject complete the survey which includes the following question, at a minimum:

      "The user guide and instructional materials provided the instructions I needed." (strong agreement or disagreement ranked using 7 point Likert scale)
- Return all used and unused Disposable Sensor (including inserter component), devices, unused supplies and study guides from subjects

- Subjects who have new or unresolved adverse event(s) from device-related skin reactions should schedule a follow up visit 3-7 days after Visit 8.
- An Exit eCRF will be completed at this visit if no follow up visit is required.

11.2.1.9. Unscheduled Visit: For AE Follow Up, if Required (3-7 Days after Visit 8)

Investigational center staff will:

- Assess for adverse events including adverse event from device-related skin reaction ongoing at Visit 8.
- Update adverse event form or fill in new adverse event form, as applicable.
- An Exit eCRF will be completed at this visit if applicable.

12. Assessment of Safety

Adverse Event information is collected in this study. See Section 22 for further information on the collection of AEs and safety information.

13. Replacement Sensors

13.1.1. Training Period Sensor Wear Rules

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

13.1.2. Study Period Sensor Wear Repeat Rules

A subject can replace their ***primary*** sensor(s) (See Section 25.8.1) once.

Subject will wear the replaced sensors for 7 days (T= 176-188 hours) and attempt to complete the required YSI™*/SMBG FST visits.

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 FST Group.

14. 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.

15. 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 diabetic patients must be available during the entire hypoglycemic and hyperglycemic challenge.

- A nurse, physician or mid–level provider, such as a nurse practitioner or a physician assistant, who has managed diabetic patients must be available during FST.
- The Investigator (or designee) will need to have one of the following qualifications; endocrinology fellowship, management in patients with diabetes in a clinical practice 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 who undergo challenge(s) will meet the desired range or desired time per Hyperglycemic and Hypoglycemic Challenge range or time. 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.

16. Glucose and Glycemia Measurements

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

- **Daily BG-** Values will be assessed during the study by all subjects using the CONTOUR® NEXT LINK 2.4 study meter (**US only**)/ CONTOUR® PLUS study meter (**China only**). 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(**US only**)/ CONTOUR® PLUS study meter (**China only**) per the manufacturer's IFU.
- **YSI™* FST BG values -**During the YSI™* FSTs at the investigational center, blood plasma glucose will be determined using the laboratory BG analyzer (YSI™*).
- **SMBG FST BG Values** -During the SMBG FST at the investigational center, the BG will be obtained by SMBG from Study Meter BG readings. Subjects may also use the Study Meter SMBG readings for diabetes management.
- **Blood ketone values** – During the YSI™*/SMBG FSTs at the investigational center, blood ketones will be determined by subjects using the Precision Xtra™* ketone meter **(US only**)/ FreeStyle Optium Neo ketone meter **(China only)**. 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™* **(US only**)/ FreeStyle Optium Neo ketone meter **(China only)** ketone meter per the manufacturer's IFU. All blood ketone measurements will be logged in the subject records, and recorded on the appropriate eCRF.
- **Sensor Glucose (SG) Values** - Assessed using the following methods:
    - SG values collected by subject's DS5
- **HbA1c** - Collected at baseline (Visit 1) and will be used as demographic information.
- **Alternate POC BG values**- During the YSI™*/SMBG FST at the investigational center, alternate POC BG measurements will be used (CONTOUR® NEXT LINK 2.4 study meter(**US**

only)/ CONTOUR® PLUS study meter (**China only**)) 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 (**US only**)/ CONTOUR® PLUS study meter (**China only**) 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.

17. Recording Data

All data required for analysis will be captured on eCRFs using Oracle Clinical Remote Data Capture's (OC-RDC) module. Original eCRFs will not be considered as source data and supporting documentation will be required. The subject survey on paper is considered source data, then source data is transferred to an eCRF.

US only: Blood glucose data will be collected from the CONTOUR® NEXT LINK 2.4 study meter using CareLink™ Personal For Clinical Research software. The system uses Secure Sockets Layers (TLS) technology, which encrypts all data it stores (21 CFR Part 11 compliant).

China only: Blood glucose data will be collected from the CONTOUR® PLUS study meter and will be provided to sponsor.

All regions:
Data from the DS5 will be collected using the Synergy Download Utility Software. Certain data points stored in the downloaded information may also be captured on the appropriate eCRF. These data files will be sent to the sponsor electronically using the internet and a secure cloud-based site (Box).

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

Laboratory results will be recorded on eCRFs.

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

Medtronic will only consider eCRFs to be complete when all discrepancies between source data and eCRF have been resolved and eCRF content has been reviewed by a Study Monitor. In addition, specific eCRFs must also be reviewed and electronically signed by the Investigator, indicating his/her agreement with

the accuracy of all recorded data. It is expected that the Investigator and his/her staff will cooperate with the monitoring team and provide any missing data in a timely manner.

18. 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, or EC 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/EC, except where necessary to eliminate an immediate hazard(s) to trial subjects or when the change does not affect the scientific soundness of the plan or the rights, safety, and welfare of the subjects.

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

- Blood glucose range and duration targets

  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.

  If challenge(s) targets are not met, this will not be considered a deviation.

  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 ONLY if the FST is not performed during the scheduled testing day.

- 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 only 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 2 missing YSI™*/SMBG FST:

- YSI™*/SMBG FST at 8 A.M. which is 65 mg/dL (3.6 mmol/L)
- YSI™*/SMBG FST at 8:15 A.M. which is 60 mg/dL (3.3 mmol/L)

Since the 1st sample is less than (<) 75 mg/dL (4.2 mmol/L) , the next draw should be in 5 mins; but the 2nd sample is at 8:15 AM, so there are at least 2 missing samples

- 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 investigational center staff did not train subject on SMBG study procedures.

- FST Duration:

  A study deviation will not be given if the FST is completed within 15 minutes prior to the 8-hour, 6-hour, and 4-hour duration respectively.

18.1.1. Documenting Requirements for Study Deviations

18.1.1.1. Unplanned CIP Deviations

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

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

CIP deviations should be reported as follows:

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

18.1.1.2. Reporting Requirements for Study Deviations

All study deviations must be reported on the eCRF regardless of whether medically justifiable, an inadvertent occurrence, or taken to protect the subject in an emergency. Any deviations from the CIP will be documented in the clinical study report. The date and reason for each deviation will be documented.

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

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

- Failure to obtain informed consent and assent **(**if applicable**),** i.e., there is no documentation of consenting
- Informed consent and assent **(**if applicable**)** 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/EC
- Failure to inform IRB/EC and sponsor of reportable AEs (see Section 22)
- Investigational study device dispensed without obtaining informed consent and assent **(**if applicable**)**

Reporting of all other study deviations should comply with:

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

They must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation. Refer to Investigator Reports, Section 27.11.2 , for specific deviation reporting requirements and timeframes for reporting to Medtronic, IRB/EC, and regulatory agency (if applicable).

