Medtronic	
Study Title	A Pivotal Study to Evaluate Enlite™ Sensor Performance with iPro™2 in China
NCT Number	NCT03417466
Document Description	Study Protocol (Version B)
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Medtronic

Clinical Investigation Plan (CIP)

Study Title	A Pivotal Study to Evaluate Enlite™ Sensor Performance with iPro™2 in China
CIP Identifier	313
Study Product Name & Study Product Model	• Enlite Sensor (MMT-7008) • Enlite Serter (MMT-7510)-referred to as Serter in the CIP • iPro2 recorder (MMT-7741)-referred to as iPro2 in the CIP
Category of investigational medical device	Class III
Class III medical devices requiring clinical trial approval	No
Similar product in China	Yes
Sponsor	Medtronic MiniMed ("Medtronic") 18000 Devonshire St Northridge, CA 91325 866.948.6633
Local Sponsor (Agent)	Medtronic (Shanghai) Management Co., Ltd. 3rd Floor, No. 180. Rijing Road, China (Shanghai) Pilot Free Trade Zone, 200131, Shanghai, P.R.China
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Lead Principal Investigator(s)/Lead Study Site	Weipjng Jia, President of Shanghai Sixth People's Hospital

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1. Investigator Statement

Study product Name	iPro2 with Enlite Sensor and Enlite Serter
Sponsor	Medtronic MiniMed
Clinical Investigation Plan Identifier	313
Version Number/Date	B/18-SEP-2017

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;

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

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;

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;

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

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

Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

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2. Glossary

Term	Definition
A1C	Glycosylated hemoglobin
AE	Adverse Event
ARD	Absolute Relative Difference
BG	Blood Glucose
BMI	Body Mass Index
CEC	Clinical Events Committee
CFDA	China Food and Drug Administration
CGM	Continuous Glucose Monitoring
CGMS	Continuous Glucose Monitoring System
CIP	Clinical Investigation Plan
CTA	Clinical Trial Approval
CV	Curriculum Vitae
DKA	Diabetic Ketoacidosis
EC	Ethics Committee
eCRF	Electronic Case Report Form
EGA	Error Grid Analysis
ER	Emergency Room
EOS	End of Study
FST	Frequent Sample Testing
Hct	Hematocrit

Term	Definition
ICF	Informed Consent Form
ISIG	Interstitial Signal
IV	Intravenous
MARD	Mean Absolute Relative Difference
OC-RDC	Oracle Clinical Remote Data Capture
PC	Personal Computer
POC	Point of Care
QC	Quality Control
SAE	Serious Adverse Event
SGV	Sensor Glucose Value
SID	Subject Identification
SMBG	Self-Monitoring of Blood Glucose
SQ	Subcutaneous
SSL	Secure Socket Layer
UADE	Unanticipated Adverse Device Effect
USB	Universal Serial Bus
YSI	Yellow Springs Instrument

3. Synopsis

Title	A Pivotal Study to Evaluate Enlite™ Sensor Performance with iPro™2 in China
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. 3rd Floor, No. 180. Rijing Road, China (Shanghai) Pilot Free Trade Zone, 200131, Shanghai, P.R.China
Indication under investigation	Type 1 diabetes, Type 2 diabetes
Devices	*Investigational Devices:* • Enlite Sensor (MMT-7008) • Enlite Serter (MMT-7510)-referred to as Serter in the CIP • iPro2 recorder (MMT-7741)-referred to as iPro2 in the CIP *Non-Investigational Devices:* • iPro2 Docking Station (MMT-7742)-referred to as iPro2 Dock in the CIP • Universal Serial Bus (USB) cable and AC PowerAdapter (MMT-7747) • iPro2 Cleaning Plug (MMT-7744) • CareLink™ iPro Therapy Management Software for Diabetes (MMT-7340)- referred to as CareLink iPro in the CIP (desktop software) • Ascencia CONTOUR® PLUS Blood Glucose Meter (7619) • Ascencia CONTOUR PLUS Blood Glucose Test Strips (7662) • Ascencia CONTOUR PLUS Control Solution (7680)
Category of investigational medical device	Class III

Class III medical devices requiring Clinical Trial Approval (CTA)	No
Purpose	The purpose of this study is to demonstrate the performance and safety of the Enlite Sensor over 144 hours (6 days) when inserted in the abdomen and used with the iPro2 in subjects age 14 – 75 years.
Objective(s)	The primary objective of the study is to demonstrate the accuracy of Enlite Sensor when connected to iPro2 when used over a period of 6 days.
Study Design	This study is a multi-center, randomized, prospective single-sample correlational design without controls. Up to 72 subjects will be enrolled in order to have approximately 60 subjects complete the study. Three investigational centers in China will be used during this study. Each subject will wear the following devices: • Two Enlite Sensors each connected to an iPro2 for approximately 6 days Sensor Location: • The 2 Enlite Sensors will be worn in the abdomen area. Investigational center staff will insert sensors and connect to the iPro2s. During the study, each subject will be randomized and undergo one Yellow Springs Instrument (YSI™) frequent sample testing (FST) (Day 1, 3-4, or 6). On the evening prior to FST, subjects will be asked to fast for approximately 12 hours and adjust their insulin and medications according to routine care (for example as they would do for fasting lipid panel). Subjects may fast for shorter period of time **based on investigator discretion.** The subject should be in fasting status upon arrival hospital to start FST process. **The feeding protocol may be modified based on investigator discretion.** The duration of FST will be approximately 7 hours. During the study, 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. The Study Meter may be used for treatment decisions and calibration of Enlite Sensor.

	Fingerstick Testing: A minimum of 4 fingerstick glucose readings per day will be requested for subjects. Subjects should test prior to meals and at bedtime.
Randomization	Subjects will be randomized to one of the following sensor wear days: Day 1, 3-4, or 6 which determines when they will be participating in the in-clinic YSI FST.
Sample Size and Investigational Centers	Up to 72 subjects will be enrolled in order to have approximately 60 subjects complete the study. Three investigational centers in China will be used during this study. A minimum of 12 subjects and a maximum of 30 subjects will be enrolled at each investigational centers. • Diabetes cohorts based on insulin requirement ○ N= Minimum of 4 type 1 insulin requiring ○ N= Minimum of 20 type 2 insulin requiring ○ N= Minimum of 25 type 2 non-insulin requiring
Duration	The study is anticipated to last no more than 12 months from investigational center initiation to finalization of all data entry and monitoring procedures. The subject's maximum participation from study start to completion is approximately 1 – 3 weeks (including replacement sensor wear and repeat in clinic procedures).
Inclusion/Exclusion Criteria	**Inclusion Criteria:** 1. Subject is 14 - 75 years of age at time of screening 2. Subject has a clinical diagnosis of type 1 or 2 diabetes as determined via medical record or source documentation by an individual qualified to make a medical diagnosis 3. Subject has adequate venous access as assessed by investigator or appropriate staff 4. Subject is willing to follow the study procedures and willing to come to study visits. 5. Subject is willing to perform at least 4 self-monitoring of blood glucose (SMBG) per day for 6 days