18.1.2. 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.

19. Subject Exit, Withdrawal or Discontinuation

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

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

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

- In the opinion of the Investigator, the subject's health or safety would be compromised by continuing in the study (e.g., infection at skin site, severe skin reaction to adhesive)
- 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
- The subject is lost to follow up

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

20. Stopping Rules

20.1.1. Stopping Rules for Subjects for FST

- 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 3 mL/kg of blood volume in a 24-hour period is to be drawn.
    - 4 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 during the study. However, no more than 1 mL/kg of blood volume in a 24-hour period is to be drawn.

  Please note that the time of the 24-hour blood draw limit would begin at the start of the first blood draw of an FST and end 24 hours after that. Because patients may have FSTs on two consecutive days (Day 3 and Day 4 or Day 4 and Day 5), please be careful not to exceed the 24-hour blood draw volume maximum. For example, when FSTs occur on two consecutive days it may be preferable to have a hyperglycemic challenge on one day and then a hypoglycemic challenge on the subsequent day, or vice versa, in subjects who may be more likely to reach the maximum 24-hour blood draw volume.
- Severe hypoglycemia (see severe hypoglycemia definition Section 22.1). Subject may continue in study (including observational FST) but not participate in any more challenges.
- Glucose greater than (>) 500 mg/dL (27.8 mmol/L) during challenge. Subject may continue in study (including observational FST) but not participate in any more challenges.
- Ketone greater than or equal (≥) to 3 mmol/L regardless of BG during challenge. Subject may continue in study (including observational FST) but not participate in any more challenges.

20.1.2. Subject Stopping Rules for Study

Refer to Section 19 on "Subject Exit, Withdrawal or Discontinuation ".

20.1.3. Study Stopping Rules

During a hypoglycemic or hyperglycemic challenge, if a subject experiences DKA, severe hypoglycemia with seizures or severe hypoglycemia requiring glucagon, the following actions will be taken:

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. The Clinical Events Committee (CEC) will review the event within 10 days from the time that the sponsor is notified and provide one of the following recommendations:
    - enrollment and study procedures may continue
    - stop enrollment, previously enrolled subjects are still allowed to continue in study
    - stop entire study, withdraw previously enrolled subjects

21. Risks and Benefits

21.1. 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 will be removed and another placed in a new location
Risks with Transmitter	**Prevention and Mitigation**
Risks with Transmitter may include: • Skin irritation or reaction to adhesives • Bruising • Discomfort • Redness • Pain	Prevention and mitigation include: • Follow the provided user guides. • Train on the proper use of the transmitters.

• 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	
Risks with Inserter	**Prevention and Mitigation**
Risks with inserters may include: • Improper insertion may lead to device performance issue	Prevention and mitigation include: • Follow the provided user guides for insertions and care of device. • Train on the proper use of the inserter 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 the study meter with fingerstick testing. • Train on the proper use of the meter and fingerstick testing.
Risks with IV Catheter Insertion	**Prevention and Mitigation**
Risks with IV catheter insertion may include: • Pain • Bruising • Infection • Irritation • Syncopal episode secondary to catheter insertion • Swelling. • Discomfort • Anxiety	Prevention and mitigation include: • Qualified individual to perform IV catheter insertion • Constant observation and monitoring of the subject during FST(s) • Sterile technique will be used to insert the IV Treatment of these risks include: • Removal of IV catheter if subject experiences significant discomfort • Removal of IV catheter if infection develops • Antibiotics will be given, if needed
Risks for indwelling IV catheter	**Prevention and Mitigation**
Risks with indwelling IV catheters may include: • Infection • Irritation • Swelling	Prevention and mitigation include: • Management of IV per investigational center protocol • Use of universal precautions to avoid infection

• Thrombosis • Phlebitis • Bruising	• Qualified investigator will be present during experiment • Constant observation and monitoring of the subject during FST(s) • Observation for redness at IV insertion site by qualified staff Treatment of these risks include: • Removal of IV catheter if infection develops and antibiotics will be given.
Risks with Blood Draw	**Prevention and Mitigation**
Risks with drawing blood may include: • Discomfort and bruising • Insertion of an IV catheter and drawing blood may also result in faintness, inflammation of the blood vessel, pain and bruising at the needle site • There is also a slight possibility of infection.	Prevention and mitigation include: • Qualified staff to perform blood draw
Risks with IV Saline Infusion	**Prevention and Mitigation**
Risks with saline infusion may include: • Edema • Congestive heart failure • Third spacing	Prevention and mitigation include: • Qualified investigator will be present during experiment • Constant observation and monitoring of the subject during FST(s) Treatment of these risks include: • Reduction of IV fluid if subject shows signs of congestive heart failure (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 10.2.1.6.4.1 and 11.2.1.6.2.1) • Clear guidelines for management during hyperglycemic challenge • IV access to give immediate insulin • Qualified investigator will be present 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 normal saline (NS) will be per investigator's discretion • IV insulin administration will be per investigator's discretion • 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 10.2.1.6.4.1 and 11.2.1.6.2.1) • Clear guidelines for management during hypoglycemic challenge IV access to give immediate dextrose or other emergency drugs • Qualified investigator will be present 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 and insulin sensitivity factor 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 administration of dextrose per investigator's discretion • Glucagon per investigator's discretion • 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 10.2.1.6.4.1 and 11.2.1.6.2.1) • Clear guidelines for management during both hypoglycemic and hyperglycemic challenge • IV access to give immediate insulin or dextrose • Qualified investigator will be present 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 FST(s) • 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 per investigator's discretion • IV dextrose for severe hypoglycemia per investigator's discretion • 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

21.2. Risk Minimization

Refer to "Prevention and Mitigation" column in the table under Section 21.1.

21.3. Potential Benefits

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

21.4. Risk-Benefit Rationale

The risks associated with insertion and wear of the Disposable Sensor are minimal and limited to minor bleeding at the sensor insertion site or minor skin irritation. Since the sensor is being used as a recording device during the study and does not provide any glucose information to the subject while it is worn, there is no risk of any adverse impact on the subjects' diabetes therapy.

Although subjects are not anticipated to receive any benefit specific to use of the Disposable Sensor, they may benefit from additional knowledge about their health as a result of the information collected to determine if they meet the specified inclusion/exclusion criteria. As a result, the minimal risks associated with participating in the study are outweighed by the potential benefits related to the additional knowledge about a subject's health status.

21.5. Risk Determination

US only:

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 hypoglycemic 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).

China only:

The Disposable Sensor is not within the scope of the Catalogue of Class III Medical Devices requiring the Clinical Trial Approval (CTA). Therefore, submission of an CTA application to NMPA is not required.

22. 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.

22.1. Definitions and Classification of Adverse Events

Medtronic uses the definitions provided in NMPA (former CFDA) Order No. 25, ISO 14155:2011 and 21 CFR 812 for AE definitions. ISO14155:2011 definitions are used for AE classifications while expedited reporting to local authorities/EC should be done based on local definitions of local regulations. Where the definition indicates "device", it refers to any device used in the study. This might be the device under investigation, or any market released component of the system. Medtronic follows MEDDEV 2.7/3 revision 3 guidelines for classifying causality levels; but will apply these causality definitions across all events, not only serious adverse events and definitions have been adapted accordingly.

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

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

Diabetic Ketoacidosis/DKA diagnostic criteria: blood glucose greater than (>) 250 mg/dL or greater than (>) 13.9 mmol/L, arterial pH less than (<) 7.3, bicarbonate less than (<)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 (<) 15 mEq/L
- Blood glucose greater than (>) 250 mg/dL or greater than (>) 13.9 mmol/L
- Serum ketones or large/moderate urine ketones
- Symptoms such as polyuria, polydipsia, nausea, or vomiting
- Treatment provided in a health care facility

Adverse Event (AE) (ISO 14155-2011)

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

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

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

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

Adverse Event (AE) (NMPA [former CFDA] Order No.25 Article 93)

The medical events with disadvantages occurred during the clinical trials, no matter whether they are related to investigational medical devices or not.

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 a 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 Event (SAE) (NMPA [former CFDA] Order No.25 Article 93)

Any untoward medical occurrence during the clinical trial: results in death or serious deterioration in health; life-threatening diseases or injuries; causing permanent damage to the body structure or function; requires hospitalization or prolongation of hospitalization; requires medical operations or intervention for preventing from persistent or significant disability/incapacity; results in fetal distress, fetal death, or congenital anomaly/birth defect.

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.

22.2. 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 as this is not considered an untoward event, but rather an expected occurrence. Any glycemic excursion that meets the protocol definition of Severe Hypoglycemia or DKA is considered an untoward event and a worsening from the subject's baseline and would be reported to sponsor on an AE eCRF.

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

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

Narratives gathered from completed survey will not provide the basis of an AE report however could lead to discussions that result in the identification of a reportable AE.

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

22.3. Notification of Adverse Events

Sponsor Notification:

The investigational center staff must report all AEs to Medtronic in a timely manner. All Severe Hypoglycemia, DKA, SAE, and SADE should be reported as soon as possible (desired within 24 hours of investigator or study coordinator awareness) to Medtronic. Refer to Table 3 below for China Investigator Reporting Requirements. For the previously mentioned events, the AE eCRF will be completed with all known details as soon as possible, this will serve as notification to Medtronic. If the study database cannot be accessed due to technical problems, contact the sponsor via email at dl.diabetesclinicalresearchsafety@medtronic.com and provide the known details of the event. Once the access issue has been corrected, the event should be entered onto an AE eCRF.

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

22.4. Expedited Safety Reporting Requirements

US only:

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.

China only:

Sponsor submits adverse events and device deficiencies to regulatory authorities, other clinical research institutions and investigators participating in the study per local regulatory requirements and EC requirements.

Documentation of GCP office and EC notification of any safety event must be kept at the investigational center and a copy sent to the sponsor.

Table 3. Investigator Reporting Requirements for AE and Device Deficiencies (China Only)

For the following events, reporting requirements are: • **Serious Adverse Events (SAE)**	
Investigators shall immediately adopt appropriate therapeutic measures for subjects, and simultaneously report to the management department of medical device clinical study in investigational center in written form. Management department of medical device clinical study shall report to:	
Medtronic	Immediately
Local food and drug regulatory authority and health and family planning competent authority of the province, autonomous region and municipality directly under the central government where the investigational center locates	Within 24 hours
EC	Within 24 hours/per EC's requirements
For the following events, reporting requirements are: • **All other AEs** • **All Device Deficiencies**	
Investigators shall record all the AEs and device deficiencies occurred during the clinical study. Investigators shall analyze the reasons for the events with Medtronic and document the analysis result in written report, including the comments of continuing, suspending or terminating study, which shall be reported to the EC through management department of medical device clinical study in investigational center for review.	
To Medtronic	Submit in a timely manner after the investigator first learns of the event.
To EC	Per EC's requirements

NOTE: In case there is/are additional AE reporting requirement(s) and/or process(es) (e.g. internal hospital policy or province regulatory authority instruction, etc.), these specific AE reporting requirement and process must be documented in a separate cover.

22.5. Causality Assessment

An AE is not automatically related to the study device or procedure simply because the subject is wearing the device and participating in the study. The event should be reviewed to determine if the device or study procedure could have possibly caused the event and therefore is related to the study device or procedure. Causality assessment is the determination of the relationship between an AE and the device being studied. It is expected that the investigational center will review all elements surrounding the AE to properly assess the causality of the event to the study device or to a study procedure.

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

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

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

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

- **Possible:** the relationship with the use of the investigational device is weak. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of

another device, drug or treatment). Cases where relatedness cannot be assessed should also be classified as possible.

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

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

22.6. 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.

22.7. 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 by investigational center staff following the removal of each device. 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.

22.8. Documentation of Symptoms During Frequent Sample Testing

During FST it is expected that subjects 14-80 year old may experience minor symptoms that are related to the procedure requirement of driving glucose levels high and low. Subjects who participate in exercise during the FST observation may also experience minor symptoms.

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

23. Data Review Committees

23.1. Clinical Events Committee

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

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

During a hypoglycemic or hyperglycemic challenge, if a subject experiences DKA, severe hypoglycemia with seizures or severe hypoglycemia requiring glucagon, the following actions will be taken:

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. The Clinical Events Committee (CEC) will review the event within 10 days from the time that the sponsor is notified and provide one of the following recommendations:
    - enrollment and study procedures may continue
    - stop enrollment, previously enrolled subjects are still allowed to continue in study
    - stop entire study, withdraw previously enrolled subjects

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.

24. Device Deficiencies and Troubleshooting

US only: 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 call reports 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. Refer to device deficiency definition in the table below.

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

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

All device deficiencies reported directly to the Investigational Center staff by a subject be reported on the appropriate eCRF. Refer to device deficiency definition in the table below.

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

Device Deficiency	**All regions:** 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.* (ISO 14155:2011 section 3.15)
	China Only: Any unreasonable risk caused by a medical device in normal use during clinical trial that may endanger human health or life safety, such as label error, quality issues, malfunction and etc. (NMPA Order No.25 Article 93)

All regions:
It is the responsibility of the investigator to follow their IRB/EC reporting requirements.