	Exclusion Criteria: 1. Subject will not tolerate tape adhesive in the area of Enlite Sensor placement as assessed by qualified individual. 2. Subject has any unresolved adverse skin condition in the area of study device or device placement (e.g., psoriasis, rash, *Staphylococcus* infection) 3. Subject is actively participating in an investigational study (drug or device) wherein they have received treatment from an investigational study (drug or device) in the last 2 weeks 4. Subject is female and has a positive pregnancy screening test 5. Females of child bearing age and who are sexually active should be excluded if they are 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 a hematocrit (Hct) lower than the normal reference range 8. Subject may not be on the research staff of those performing this study

Study Timeline:	The subject's participation from study start to completion is approximately 1 – 3 weeks (including replacement sensor wear and repeat in clinic procedures).
	Additional rescheduled visits could occur if Enlite Sensors dislodge and new Enlite Sensors must be re-inserted (See Replacement Sensors, Section 9.6)
	• Visit 1: Consent and Screening
	• Visit 2: Randomization
	  ○ Visit 1 and 2 can be combined, however all eligibility criteria on Visit 1 should be met, including review of Hct prior to Visit 2.
	  ○ Visit 1 and Visit 2 should be no more than 2 weeks apart.
	• Visit 3: Study Training and iPro2 Placement & Sensors Insertion
	  ○ Two Enlite Sensors each connected to an iPro2
	  ○ Dispense Patient Log Sheet
	• Visit 4: YSI FST.
	  ○ Study training and iPro2 placement & sensors

	insertion (Day 1 subjects who have not already received study training and iPro2 placement and sensor insertion from Visit 3) ○ Subjects will undergo one YSI FST on any one of the following sensor wear days: ▪ Day 1 (1 – 25 hours) ▪ Day 3 – 4 (49 – 97 hours) ▪ Day 6 (121 – 145 hours) ▪ • Visit 5: End of Study (EOS) Visit ○ iPro2 removed **(Please note that the subject should target wearing the device for 145 hours or longer from time of insertion)** ○ Investigational center staff will: ▪ Download the iPro2 data from CareLink iPro following completion of the study devices wear ▪ Obtain subject's Study Meter BG values and enter into CareLink iPro ▪ Collect subject's Patient Log Sheet ▪ Provide iPro2 data to sponsor ○ Return study devices ○ Subject complete questionnaires ○ Random assignment for primary sensor and secondary sensor via RDC Guidelines for Combining Visits: • All subjects meeting eligibility criteria: ○ Visit 1 and 2 can be combined, however all eligibility criteria on Visit 1 should be met, including review of Hct prior to Visit 2. • Subjects randomized to FST Day 1

	○ Subjects doing FST on Day 1 may combine Visit 2 and Visit 3 as long as they are able to perform Visit 4 FST in the second half of FST day. ○ For example, subject does Visit 1 and 2 in the morning and performs Visit 3 in the afternoon. Subjects comes in the next day for Visit 4 in the morning within approximately 25 hours from time of insertion. • Subjects randomized to FST Day 3-4 ○ May combine Visit 2 and Visit 3 • Subjects randomized to FST Day 6 ○ May combine Visit 2 and Visit 3 ○ May combine Visit 4 and Visit 5 as long as the subject has worn N=145 hours.
Device Deficiencies:	Subject and investigational center reports of device deficiencies will be collected by electronic Case Report Forms (eCRF) for device troubleshooting and device complaints. For additional information, see Section 13.
Subject Stopping Rules	The subject will stop the study if there is an Unanticipated adverse device effect (UADE).
Stopping Rules Entire Study	The study will stop if there is an UADE
Repeat Rules for In-Clinic Procedures	• Concurrent failure of both the primary and back-up YSI instruments (if applicable) during YSI FST. • If a sensor dislodges prior to YSI FST, the sensor will be replaced per sponsor's recommendation. • If subject experiences unresolved intravenous (IV) occlusions during YSI FST requiring fingerstick measurements for a prolonged time period, the FST procedures may be rescheduled per sponsor recommendation.
Statistical Analysis for Endpoints and Hypothesis:	*Primary Endpoint* Sensor values from primary sensor 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 Reference BG less than or equal to (≤) 80 mg/dL (4.4 mmol/L) between Enlite Sensor values and YSI plasma glucose values during YSI FST days defined as μ will be evaluated against the null Hypothesis:

H0: μ ≤ 60%

H1: μ > 60%

One sample T test will be used for the analysis of the primary endpoint. The 97.5% lower confidence limit of the mean agreement rate will be tested against corresponding threshold.

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Secondary Endpoints

Sensor values from primary sensor will be compared to YSI plasma glucose values during YSI FSTs. And the 95% Confidence Interval of Mean Absolute Relative Difference (MARD), mean rate in Zone A+B of Clarke Error Grid and Consensus Error Grid will be provided.

Other descriptive endpoints

- 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 Reference BG less than or equal to (≤) 80 mg/dL (4.4 mmol/L)) for all fingersticks (capillary SMBG) collected, Clarke Error Grid Analysis (EGA), Consensus Error Grid analysis, Absolute Relative Difference (ARD), bias, correlation between Enlite Sensor and fingersticks (capillary SMBG), and Bland-Altman plots. In addition, 20% mean agreement rate (±20 mg/dL (1.1 mmol/L) when Reference BG less than or equal to (≤) 80 mg/dL (4.4 mmol/L) will be described by the subgroups mentioned below: frequent sampling. The number of actual calibrations performed per day by study subjects will be tabulated and presented.
- Similar descriptive subgroup analysis of Enlite Sensor performance with YSI in all devices will be performed, in additional to Continuous Error Grid analysis:
  - **FST:**
    - Day 1
    - Day 3-4
    - Day 6
- Precision analysis: ARD, bias, and 20% mean agreement rate (±20 mg/dL (1.1 mmol/L) when Reference BG less than or equal to (≤) 80 mg/dL (4.4 mmol/L)) will be performed.