25. Statistical Design and Methods

25.1. General Aspects of Analysis

All data collected from the time of screening until the end of the study will be collected either on eCRFs, subject survey or electronically by downloading the various devices and used as source data for analysis. Data and analysis will be summarized in a Clinical Study Report. Any deviations from original statistical plan and the rationale will be described in the Clinical Study Report.

Two study reports will be generated: one study report including data from US and China; another study report including data from US.

China only: The Clinical Study Report will be compliant with the elements from the NMPA 2016 No. 58 Announcement Annex 5 "Template of Clinical Trial Report of Medical Devices". There are no criteria and/ reasons for trial termination based on statistics.

25.2. 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.

25.3. Sensor Disposition

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

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

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

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

25.4. Subject Demographics and Baseline Characteristics

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

25.5. Sample Size and Power

A total of up to 376 previously-diagnosed type 1 or type 2 diabetes subjects in the U.S. and China will be enrolled in order to have 260 subjects complete the study.

25.5.1. DS5 sensor 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 [1.1 mmol/L] when SG less than (<) 80 mg/dL [4.4 mmol/L]) in comparative readings of paired sensor 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 one sided 95% lower confidence limit of the mean agreement rate was tested against the threshold of 75%. The results of the simulation indicated that a sample size of 100 will yield greater than 80% power.

25.6. Analysis Populations, Handling of Missing Data, Error

Data entry error or non-reasonable values will be resolved before data analysis. No imputations will be done for missing data.

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

25.7. Assignment to Day of YSI™* FST

Adult subjects age of 18-80 and adolescent subjects with age of 14 - 17 will be required to attend four 8-hour sessions of frequent sampling in which agreement between YSI™* and sensors will be summarized.

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 sensors will be summarized.

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 sensors will be summarized.

25.8. General Considerations for Data Analysis

25.8.1. Datasets Expected

The following datasets will be generated by the combination of:

- Primary sensors: For subjects 18 years and older and wearing 2 sensors, primary sensor will be assigned to the sensor with lower serial number in the same location. For subjects 7-17 years old 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 in the different locations, both sensors will be considered primary sensors.
- Secondary sensor: For subjects 18 years and older and wearing 2 sensors, secondary sensor will be assigned to the sensor with higher serial number in the same location. For subjects 7-17 years old and wearing 3 sensors, one secondary sensor will be assigned to the sensor with higher serial number in the same location.
- Athena Algorithm
    - 0 Calibration
    - Two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Athena Plus Algorithm
    - 0 Calibration
    - Two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
    - Three Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
    - Daily Calibrations (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)

For NMPA CGM analysis, all subjects (2 – 80 years) will be analyzed together.

- Location
  - Buttock
  - Arm

25.8.2. Pairing Scheme

All YSI™* and fingerstick values collected will be presented. However, the primary endpoint analysis will only include sensor values of 50-400 mg/dL (2.8-22.2 mmol/L) and paired YSI™*.

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

25.8.3. YSI™* Retention

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

25.9. Endpoints

25.9.1. Primary Endpoints -Will Be Performed on Primary and Secondary Datasets

Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 20% mean agreement rate (±20 mg/dL [1.1 mmol/L] when SG less than (<) 80 mg/dL [4.4 mmol/L]), μ, between sensor 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 (GEE) 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, Exchangeable (exch) or Auto-regressive (AR1) or Independence (IND) correlation structure will be used, based on quasi-AIC (QIC).

Site effect will be evaluated. If it is not significant (p-value greater than (>) 0.1), site will not be included in the model.

The primary endpoint will be independently evaluated for each of the 18 datasets, as described below:

Datasets

Primary Datasets

Athena Plus algorithm

- Dataset 1: Adult (18 – 80 years), arm insertion location and 0 Calibration
- Dataset 2: Peds (2 to 17 years), buttock insertion location and 0 Calibration
- Dataset 3: Peds (2 to 17 years), arm insertion location and 0 Calibration

Secondary Datasets

Athena algorithm

- Dataset 4: Adult (18 – 80 years), arm insertion location and 0 Calibration
- Dataset 5: Adult (18 – 80 years), arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Dataset 6: Peds (2 to 17 years), buttock insertion location and 0 Calibration
- Dataset 7: Peds (2 to 17 years), buttock insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Dataset 8: Peds (2 to 17 years), arm insertion location and 0 Calibration
- Dataset 9: Peds (2 to 17 years), arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)

Athena Plus algorithm

- Dataset 10: Adult (18 – 80 years), arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Dataset 11: Adult (18 – 80 years), arm insertion location and three Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)

- Dataset 12: Adult (18 – 80 years), arm insertion location and daily Calibrations (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)
- Dataset 13: Peds (2 to 17 years), buttock insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Dataset 14: Peds (2 to 17 years), buttock insertion location and three Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration
- Dataset 15: Peds (2 to 17 years), buttock insertion location and daily Calibrations (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)
- Dataset 16: Peds (2 to 17 years), arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Dataset 17: Peds (2 to 17 years), arm insertion location and three Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Dataset 18: Peds (2 to 17 years), arm insertion location and daily Calibrations (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)

Pass/Fail Criteria:
The study pass/fail criteria is based on statistical hypothesis of the primary endpoints. The study will be considered as success when the evaluation criteria meets the predefined threshold.

Justification for Exclusion of Particular Information from the testing of the Hypothesis:
Not Applicable.

25.9.2. Secondary Endpoints- Will Be Performed on Primary and Secondary Datasets

25.9.2.1. National Medical Products Administration (NMPA) CGM for DS5

The four secondary endpoints will be evaluated in a fixed sequence of testing for adjustment of multiplicity. The results will be compared to the NMPA CGM criteria for sensor accuracy (SG limit of 50-400 mg/dL [2.8-22.2 mmol/L]):

- Sensor values from primary sensor will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 20% agreement rate (±20 mg/dL [1.1 mmol/L] when Reference BG less than or equal to (≤) 80 mg/dL [4.4 mmol/L]) between sensor values and YSI™* plasma glucose values during YSI™* FST days defined as p will be evaluated against the null Hypothesis:

  H0: $p \leq 60\%$

  H1: $p > 60\%$

- Sensor values from primary sensor will be compared to YSI™* plasma glucose values during YSI™* FSTs. A mean rate in Zone A+B of Consensus Error Grid between sensor values and YSI™* plasma glucose values during YSI™* FST days defined as p will be evaluated against the null Hypothesis:

  H0: $p \leq 90\%$

  H1: $p > 90\%$

- Sensor values from primary sensor will be compared to YSI™* plasma glucose values during YSI™* FSTs. A mean rate in Zone A+B of Clarke Error Grid between sensor values and YSI™* plasma glucose values during YSI™* FST days defined as p will be evaluated against the null Hypothesis.

  H0: $p \leq 90\%$

  H1: $p > 90\%$

- Sensor values from primary sensor will be compared to YSI™* plasma glucose values during YSI™* FSTs. A mean absolute relative difference (MARD) between sensor values and YSI™* plasma glucose values during YSI™* FST days defined as μ will be evaluated against the null Hypothesis.

  H0: $\mu \geq 20\%$

  H1: $\mu < 20\%$

- Statistical testing

One proportion Z test will be used to obtain 97.5% lower confidence limit of the agreement rate, the mean rate in Zone A+B of Consensus Error Grid, and the mean rate in Zone A+B of Clarke Error Grid, which will be tested against corresponding threshold, respectively.

One sample T test will be used to obtain the 97.5% upper confidence limit of the MARD, which will be tested against corresponding threshold.

The secondary endpoints will be independently evaluated for each of the 12 datasets, as described below:

Datasets

Primary Datasets

Athena Plus algorithm

- Dataset 1: Arm insertion location and 0 Calibration
- Dataset 2: Buttock insertion location and 0 Calibration

Secondary Datasets

Athena algorithm

- Dataset 3: Arm insertion location and 0 Calibration
- Dataset 4: Arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Dataset 5: Buttock insertion location and 0 Calibration
- Dataset 6: Buttock insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)

Athena Plus algorithm

- Dataset 7: Arm insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Dataset 8: Arm insertion location and three Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Dataset 9: Arm insertion location and daily Calibrations (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)
- Dataset 10: Buttock insertion location and two Calibrations (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)

- Dataset 11: Buttock insertion location and three Calibrations (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Dataset 12: Buttock insertion location and daily Calibrations (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)

25.9.2.2. Integrated Continuous Glucose Monitoring (iCGM) for DS5

The 11 secondary endpoints 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 [2.8-22.2 mmol/L]). 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
- Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 20% mean agreement rate between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated.
- Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 15% mean agreement rate when SG >180 mg/dL (10.0 mmol/L) between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated.
- Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 40% mean agreement rate when SG >180 mg/dL (10.0 mmol/L) between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated.

- When iCGM values are greater than 180 mg/dL (10.0 mmol/L), the number of corresponding blood glucose values that read less than 70 mg/dL (3.9 mmol/L).

- Sensor 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 (3.9 and 10.0 mmol/L) between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated.

- Sensor 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 (3.9 and 10.0 mmol/L) between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated.

- When iCGM values are less than 70 mg/dL (3.9 mmol/L), the number of corresponding blood glucose values that read above 180 mg/dL (10.0 mmol/L).

- Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±15 mg/dL (0.8 mmol/L) mean agreement rate when SG less than (<) 70 mg/dL (3.9 mmol/L) between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated.

- Sensor values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±40mg/dL (2.2 mmol/L) mean agreement rate when SG less than (<) 70 mg/dL (3.9 mmol/L) between sensor values and YSI™* plasma glucose values during YSI™* FST days will be evaluated.

The iCGM secondary endpoints will be independently evaluated for each of the 6 datasets as described for primary endpoints on the Athena algorithm, and 12 datasets as described for primary endpoints on the Athena Plus algorithm.

25.9.3. Agreement, ARD, Bias (Accuracy Analyses) - Will Be Performed on Primary and Secondary Datasets

The agreement, ARD (the absolute differences), and bias 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.

25.9.4. Numbers of Readings in the Low and High Ranges - Will Be Performed on Primary Datasets Only

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

25.9.5. Difference Tables Comparing Sensor and Reference Readings - Will Be Performed on Primary Datasets Only

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 (0.6 mmol/L), 15 mg/dL (0.8 mmol/L), 20 mg/dL (1.1 mmol/L), 30 mg/dL (1.7 mmol/L), 40 mg/dL (2.2 mmol/L), 50 mg/dL (2.8 mmol/L), 60 mg/dL (3.3 mmol/L), 70 mg/dL (3.9 mmol/L), 80 mg/dL (4.4 mmol/L), 90 mg/dL (5.0 mmol/L) and 100 mg/dL (5.6 mmol/L) of the reference method (YSI™* for in-clinic portion and meter BG for home-use portion) will be summarized.

25.9.6. Clarke Error Grid Analysis (EGA) of Paired Sensor and YSI™* and Reference Values - Will Be Performed on Primary Datasets Only

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 (2.2 – 4.4 mmol/L), greater than (>) 80-120 mg/dL (4.4 – 6.7 mmol/L), greater than (>) 120-240 mg/dL (6.7 – 13.3 mmol/L), and greater than (>) 240 mg/dL (13.3 mmol/L).

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].

25.9.7. Precision Analysis - Will Be Performed on Primary Datasets Only

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

25.9.8. Comparison of CGM Performance to Reference under conditions leadings to Alert - Will Be Performed on Primary Datasets Only

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 (2.8 mmol/L), 60 mg/dL (3.3 mmol/L), 70 mg/dL (3.9 mmol/L), 80 mg/dL (4.4 mmol/L), 90 mg/dL (5.0 mmol/L) and 100 mg/dL (5.6 mmol/L) and theoretical hyperglycemia threshold setting at 180 mg/dL (10.0 mmol/L), 220 mg/dL (12.2 mmol/L), 250 mg/dL (13.9 mmol/L) and 300 mg/dL (16.7 mmol/L).

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 (2.2 mmol/L) and greater than (>) 400 mg/dL (22.2 mmol/L).

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.
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.

25.9.9. Other Accuracy Analyses - Will Be Performed on Primary Datasets Only

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% confidence interval (CI), will be provided. 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 DS5 sensor performance (20% mean agreement rate (±20 mg/dL [1.1 mmol/L] when SG less than (<) 80 mg/dL [4.4 mmol/L]) will be performed in the following cohorts:

- **Diabetes cohorts based on insulin requirement:**
  - Type 1 insulin requiring
  - Type 2 insulin requiring
  - Type 2 non-insulin requiring

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

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

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

  A description of the following 5 groups will be performed:
  - Underweight subjects (BMI less than (<)18.5 kg/m²)
  - Normal weight subjects (BMI 18.5 to 24.99 kg/m²)
  - Overweight and obese subjects (BMI 25.00 to 40 kg/m²)
    - 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)

- **Diabetes cohorts based on prior real-time CGM experience (by self-report)**
  - CGM naïve
  - CGM experienced

- **Diabetes cohorts based on prior pump experience (by self-report)**

- Pump naïve
- Pump experienced

- **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:**
  - Per Investigator's discretion, subjects may participate in the exercise in order to obtain low glucose values.