	Safety
	For Safety analysis, no formal hypothesis testing will be performed. Descriptive analytics will be used to summarize safety events. Safety events which will be characterized include:
	• Skin assessment of Enlite Sensor insertion sites
	• All adverse events (AEs) to include but not limited to:
	  ○ Device Related AE
	  ○ Procedure Related AE
	  ○ Serious Adverse Event (SAE)
	  ○ Serious Adverse Device Effects (SADE)
	  ○ UADE
	  ○ Severe Hypoglycemia
	  ○ Diabetic Ketoacidosis (DKA)
	
	Device Deficiencies
	Descriptive summary will be used to characterize device deficiencies.
	
	Subject Feedback
	Descriptive summary will be used to characterize study questionnaire results. The questionnaire will use a Likert scale rating to assess their Enlite Sensor experience.

4. Introduction

4.1. Background

The iPro2 recorder is intended to continuously record interstitial glucose levels in persons with diabetes mellitus. This information is intended to supplement, not replace, blood glucose (BG) information obtained using standard home glucose monitoring devices. The information collected by the iPro2 recorder may be downloaded to a computer and reviewed by healthcare professionals. The information may allow identification of patterns of glucose-level excursions above and below a desired range, facilitating therapy adjustments, which may minimize these excursions.

The study is designed to demonstrate the performance of the Enlite Sensors used with the iPro2 when inserted in the abdomen of subjects ages 14 – 75 years and used for 6 days.

Accuracy data will be calculated based on comparing values from the iPro2 and Enlite Sensor to a "gold standard" (Yellow Springs Instrument [YSI™] plasma glucose values) in subjects during YSI frequent sample testing (FST). YSI glucose analyzers have been recognized standards for the measurement of BG and will be utilized across the investigational centers for the tests.

4.2. Purpose

The purpose of this study is to demonstrate the performance and safety of the Enlite Sensor over 6 days when inserted in the abdomen and used with the iPro2 in subjects age 14 – 75 years.

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 Enlite sensor when connected to iPro2 when used over a period of six days.

5.2. Endpoints

5.2.1. Primary Endpoint

Sensor values from primary sensor 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 Reference BG less than or equal to (≤) 80 mg/dL (4.4 mmol/L) between Enlite Sensor values and YSI plasma glucose values during YSI FST days defined as μ will be evaluated against the null Hypothesis:

H0: $\mu \leq 60\%$

H1: $\mu > 60\%$

One sample T test will be used for the analysis of the primary endpoint. The 97.5% lower confidence limit of the mean agreement rate will be tested against corresponding threshold.

5.2.2. Secondary Endpoint(s)

Sensor values from primary sensor will be compared to YSI plasma glucose values during YSI FSTs.The 95% Confidence Interval of Mean Absolute Relative Difference (MARD), mean rate in Zone A+B of Clarke Error Grid and Consensus Error Grid will be provided.

5.2.3. Other Descriptive endpoints

- Data from the home-use portion will be described. Analysis will include but not be limited to: Consensus Error Grid analysis, 20% mean agreement rate (±20 mg/dL (1.1 mmol/L) when Reference BG less than or equal to (≤) 80 mg/dL (4.4 mmol/L)) for all fingersticks (capillary SMBG) collected, Clarke Error Grid Analysis (EGA), Consensus Error Grid analysis, Absolute Relative Difference (ARD), bias, correlation between Enlite Sensor and fingersticks (capillary SMBG), and Bland-Altman plots. In addition, 20% mean agreement rate (±20 mg/dL (1.1 mmol/L) when Reference BG less than or equal to (≤) 80 mg/dL (4.4 mmol/L)) will be described by the subgroups mentioned below: frequent sampling. The number of actual calibrations performed per day by study subjects will be tabulated and presented.
- Similar descriptive subgroup analysis of Enlite Sensor performance with YSI in all devices will be performed, in additional to Continuous Error Grid analysis:
    - **FST:**
        - **Day 1**
        - **Day 3-4**
        - **Day 6**

- Precision analysis: ARD, bias, and 20% mean agreement rate (±20 mg/dL (1.1 mmol/L) when Reference BG less than or equal to (≤) 80 mg/dL (4.4 mmol/L) will be performed.

5.2.4. Safety

For Safety analysis, no formal hypothesis testing will be performed. Descriptive analytics will be used to summary safety events. Safety events which will be characterized include:

- Skin assessment at Enlite Sensor insertion sites
- All adverse events (AEs) to include but not limited to:
    - Device Related AE
    - Procedure Related AE
    - Serious Adverse Event (SAE)
    - Serious Adverse Device Effects (SADE)
    - Unanticipated adverse device effect (UADE)
    - Severe Hypoglycemia
    - Diabetic Ketoacidosis (DKA)

5.2.5. Device Deficiencies

Descriptive summary will be used to characterize device deficiencies.

5.2.6. Subject Feedback

Descriptive summary will be used to characterize study questionnaire results. The questionnaire will use a Likert scale rating to assess their Enlite Sensor experience.

6. Study Design

This study is a multi-center, randomized, prospective single-sample correlational design without controls. Up to 72 subjects will be enrolled in order to have approximately 60 subjects complete the study. Three investigational centers in China will be used during this study.

Each subject will wear the following devices:

- Two Enlite Sensors, each connected to an iPro2, for approximately 6 days

Sensor Location:

- The 2 Enlite Sensors be worn in the abdomen area. Investigational center staff will insert sensors and connect to the iPro2s.

During the study, each subject will be randomized and undergo one YSI FST (Day 1, 3-4, or 6).

On the evening prior to FST, subjects will be asked to fast for approximately 12 hours and adjust their insulin and medications according to routine care (for example as they would do for fasting lipid panel). Subjects may fast for shorter period of time **based on investigator discretion.**

The subject should be in fasting status upon arrival hospital to start FST process. **The feeding protocol may be modified based on investigator discretion.**

The duration of FST will be approximately 7 hours.

During the study, 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. The Study Meter may be used for treatment decisions and calibration of Enlite Sensor.

Fingerstick Testing: A minimum of 4 fingerstick glucose readings per day will be requested for subjects. Subjects should test prior to meals and at bedtime.

6.1. Duration

The study is anticipated to last no more than 12 months from investigational center initiation to finalization of all data entry and monitoring procedures. This includes an estimated time of study enrollment being completed in approximately 6 months. The subject's maximum participation from study start to completion is approximately 1 – 3 weeks (including replacement sensor wear and repeat in clinic procedures).

6.2. Rationale

The clinical study will evaluate Sensor Glucose Values (SGVs) compared to YSI plasma glucose values in patients with type 1 or 2 diabetes during in-clinic testing. The study will evaluate the use of Enlite glucose sensor with iPro2 for performance and safety.

Currently, iPro2 with Enlite is not approved by the China Food and Drug Administration (CFDA). iPro2 is a commercially available Continuous Glucose Monitoring (CGM) device that is indicated for use in all patients with diabetes only with the use of Sof-sensor™. This study is being done for regulatory approval of Enlite Sensor and Serter with iPro2. In addition, performing this study will help assess the subjects' feedback on the devices being studied.

7. Product Description

7.1. Investigational Devices

The following 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 guides.

7.1.1. Enlite Sensor (MMT-7008)

The Enlite Sensor (MMT-7008) contains a microelectrode with a thin coating of glucose oxidase beneath several layers of biocompatible membrane. It is intended to penetrate the skin at a 90-degree angle and is shorter and thinner than the Medtronic MiniMed Glucose Sof-Sensor. An introducer needle penetrates the skin surface and provides support for the sensor microelectrode during insertion. The electrode tubing maintains the electrode structure by providing support during and after subcutaneous insertion. The sensor continuously converts small amounts of glucose from the subject's interstitial fluid into an electronic signal that is received by a transmitter or recorder, the strength of which is proportional to the amount of glucose present in the blood. The electrode is composed of embedding, signal-conducting and insulating layers.

7.1.2. Enlite Serter (MMT-7510)

The Enlite Serter (MMT-7510, Figure 1), referred to as Serter in the CIP, is an insertion device used to ensure correct placement of the Enlite Sensor into the user's subcutaneous tissue. The Serter injects the sensor into the insertion site when the button releases.

The Serter is intended as a single patient, non-sterile, multi-use device.

Figure 1. Enlite Serter

7.1.3. iPro2 Recorder (MMT-7741)

The iPro2 recorder (MMT-7741), referred to as iPro2 in the CIP, is a commercial glucose sensor data gathering device with a built-in rechargeable battery and is identical both in construction and components to the MiniLink. The iPro2 stores the sensor data until it is downloaded using an iPro2 Dock, which functions as both a charger and an downloader. Unlike the Continuous Glucose Monitoring System (CGMS) Gold, no set-up of the iPro2 is required before use and data can be downloaded using the desktop CareLink iPro system.

7.2. Non-Investigational Devices

The following non-investigational devices will be 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. iPro2 Docking Station (MMT-7742)

The iPro2 Docking station (MMT-7742) , referred to as iPro2 Dock in the CIP, functions as both a charger and an downloader. The iPro2 Dock has two main functions:

1. It creates a communication link between the iPro2 and a personal computer (PC) to be used for downloading the data stored on the iPro2. In this function, a cable connects the iPro2 Dock to a Universal Serial Bus (USB) port on the PC.
2. It charges the internal battery of the recorder while it is docked in the charger that is either connected to a PC (while the PC is on) or to a wall power adapter. This configuration will only charge the recorder and will not provide the download functionality.

The iPro2 Dock may allow for communication between the PC and recorders for device set up, charging and/or downloading or data.

7.2.2. USB Cable and WAC PowerAdapter (MMT-7747)

The small end of the USB cable (MMT-7747) connects to the iPro2 Dock. The other end of the cable connects to a USB port on a computer, so that the user can download data into CareLink iPro, and charge the iPro2. The USB cable can also be connected to a AC adapter.

The AC adapter for iPro2 lets the user charge the iPro2 by connecting the iPro2 Dock to a regular socket, instead of a computer. It comes with 4 interchangeable power plugs. The appropriate power plug to the AC adapter for iPro2 needs to be connected for use.

For the purposes of this study, charging and uploads of iPro2 are performed only by the Investigational Center or sponsor designee.

7.2.3. iPro2 Cleaning Plug (MMT-7744)

The cleaning plugs (MMT-7744) provide a water-tight seal to protect the connector on the iPro2. The cleaning plug is used when cleaning and disinfecting the iPro2.

7.2.4. CareLink™ iPro Therapy Management Software for Diabetes (MMT-7340) - Desktop Software

CareLink iPro Therapy Management Software for Diabetes(MMT-7340), referred to as CareLink iPro in the CIP, is a PC-based software desktop application. Refer to 10572826DOC for the software version. It will manage the data flow to and from the iPro2; merge sensor and BG meter data to produce glucose sensor values; produce user-friendly graphics and text displaying the data downloaded from the iPro2; store the data on computer and allow for data retrieval in both graphical and textual format.

This software receives the uploaded data via the hardware physical port (USB) of the recorder dock processes and analyzes the uploaded data, and finally generates reports.

7.2.5. Ascensia CONTOUR® PLUS Blood Glucose Meter (7619)

An Ascensia Contour PLUS Blood Glucose meter (7619), referred to as the Study Meter, will be provided to all subjects for use in conjunction with the iPro2. The meter determines the subject's capillary BG level using the Ascensia CONTOUR Strips, and this value may be used to calibrate the CGM systems. For the iPro2 system, the results must be manually entered by the user.

In this study, the blood glucose measurements from the Study Meter will be manually obtained from the Patient's Log Sheet.

7.2.6. Ascensia CONTOUR Test Strips (7662), USB Connector Cable, and Control Test Solution (7680)

The Ascensia CONTOUR BG test strips, referred to as the Study Meter strips in the protocol (7662), USB connector cables, and Ascensia CONTOUR Control Solutions (7680) will be used in conjunction with the Study Meter. The Study Meter can be connected through the plug in USB port directly or via the cable to download BG data to the PC.

7.3. Anticipated Device Changes

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

7.4. Device Accountability

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

Any investigational device being used in clinical research must be strictly accounted for. This includes keeping records of:

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

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

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

Table 1 Device Accountability Requirements

Device	Investigational Center Receipt (packing slip and eCRF)	Disbursement to Subject (eCRF)	Device Accountability at Conclusion of Study (eCRF)	Record Device Accountability (eCRF)
iPro2 (MMT-7741)	Yes	Yes	Return used and unused to Sponsor	No
iPro2 Dock (MMT-7742)	No	Not Applicable	Not Applicable	No
USB cable and AC power adapter (MMT-7747)	No	Not Applicable	Not Applicable	No
iPro2 Cleaning Plug (MMT-7744)	No	Not Applicable	Not Applicable	No
Enlite Sensor (MMT-7008)	Yes	Yes	Return unused to Sponsor and disposed used per hospital practice	Yes
Enlite Serter (MMT-7510)	Yes	Yes	Return used and unused to Sponsor	Yes
Study Meter (7619)	Yes	Yes	Return used and unused to Sponsor	Yes

Demo devices should not be disbursed to subjects.