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

25.9.10. Home-Use Portion Data Analysis - Will Be Performed on Primary Datasets Only

Data from the home-use portion will be described. Analysis will include but not be limited to: 20% mean agreement rate (±20 mg/dL [1.1 mmol/L] when SG less than (<) 80 mg/dL [4.4 mmol/L]) for all fingersticks (capillary SMBG) collected, Clark Error Grid, other accuracy analysis, absolute relative difference (ARD), bias, correlation between sensor and SMBG and Bland-Altman plots. In addition, 20% mean agreement rate (±20 mg/dL [1.1 mmol/L] when SG less than (<) 80 mg/dL [4.4 mmol/L]) will be described by subgroups of: age, YSI™* FST, diabetes classification, BMI/weight, CGM experience, HbA1c and exercise activity (if applicable).

25.10. Safety

Descriptive summary will be used to characterize adverse events:

- Skin assessment at sensor insertion sites
- All adverse events

25.11. Device Deficiencies

Descriptive device deficiencies will include all reports of sensor damage, breakage or fracture.

25.12. Subject Feedback

Descriptive summary will be used to characterize study survey results.

26. Ethics

26.1. Statement(s) of Compliance

IRB/EC

This CIP, any subsequent amendments to this CIP, the ICF and assent form (if applicable), subject materials and any form of subject recruitment information (e.g. advertisements) relating to this study will be approved by the responsible IRB/EC in accordance with 21 CFR Part 56 **(US only)**/ NMPA Order No. 25 **(China only)** and local regulatory requirements as applicable. The investigational center will not initiate any subject activities until IRB/EC approval has been granted, the sponsor has cleared the investigational center to begin the study, and the investigational center staff has been appropriately trained to conduct the study.

China only:
This study is a pre-market clinical trial for product registration. The study will be conducted in accordance with the laws and regulations of China, including any future applicable laws and regulations in China.

Regulatory Compliance

US only:

This clinical study will be conducted in compliance with the Clinical Investigation Agreement; United States Code of Federal Regulations (CFR) Title 21 Part 50 (Protection of Human Subjects), Part 54 (Financial Disclosure by Clinical Investigators), Part 11 (Electronic Records; Electronic Signatures), Part 812 (Investigational Device Exemptions), and Part 56 (Institutional Review Boards) and all other applicable federal and local regulatory requirements.

China only:

To protect the rights and welfare of patients, this clinical study will be conducted in compliance with the latest version of the Declaration of Helsinki , the Clinical Trial Agreement and CIP, the laws and regulations of China including NMPA Order No. 25 (which includes Good Clinical Practice for Medical

Devices and the exclusion stated below), Announcement of NMPA on Filing of Medical Device Clinical Trial (2015, No.87) and also including applicable data protection laws. Investigational centers will also comply with any additional EC requirements applicable. As this is a multiple center global study, per agreement by Center for Medical Device Evaluation (CMDE), the requirements of the leading site and coordinating investigator(s) will not be applicable for the study (exception to the NMPA Order No.25).

All regions:

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 and assent (if applicable) process, IRB/EC 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. Per IRB/EC, 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.

Regulatory Submission

China only:

The clinical trial filing will be completed prior to conduct of this study per the requirement of the Announcement of NMPA on Filing of the Medical Device Clinical Trial (2015, No. 87). Sponsor should be responsible for filing the study to Shanghai Municipal Food and Drug Administration after EC approval of the current version of the CIP and fully executed Clinical Trial Agreement.

All regions:

Ethical Considerations

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

Sponsor's Support

Sponsor representatives may provide support as required for the study, such as technical support at investigational center. Sponsor representatives may provide technical support as required for the study under supervision of the PI, including:

1) Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities.
2) Technical support will be provided during study period.
3) Technical support will be under the supervision of a study investigator, but no data entry on the eCRF shall be performed by Medtronic personnel or their representatives at investigational centers.
4) Technical support to conduct device interrogations.

26.2. Investigator's Responsibilities

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. Each investigational center shall designate a primary investigator who will have overall responsibility for the conduct of the investigation at the investigational center.

The primary investigators (and co-investigators if applicable) are responsible for:

- **US only**: Conduct of the investigation in accordance with the signed Form of Investigator Statement for clinical investigations of medical devices, CIP, applicable regulations set forth in 21 CFR 812 and other applicable FDA regulations, and any conditions of approval imposed by the reviewing IRB or FDA regulatory requirements
- **China only**: Conduct of the investigation in accordance with the signed Investigator Statement, CIP, applicable regulations set forth in NMPA Order No.25 and other applicable NMPA regulations and any conditions of approval imposed by the reviewing EC or NMPA regulatory requirements
- **US only:** 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.
- **China only:** Conduct of investigation in accordance to regulations from NMPA 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 NMPA'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.
- Protecting the rights, safety, and welfare of subjects under the investigator's care

1) Providing reasonable medical care for study subjects for medical problems that arise during participation in the trial that are, or could be, related to the study intervention
2) Providing reasonable access to needed medical care, either by the investigator or by another identified, qualified individual (e.g., when the investigator is unavailable, when specialized care is needed)
3) Adhering to the CIP so that study subjects are not exposed to unreasonable risks

- Controlling devices under investigation
- Providing adequate supervision of those to whom tasks have been delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of a clinical study.
- Ensuring that the requirements for obtaining informed consent and assent are met in accordance with 21 CFR 50(**US only)**/ NMPA (**China only)**
- Supervising the use of investigational device. An investigator shall permit an investigational device to be used only with subjects under the investigator's supervision. An investigator shall not supply an investigational device to any person not authorized to receive it.
- Disposing of device properly. Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.
- 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 another investigator (if applicable), an IRB/EC, the sponsor, a monitor, or FDA (if applicable)/ NMPA (if applicable), including required reports.
    - records of each subject's case history and exposure to the device
    - the CIP, with documents showing the dates of and reasons for each deviation from the CIP
    - any other records the FDA/NMPA requires to be maintained by regulations or by specific requirement for a category of investigations or a particular investigation
- Preparation and submission to Medtronic and, when required, FDA/NMPA and the reviewing IRB/EC, the following complete, accurate, and timely reports:
    - any reportable AEs (see Section 22) occurring during an investigation
    - progress reports on the investigation as required by the FDA/NMPA and IRB/EC
    - any deviation from the CIP made to protect the life or physical well-being of a subject in an emergency
    - any use of the device without obtaining informed consent and assent (if applicable)
    - any further information requested by FDA/NMPA and the IRB/EC about any aspect of the investigation

- Permitting FDA/NMPA or other regulatory authorities to inspect and copy any records pertaining to the investigation including, in certain situations, those which identify subjects
- Meeting with the monitor to discuss study progress and findings
- Ensuring that investigational center resources are adequate to fulfill the obligations of the study
- Ensuring completion of eCRF to include: entry and addressing discrepancies in a timely fashion and approving selected eCRFs.