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 take inventory of the shipment, making sure that information on the packing slips/invoices matches exactly the contents of the containers, as applicable, including:

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

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

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

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

7.4.4. Return or Disposal Study Devices

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

All serialized devices, as described Table 1 will be returned by subjects to the investigational center and then to the sponsor. Serialized devices provided to the investigational center may be returned as subjects complete the study, at the end of study (EOS) or upon sponsor request. The quantity received by the investigational center and the quantity returned to sponsor should be equal. The investigational center will provide details of the disposition of all unreturned serialized devices in the eCRF.

Other consumable devices (i.e., alcohol wipes, Study Meter supplies, overtape, etc.), supplies or materials may be returned to the sponsor or retained by investigational center for educational purposes only, or may be disposed of properly by the investigational center staff.

Disposable devices and supplies that have been ***used*** by a subject will be disposed of properly by the subject or the investigational center staff during the conduct of the study. This would include meter testing strips and supplies, and adhesive overtape.

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

8. Selection of Subjects

8.1. Study Population

Up to 72 subjects will be enrolled in order to have approximately 60 subjects complete the study. Three investigational centers in China will be used during this study. A minimum of 12 subjects and a maximum of 30 subjects will be enrolled at each investigational centers.

- Diabetes cohorts based on insulin requirement
  - N= Minimum of 4 type 1 insulin requiring
  - N= Minimum of 20 type 2 insulin requiring
  - N= Minimum of 25 type 2 non-insulin requiring

A diverse population of patients with type 1 and type 2 diabetes will be studied. The study population will have a large range for duration of diabetes and glycemic control, as measured by glycosylated hemoglobin (A1C).

8.2. Subject Enrollment

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

A subject will be assigned a unique study subject identification (SID) via the eCRF, which is a 9-digit code (313XXXXXX). The first three numbers refer to the CIP number, the next three numbers refer to the investigational center number, and the last 3 numbers refer to the subject number assigned during Visit 1.

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

8.3. Inclusion Criteria

1. Subject is 14 - 75 years of age at time of screening.
2. Subject has a clinical diagnosis of type 1 or 2 diabetes as determined via medical record or source documentation by an individual qualified to make a medical diagnosis.
3. Subject has adequate venous access as assessed by investigator or appropriate staff
4. Subject is willing to follow the study procedures and willing to come to study visits.
5. Subject is willing to perform at least 4 self-monitoring of blood glucose (SMBG) per day for 6 days

8.4. Exclusion Criteria

1. Subject will not tolerate tape adhesive in the area of Enlite Sensor placement as assessed by qualified individual
2. Subject has any unresolved adverse skin condition in the area of study device or device placement (e.g., psoriasis, rash, *Staphylococcus* infection)
3. Subject is actively participating in an investigational study (drug or device) wherein they have received treatment from an investigational study (drug or device) in the last 2 weeks
4. Subject is female and has a positive pregnancy screening test
5. Females of child bearing age and who are sexually active should be excluded if they are 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 a hematocrit (Hct) lower than the normal reference range
8. Subject may not be on the research staff of those performing this study

9. Study Procedures

9.1. Study Timeline

The subject's participation from study start to completion is approximately 1 – 3 weeks (including replacement sensor wear and repeat in clinic procedures).

Additional rescheduled visits could occur if Enlite Sensors dislodge and new Enlite Sensors must be re-inserted (See Replacement Sensors, Section 9.6)

- Visit 1: Consent and Screening
- Visit 2: Randomization
    - Visit 1 and 2 can be combined however all eligibility criteria on Visit 1 should be met including review of Hct prior to Visit 2.
    - Visit 1 and Visit 2 should be no more than 2 weeks apart.
- Visit 3: Study Training and iPro2 Placement & Sensors Insertion
    - Two Enlite Sensors, each connected to an iPro2
    - Dispense Patient Log Sheet

- Visit 4: YSI FST
    - Study training and iPro2 placement & sensors insertion (Day 1 subjects who have not already received study training and iPro2 placement and sensor insertion from Visit 3)
    - Subjects will undergo one YSI FST on any one of the following sensor wear days:
        - Day 1 (1 – 25 hours)
        - Day 3 – 4 (49 – 97 hours
        - Day 6 (121 – 145 hours)

- Visit 5: End of Study (EOS) Visit
    - iPro2 removed **(Please note that the subject should target wearing the device for 145 hours or longer from time of insertion)**
    - Investigational center staff will:
        - Download the iPro2 data from CareLink iPro following completion of the study devices wear
        - Obtain subject's Study Meter BG values and enter into CareLink iPro
        - Collect subject's Patient Log Sheet
        - Provide iPro2 data to sponsor
    - Return study devices
    - Subject complete questionnaires
    - Random assignment for primary sensor and secondary sensor via RDC

Guidelines for Combining Visits:

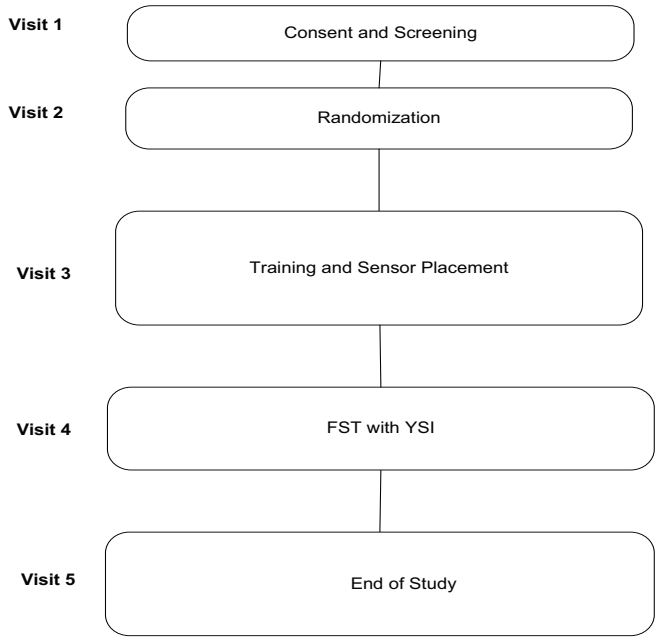
- All subjects meeting eligibility criteria:

    - Visit 1 and 2 can be combined, however all eligibility criteria on Visit 1 should be met, including review of Hct prior to Visit 2.
- Subjects randomized to FST Day 1
    - Subjects doing FST on Day 1 may combine Visit 2 and Visit 3 as long as they are able to perform Visit 4 FST in the second half of FST day.
    - For example, subject does Visit 1 and 2 in the morning and performs Visit 3 in the afternoon. Subjects comes in the next day for Visit 4 in the morning within approximately 25 hours from time of insertion.
- Subjects randomized to FST Day 3-4
    - May combine Visit 2 and Visit 3
- Subjects randomized to FST Day 6
    - May combine Visit 2 and Visit 3
    - May combine Visit 4 and Visit 5 as long as the subject has worn N=145 hours.

9.2. Schedule of Events

9.2.1. Visit Schedule

Figure 2. Visit Schedule Flowchart



9.2.2. Visit 1: Consent and Screening

Overview General

Investigational center staff will:

- Obtain ICF from the subjects
- Assess subject eligibility to participate in the study
- Obtain demographic and baseline characteristics including:
    - Age
    - Gender
    - Race
    - Ethnicity
    - 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)
    - Type of diabetes
    - Date of diabetes diagnosis
- Complete required screening tests, if all eligibility criteria are met:
    - Perform urine test for pregnancy, female subjects of child bearing age or capability
    - Obtain blood sample for Hct
        - Send to local laboratory for required screening tests. (There is no point of care (POC) testing for Hct).
        - Subjects may not participate in the study training without Hct; Hct value must be reviewed for exclusion criteria prior to Visit 2
        - Note: For out of range lab result, a single re-test is permitted
- Obtain blood sample and send to local laboratory for A1C (not an eligibility criteria)
- Enter eCRFs into the study database as appropriate
- Schedule next visit date and time

The study is open to all individuals who meet the eligibility criteria of the study. The investigational center will be responsible for determining adequate source documents to verify subject eligibility. Subjects who do not meet the eligibility requirements for participation in the study will be entered into the database as screen failures. Applicable eCRF(s) will be completed for all subjects who signed an ICF, 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 be randomized and begin study training at Visit 2.

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

9.2.3. Visit 2: Randomization

Visit 2 can be done the same day as Visit 1 if all eligibility criteria on Visit 1 is met, including review of Hct. Visit 1 and Visit 2 should be no more than 2 weeks apart.

Overview general study procedures

Investigational center staff will:

- Randomize eligible subjects
  - Subjects will not be blinded to the investigational devices used.
  - Subjects will be randomly assigned to one of the following sensor wear Day 1, 3-4, or 6, which determines when they will be participating in the in-clinic YSI FST.
- Enter eCRFs into the study database as appropriate
- Schedule the next visit date and time
- The YSI FST visits may 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 Table 2.

9.2.3.1. Procedures Including YSI FST Timing and Fingerstick Requirements

Table 2. YSI FST Timing and Fingerstick Requirements

Visit	Sensor Wear	Group	Timing of YSI FST from Sensor Insertion T=0	Timing of fingerstick from Sensor insertion T=0
4	Day 1	Day 1	The 7 hour FST may be performed anytime between Time = 1 hour to Time = 25 hours	• Time = 0 hour Enlite Sensor insertions will be performed at the investigational center. The 0 hour represents the time after sensors have been connected to the iPro2 . • Target Time = 60 minutes check SMBG and record in Patient Log Sheet • Target Time =3 hours and check SMBG and record in Patient Log Sheet Minimum of 4 fingerstick glucose readings per day and record in Patient Log Sheet
4	Day 3-4	Day 3-4	The 7 hour FST may be performed anytime between Time = 49 hours to Time = 97 hours	Minimum of 4 fingerstick glucose readings per day and record in Patient Log Sheet

Visit	Sensor Wear	Group	Timing of YSI FST from Sensor Insertion T=0	Timing of fingerstick from Sensor insertion T=0
4	Day 6	Day 6	The 7 hour FST may be performed anytime between Time = 121 hours to Time = 145 hours	Minimum of 4 fingerstick glucose readings per day and record in Patient Log Sheet

9.2.4. Visit 3: Study Training & Sensor Insertion

The main purpose of Visit 3 is to provide subjects with study procedure training and sensor insertions. The subjects will receive training on the study requirements before completing the FST visit.

9.2.4.1. Overview general study procedures

Investigational center staff will:

- Synchronize time on Study Meter using investigational center's designated study clock
- Register study subjects in CareLink iPro
- Perform iPro2 activation
- Insert Enlite Sensors and perform connection of Enlite Sensors to the iPro2
- Document time of insertion
- Calculate T=145 hours where the sensor may be removed at that time or after that time.
- Apply sensor tape according to the user guide
- Both sensor site locations may be inserted on left side and right side of the abdomen area based on principal investigator (PI) discretion.
- Perform applicable quality control (QC) testing (Study Meter). Shake control solution bottle well prior to use.
- Review requirements and schedule study visit with subjects
- Review the visit date and time for YSI FST
- Remind subject to bring any medication, syringes, insulin, that might be needed to treat his/her diabetes during the YSI FST visit.
- Enter eCRFs into the study database as appropriate

9.2.4.2. Overview study devices and supplies

Investigational center staff will disburse the following to subjects:

- iPro2s
- Enlite Sensors
- Serter
- Study Meter to take home

- BG supplies (e.g., batteries, meter strips, and lancets) to take home
- Other study materials (e.g. study reference card, subject information materials, Study Meter device user guide and Patient Log Sheet) to take home

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

9.2.4.3. Overview training and instructions

Investigational center staff will:

- Train each subject on study procedures (e.g. how to use of Patient Log Sheet)
- Train subjects on use of Study Meter
    - Subject will be instructed to wash his/her hands thoroughly with warm, soapy water, rinse and dry before testing BG
    - Consider best practice to use "second drop" technique, express first drop and wipe away, express second drop for meter BG testing
    - Subjects will be instructed to use only the Study Meter during the course of the study to perform Enlite Sensor calibration of study devices
    - Subjects will also be instructed to record their BG meter data on the Patient Log Sheet
- Train subject on iPro2 wear:
    - Instruct that each iPro2 will be worn with an Enlite Sensor approximately 6 days
    - Instruct subjects that Enlite Sensor(s) will be replaced if it has dislodged any time prior to completing their YSI FST visit (see Section 9.6).
    - Instruct subjects that he/she may be asked to repeat the YSI FST (see Section 9.7)
- Instruct subjects to perform fingersticks (capillary SMBGs)
- Instruct subjects on returning to clinic for early dislodgement of Enlite Sensors.
- Instruct subjects to contact investigational center staff for technical issues and support
- Remind subjects to bring in the Study Meter (for accuracy testing) to FST visit

In addition:

- Assess subjects for the occurrence of any AEs or device deficiencies (see Section 11 and Section 13) at each visit and document on the appropriate source; record event(s) on the appropriate eCRF

Subjects will continue on 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. The Study Meter may be used for treatment decisions and fingersticks.

Prior to use, all devices will be prepared by investigational center staff following the instructions in the users' guides. Before distributing to subjects, the clocks in the Study Meter need to be synchronized with a designated study clock at the investigational center. Subjects will be instructed not to change the clocks in these devices. Subjects will be provided a Study Meter to be used to perform fingerstick (capillary SMBG). The investigational center staff will also have to register the subject into CareLink iPro and download the subject's Study Meter later (see Investigator Site Binder for details).