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

27. Study Administration

27.1. Training of Clinical Staff

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

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

27.2. Monitoring

Monitoring visits may be conducted at the start, during and at the closure of the clinical study in accordance with Medtronic SOPs and the Monitoring Plan. At minimum, it will be verified whether signed and dated ICF and assent form (if applicable) have been obtained from each subject at the point of enrollment and that AEs discussed in Section 22 were reported via completion of the AE eCRFs. More details regarding the monitoring activities (frequency of monitoring visits, planned extent of source data verification) are described in the Monitoring Plan.

27.2.1. 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, regulatory agency personnel and the Clinical Study Manager. This accessibility is of particular importance for reviewing data in the eCRF. Direct access to subject medical files for source data verification will need to be granted and prepared prior to any monitoring visits.

27.2.2. Audits and Investigational Center Inspections

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

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

27.2.3. Investigational Center Disqualification

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

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

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

27.3. Data Management

27.3.1. Data Collection

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

27.3.1.1. Electronic Case Report Forms (eCRFs)

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

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

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

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

27.3.1.1. CareLink™ Personal For Clinical Research Software (US only)

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.

27.3.1.2. Subject Survey

The subject survey will be collected on paper that will be kept at the investigational center. The investigator, or designated investigational center staff, will enter the answers of the subject on the paper survey into OC-RDC system. It is important that the investigator or designated investigational center staff verifies survey for completeness.

27.3.1.3. Synergy Download Utility Software

The investigational center will use the Synergy Download Utility Software to set time, check software/firmware version, and download data from DS5. Communication between the transmitters and the computer is done via the Blue Adapter.

Once the DS5 data is downloaded, each investigational center will access a specified database and upload the device data.

27.3.2. Time Windows For Completion and Submission of eCRFs

It is expected that eCRFs are completed in a timely manner with the exception of the reportable AEs (see Section 22.3). After data entry, eCRFs should be submitted (i.e. saved) so that Monitors can proceed with data verification without delay.

27.3.3. Data Review and Processing

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

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

27.4. Direct Access to Source Data/Documents

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

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

27.5. Confidentiality

The investigator will ensure that the subject's anonymity is maintained. Subjects will not be identified in any publicly released reports of this study. All records will be kept confidential to the extent provided by federal, state and local law **(US only)**/ Chinese law and regulation **(China only).** The study monitors and other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records. The investigator will inform the subjects that the above-named representatives will review their study-related records without violating the confidentiality of the subjects. All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified only by the subject ID code in order to maintain subject confidentiality. All records will be kept locked and all computer entry and networking programs will be done with coded numbers only.

27.6. Liability

Subjects will be paid for participation. Refer to the ICF on the details of the subject's compensation. In addition, refer to CTA for subject's compensation and indemnification.

China only:
Medtronic maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a clinical study insurance statement/certificate will be provided to the EC. Finance information will be documented in Clinical Trial Agreement.

27.7. Probability Analysis of Success

Guardian™ Sensor (3) has been evaluated in previous clinical studies and has demonstrated the within 20% mean agreement rate (±20 mg/dL [1.1 mmol/L] when SG less than (<) 80 mg/dL [4.4 mmol/L]), significantly higher than 75%. DS5 sensor is expected to perform as well as Guardian™ Sensor (3). The probability of success is high.

27.8. Probability Analysis of Failure

Guardian™ Sensor (3) has been evaluated in previous clinical studies and has demonstrated the within 20% mean agreement rate (±20 mg/dL [1.1 mmol/L] when SG less than (<) 80 mg/dL [4.4 mmol/L]), significantly higher than 75%. DS5 sensor is expected to perform as well as Guardian™ Sensor (3). The probability of failure is low.

27.9. Responsibilities of All Parties (China Only)

Investigator responsibilities will be included in Clinical Trial Agreement and subject responsibilities will be available in ICF. Sponsor will undertake all the responsibilities of the sponsor as required per NMPA regulations.

27.10. CIP Amendments

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

Sponsor can decide to review the CIP based on new information (i.e. from an investigator, the CEC or the study team) and will submit any significant amendment to the CIP, including a justification for this amendment, to the appropriate regulatory agency (if applicable) and to the investigators to obtain approval from their IRB/EC. 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.

27.11. Records and Reports

27.11.1. Investigator Records

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

- All essential study documents and correspondence that pertains to the clinical study
- CIP and, if applicable, any amendments
- Medtronic and IRB/EC-approved Subject ICF and assent form (if applicable)
- IRB/EC and Regulatory authority approval or notification
- Completed Delegated Task List
- Training documentation of all investigational center staff
- Subject Screening log and/or Subject ID log
- Signed, dated and fully executed Subject ICF and assent forms (if applicable)
- Source documentation
- Fully executed eCRFs and corrections
- Report of AEs and Device Deficiencies
- Device accountability records
- CIP Deviation/ CIP Non-Compliance, if any
- Clinical Bulletins- A brief official update or summary of current study news on a matter of immediate interest and high importance to investigational center surrounding the CIP.
- Current signed and dated curriculum vitae (CV) of PI (and key study team members if required per local requirements)
- Study Reports

US only:

- Report of Prior Investigations and/or user guide
- Fully signed clinical study agreements (i.e., including Form of Investigator Statement, Clinical Trial Agreement, Financial Disclosure and Confidential Disclosure Agreement)

China only:

- Investigator's Brochure and/or user guide
- Fully signed clinical study agreements (i.e., including Investigator Statement, Clinical Trial Agreement, and Confidential Disclosure Agreement)

27.11.2. Investigator Reporting Responsibilities

Table 4. US Investigator Reporting Requirements

Report	Submit to	Description/Constraints
AEs and Device Deficiencies	Sponsor, IRB, and regulatory authority, where applicable	Refer to section 22 and 24 for reporting requirements.
Withdrawal of IRB approval (either suspension or termination)	Sponsor	An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
Progress report	Sponsor and IRB	The investigator must submit this report to the sponsor and IRB at regular intervals, but in no event less than yearly.
Study deviations	Sponsor and IRB	Notice of deviations from the CIP to protect the life or physical wellbeing of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred.
Failure to obtain informed consent and assent prior to investigational device use	Sponsor and IRBs	If an investigator uses a device without obtaining informed consent and assent, the investigator shall report such use within 5 working days after device use.
Final report	Sponsor IRBs Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation.
Other	Sponsor, IRB and FDA	An investigator shall, upon request by a reviewing IRB, FDA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation.