In the event the subject no longer wants to participate in the study after the study procedure training or any time throughout the course of the study including the day of YSI 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.

iPro2 Setup & Fingerstick Instructions

The investigational center staff will need to perform a charge with the iPro2 prior to subject's visit:

- Refer to iPro2 setup per user guide
- Refer to Table 2for instructions at YSI FST
- Subjects will be recommended to record the fingerstick value as a calibration within 5 minutes of measuring their BG on the Patient Log Sheet

Fingerstick testing at Home and In-Clinic

A minimum of 4 fingerstick glucose readings per day will be requested and recorded on Patient Log Sheet. Consider best practice to use "second drop" technique, express first drop and wipe away, express second drop for meter BG testing.

Enlite Sensor wear duration during the study:
Investigational center staff will remove the subject's Enlite Sensors after 6 days.

9.2.5. Visit 4: YSI FST

For those subjects randomized to Day 1 who have not already received study training and iPro2 placement and sensor insertion from Visit 3, all the procedures previously listed at Visit 3 will be completed at this visit. Investigational center staff will follow:

- Overview general study procedures (Section 9.2.4.1)
- Overview study devices and supplies (Section 9.2.4.2)
- Overview training and (Section 9.2.4.3)

Subjects will undergo one YSI FST on any one of the following sensor wear days:

- Day 1 (1 – 25 hours)
- Day 3 – 4 (49 – 97 hours)
- Day 6 (121 – 145 hours)

The YSI FST is a 7 hour frequent BG sampling session using IV blood samples and a laboratory BG analyzer, YSI. The investigational center staff will set up the YSI.

9.2.5.1. Prior to Arrival at the Clinic for the YSI FST

- On the evening prior to FST, subjects will be asked to fast for approximately 12 hours and adjust their insulin and medications according to routine care (for example as they would do for fasting lipid panel). Subjects may fast for shorter period of time **based on investigator discretion.**

- **The feeding protocol may be modified based on investigator discretion.**

9.2.5.2. In-Clinic Procedures

Overview general study procedures

Investigational center staff will:

- Perfom applicable calibrations on the YSI instruments
- Synchronize study laptop computer and YSI devices at the investigational center synchronized with the designated study clock
- Refer to Table 2 for instructions on YSI FST Timing and fingerstick requirements.
- Conduct YSI FST procedures
- Provide YSI data to sponsor
- Instruct subjects on returning to clinic for early dislodgement of Enlite Sensors (Section 9.6)
- Remind subjects to perform fingersticks (capillary SMBG)
- Remind subjects to bring in the Study Meter at next visit date
- Remind subjects to contact investigational center staff for technical issues and support
- Review the next visit date and time
- Enter eCRFs into the study database as appropriate
- Address questions or concerns from subjects
- Assess subjects for the occurrence of any adverse events or device deficiencies (see Section 11 and Section 13) at each visit and document on the appropriate source; record event(s) on the appropriate eCRF
-

9.2.6. Visit 5: End of Study

- Subjects will return to the clinic to remove their study devices
- Investigational Center staff will review documentation of time they calculated for T=145 hours where the sensor may be removed at that time or after that time to ensure that the devices are not removed pre-maturely
- Investigational center staff will address questions or concerns from subjects
- Investigational center staff will ask subjects about the occurrence of any AEs or device deficiencies.
- Investigational center staff will:

- Download the iPro2 data from CareLink iPro following completion of the study devices wear
- Obtain subject's Study Meter BG values and enter into CareLink iPro
- Collect subject's Patient Log Sheet
- Provide iPro2 data to sponsor

- Investigational center staff will perform a Skin assessment on the area of each of the Enlite Sensor insertion sites and document in subject source and complete the Skin Assessment eCRFs
- Investigational center staff will collect returned devices (See Table 1 in Device Accountability section) and unused supplies from subjects
- Subjects will complete a questionnaire about their Enlite Sensor experience.
- Primary sensor and secondary sensor will be randomly assigned via RDC.
- An Exit eCRF will be completed at this visit.

9.3. Subject Consent

ICF will be obtained in accordance with the CFDA Order No. 25. Prior to entry into the study,The Ethics Committee (EC)- and Medtronic-approved ICF will be given to each subject or their legally authorized representative or guardian (if applicable) to complete. Subjects or their legally authorized representative or guardian will be offered the opportunity to review these documents away from the investigational center.

The investigator or designee will explain the purpose and duration of the study, requirements of the subject during the study, as well as the potential risks involved with participation in this study. Every attempt will be made to answer subject's or their legally authorized representative or guardian questions during the informed consent process. The process for obtaining informed consent shall not waive or appear to waive subject's legal rights. The consenting process shall use language that is non-technical and understandable to the subject or legal representative. The consenting process will be documented. It will include a dated signature of the subject or legal 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. The subject or their legally authorized representative or guardian will receive copies of the fully executed documents. A subject's participation in study procedures cannot start before the consent process has been properly executed.

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

Subjects will be informed that competent authorities from the investigational center, Medtronic, and specific agencies, such as the CFDA and the 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 violations to the sponsor:

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

9.4. Randomization and Treatment Assignment

Investigational Centers will receive this randomization assignment generated electronically in the study database from Medtronic. The first randomization scheme assigns the subjects to one of the following sensor wear days (Day 1, 3-4, or 6) which determines when they will be participating in the in-clinic YSI FST.

Once subject is assigned to the study group, subjects will stay in that randomization group during the study.

In addition, at the end of the study (Visit 5), another randomization scheme will be done to assign the primary and secondary sensor for each subject.

9.5. Assessment of Safety

Adverse Event information is collected in this study. See Section 11 for further information on the collection of Adverse Events and safety information.

9.6. Replacement Sensors

If subjects have either of the sensors which has dislodged any time prior to YSI FST visit or within a duration of 5 hours YSI FST, subject will be asked to re-insert both sensors. And re-insertion of Enlite Sensors will be done only once.

Any YSI FST with a duration of 5 hours or more before sensor dislodgement will be considered complete and will not need to be rescheduled.

Subjects will be issued replacement Enlite sensors to be inserted at Clinic but at the date and time specified by the Clinic.

Subject will wear the replaced sensors for 6 days and attempt to complete the required YSI FST visit.

Subjects will have their YSI FST visit rescheduled per the original randomized FST Group.