Table 5. China Investigator Reporting Requirements

Report	Submit to	Description/Constraints
AEs and Device Deficiencies	Sponsor, EC, and regulatory authority, where applicable	Refer to section 22 and 24 for reporting requirements.
Withdrawal of EC approval (either suspension or termination)	Sponsor	An investigator shall report to the sponsor a withdrawal of approval by the reviewing EC of the investigator's part of an investigation.
Progress report	Management department of medical device clinical study then they will submit to sponsor and EC (if needed per EC requirements)	Provide progress report, including safety summary and deviations, if required by local law or EC. (ISO 14155:2011) During the clinical trials, the investigators should notify sponsor and report to the EC in a timely manner by promptly reporting the progress report to the medical device clinical trial administration department of the investigational centers, including the safety summary and deviation report.
Study deviations	Management department of medical device clinical study then they will submit to sponsor and EC	Any deviation from the clinical investigational plan shall be recorded together with the explanation of the deviation. Protocol deviations that may affect the subjects' rights and interests, safety, health or the scientificity of clinical trials, including deviation regarding requests and reports.
Failure to obtain informed consent and assent prior to investigational device use	Sponsor and EC	Informed consent and assent shall be obtained in writing and documented before a subject is enrolled into the clinical investigation. *(Adapted from ISO 14155:2011)*
Final report	Management department of medical device clinical study then they will submit to sponsor and EC (if needed per EC requirements)	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation.

Report	Submit to	Description/Constraints
Other	Sponsor, EC and NMPA	An investigator shall, upon request by a reviewing EC, NMPA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation.

27.12. Record Retention

The sponsor and investigator will retain all records and documents pertaining to this study. They will be available for inspection by the appropriate regulatory agencies. In addition, the Investigator will retain the source documents from which the information entered on the eCRF was derived.

The Investigator should not dispose of these records without the approval of the sponsor.

US only: These records are to be retained in a secure storage facility maintained by the investigational center until 2 years (or longer if local laws require) after approval of the above-listed study devices or termination of the study, whichever is longer.

China only: These records are to be retained in a secure storage facility maintained by the investigational center for 10 years after completion of the study or termination of the study, whichever is longer. The sponsor shall keep the clinical data indefinitely.

27.13. Suspension or Early Termination

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

27.13.1. Early Investigational Center Suspension or Termination

Sponsor, IRB/EC 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/EC, non-compliance to the CIP or lack of enrollment). The suspended clinical studies cannot be resumed without permission from IRB/EC.

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/EC 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:

- **US only:** the sponsor and IRB, if applicable
- **China only:** the sponsor, EC, and department of food and drug administration of the concerned province, region and municipality

China only:

If the sponsor decides to suspend or early terminate the study, the medical device clinical trial management departments of clinical trial institutions should be notified within 5 days with the rationale in writing.

27.13.2. 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.

China only: The subject will return the study devices to the Investigational Center unless subject is allowed to keep them per country requirement, receive appropriate treatment and follow-up.

27.14. Study Close Out

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

China only: Upon completion of clinical studies, the sponsor shall send written notice to the management of food and drug administration of the concerned province, autonomous region and municipality.

27.15. Publication and Use of Information

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

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

28. References

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

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

David Klonoff et al. CLSI. Performance Metrics for Continuous Interstitial Glucose Monitoring; Approved Guideline. CLSI Document POT05-A. Wayne,PA, Clinical and Laboratory Standards Institute. 2008;28(33).

Joan Parkes et al. A New Consensus Error Grid To Evaluate The Clinical Significance of Inaccuracies In The Measurement of Blood Glucose. Diabetes Care. 2000; 23(8):1143-1148.

Medtronic, Inc. Subject Exit Market Survey. 2020

William Clarke et al. Evaluating Clinical Accuracy of Systems For Self-Monitoring of Blood Glucose. Diabetes Care. 1987;10(5):622-628.

CDC weight classification:
http://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html

World Health Organization, Global Database on Body Mass Index. Accessed May 11, 2011.
O'Brien, P.C.; Fleming, T.R. (1979). "A Multiple Testing Procedure for Clinical Trials". Biometrics. 35 (3): 549–556.

29. Appendices

29.1. Appendix A: Names and addresses

29.1.1. Investigational Centers and IRB/EC

At the time of CIP was finalized, the investigational centers at which the study will be conducted had not been identified nor had any IRBs/ECs reviewed the investigational plan. The list of investigational centers will be maintained under a separate cover.

China only:
The Investigational Centers are filed at the NMPA Filing System. The PI must have a Sub-senior and higher related professional title and qualification at the medical institutions, such as Associate Chief Physician or Associate Professor and/or Associate Researcher.

29.1.2. Monitors Contact Information

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

US only:

[redacted]

[redacted]

Medtronic

710 Medtronic Parkway

Minneapolis, MN 55432

China only:

[redacted]

Medtronic

Floor 6-17, Building B, The New Bund World Trade Center Phase I,

No.5, Lane 255 Dong Yu Rd,

Pudong, Shanghai

P.R. China

All regions:

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.

29.1.3. Sponsor's and Local Sponsor's Staff Contact

A list of sponsor's and local sponsor's staff will be kept separate from the CIP and provided to the investigators. The sponsor will maintain an updated list.

29.2. Appendix B: Labeling and IFUs of Devices

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

29.3. Appendix C: Sample Consent Materials

Samples of the following consent forms/materials will be provided in a separate cover which includes:

- **US only**: California Experimental Subject's Bill of Rights (if applicable), ICF and assent form, and the HIPAA Authorization.
- **China only:** ICF and assent form

29.4. Appendix D: Relevant Qualification Document(S) Of The Sponsor/Local Sponsor(Agent)- China Only

Relevant qualification document(s) of the sponsor/local sponsor(agent) will be provided under a separate cover.

30. Version History

Version	Summary of Changes	Author(s)/Title
A	Not Applicable, New Document.	[redacted]
B	• Updated inclusion criteria #2 • Updated Deviation Handling section	[redacted]
C (Equivalent to FDA Version C.1)	• See "Attachment 1: CIP330 Description of Protocol Changes Version B to C.1" for details on changes • Updated year to 2021 in copyright statement • Updated Primary Endpoints, Secondary Endpoints, and Datasets Expected with revised Athena algorithm and additional new Athena Plus algorithm	[redacted]

D (Equivalent to FDA Version D.1)	• See "Attachment 1: CIP330 Description of Protocol Changes Version C to D.1" for details on changes
	• Updated year to 2022 in copyright statement
	• Updated Background section
	• Updated Datasets Expected for Athena Plus Algorithm
	• Updated the following sections which will be performed on primary and secondary datasets:
	  ○ Primary Endpoints
	  ○ Secondary Endpoints
	• Modified "Agreement, ARD, Bias (Accuracy Analyses)" section
	• Updated the following sections which will be performed on primary datasets only:
	  ○ Numbers of Readings in the Low and High Ranges
	  ○ Difference Tables Comparing Sensor and Reference Readings
		[redacted]

	○ Clarke Error Grid Analysis (EGA) of Paired Sensor and YSI™* and Reference Values ○ Precision Analysis ○ Comparison of CGM Performance to Reference under conditions leadings to Alert ○ Other Accuracy Analyses ○ Home-Use Portion Data Analysis	