9.7. Repeat Rules for In-Clinic Procedures

- Concurrent failure of both the primary and back-up YSI instruments (if applicable) during YSI FST.
- If a sensor dislodges prior to YSI FST, the sensor will be replaced per sponsor's recommendation.
- If subject experiences unresolved IV occlusions during YSI FST requiring fingerstick measurements for a prolonged time period, the FST procedures may be rescheduled per sponsor recommendation.

9.8. Medical Oversight

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

- A nurse, physician or mid – level provider, such as a nurse practitioner or a physician assistant must be available during the entire YSI FST.
- Deviation from pre-specified protocol requirements for subject safety per investigator discretion is allowed.
- Investigator discretion may be used for management of patients diabetes.

9.9. YSI FST Instructions

9.9.1. Monitoring During the YSI FST

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

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

9.9.2. YSI FST Not Available (For Example, IV Occlusion)

In the event that YSI BG values are not immediately available, for safety purposes, the investigational center may use a Study Meter to measure glucose. The fingerstick glucose values will be recorded on the appropriate eCRF and not used for analysis.

Venous blood samples should still be drawn for YSI FST.

9.10. Glucose and Glycemia Measurements

During the course of the study, the subjects' BG, sensor glucose levels, A1C, 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 Study Meter. A QC test will be performed on the meter assigned to each subject before being dispensed and before each YSI FST. The results of the QC test will be documented in the subject's source documents. The QC test will be done following the manufacturer's user guide. Subjects will be trained on the use of the Study Meter per the manufactures user guide.
- **YSI FST BG values -**During the YSI FSTs at the investigational center, blood plasma glucose will be determined using the laboratory BG analyzer (YSI).
- **Sensor glucose values** - Assessed using the following methods:
    - Sensor glucose values collected by subject's iPro2 and calibrated by subject's Study Meter.
- **A1C** - Collected at baseline and will be used as demographic information.
- **Alternate POC BG values**- During the YSI FST at the investigational center, alternate POC BG measurements will be used (Study Meter) and the values recorded on the appropriate eCRF (not used for analysis). A QC test will be performed on the alternate POC BG device before each YSI FST. The results of the QC test will be documented in the subject's source documents. The QC test will be done following the manufacturer's user guide.

9.11. 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 used to capture raw/source data and supporting documentation will be required. Patient Log Sheet and subject questionnaires on paper are considered source data, then source data is transferred to an eCRF.

Electronic device data will be collected from the iPro2 using Medtronic CareLink iPro. 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. Information on case report forms must conform to the information in the source documents. Medtronic will provide detailed instructions to assist with eCRF completion. In the event of data discrepancies, investigational centers will be asked to resolve queries electronically in the OC-RDC system; otherwise,

irresolvable data-related issues will be routed to the sponsor for review and final disposition. An audit trail is maintained in OC-RDC to capture any corrections or changes of the eCRFs. If a person is only authorized to complete CRFs or to make changes to an already signed CRF, the investigator shall re-sign this CRF. System backups for data stored in the OC-RDC system will be consistent with Medtronic standard procedures.

Medtronic will only consider eCRFs to be complete when all discrepancies have been resolved, verification has been completed by the monitor and if required, the investigator has approved. It is expected that the investigator and his/her staff will cooperate with the monitoring team and provide any missing data in a timely manner.

9.12. 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/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 EC, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)).

9.12.1. Documenting requirements for study deviations

9.12.1.1. Planned CIP Deviations

Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate.

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

Planned deviations that are non-emergent and represent a major change in the approved CIP needs sponsor approval.

The investigator shall obtain pre-approval from Medtronic for the following deviations. Such approval shall be documented in writing.

- Deviations that affect the scientific soundness of the plan, such as changes that affect the subject enrollment criteria, endpoint, early study termination, sample size, or number of investigational centers.
- Deviations that affect the rights, safety, or welfare of human subjects, such as substantial changes to the ICF template approved or changes and additional procedures that put the subject at greater risk to benefit ratio than that used to approve the CIP.

Medtronic will communicate the approval or rejection of the planned CIP deviation to the investigator. Medtronic will ensure the planned CIP are reported by the Investigator to their reviewing EC and to the regulatory agency (if applicable). The Investigator will then obtain a written approval from EC.

9.12.1.2. Unplanned CIP Deviations

Prior approval is not required when a deviation is 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).

As soon as possible, the implemented deviation or change and the reasons for it, should be submitted as follows:

- Investigator should report the deviation to the medical device clinical trial administration department of the investigational center.
- The medical device clinical trial administration department of the investigational center then report the deviation to:
    - EC for notification/acknowledgement
    - Sponsor

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation which will apply to all visits going forward. This may also apply for other unforeseen situations (e.g. the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary end point analysis). However, prior approval from Medtronic is required for such situations.

Blood glucose range and duration targets:

Blood glucose in the 70 mg/dL (3.9 mmol/L) range and 2 hour duration 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 FSTs, but the sponsor understands that managing diabetes itself is a challenge, and meeting the target value and duration for all subjects may not always be possible.

In the event that samples are not able to be collected or analyzed for technical reasons (YSI or IV line problems) reasons must be recorded on the YSI Activity Log eCRF. See Section 9.9 for further details on deviations pertaining to YSI blood samples.

Sensor wear:
Protocol deviation will only be given if the subject is told by site to remove sensor pre-maturely before Day 6.

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

FST missing samples:
It is noted that collecting YSI FST every 5 – 15 minutes may be challenging. Deviations for missing YSI FST samples will be reported for the following reasons:

- If there are 2 consecutive YSI FST samples missing (unless they were missed for safety issues, IV or YSI FST device issues). Example of 1 missing YSI FST:
    - YSI FST at 8 A.M. which is 65 mg/dL (3.6 mmol/L)
    - YSI 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 (+ 3 - 8 minutes); but the 2nd sample is at 8:15 AM, so there is at least 1 missing sample which could have occurred at latest 8:08 AM
- If there are 4 or more total YSI FST samples missing per subject (unless they were missed for safety issues, IV or YSI FST device issues).

9.12.1.3. Minor or administrative CIP deviations

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

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

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

9.12.2. Reporting requirements for study deviations

All study deviations must be reported on the eCRF regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. The description of each deviation will be documented in the clinical trial summary of each investigational center for multi-center study. In the occurrence of a corrupted device interrogation file, Medtronic may request a deviation to document that a readable interrogation file is unavailable.

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

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

- Failure to obtain informed consent, i.e., there is no documentation of informed consent
- Informed consent obtained after initiation of study procedures
- Enrollment of a subject who did not meet all inclusion/exclusion criteria
- Performing study procedure not approved by the EC
- Failure to inform EC and sponsor reportable AEs (see Section 11.3)
- Investigational study device dispensed without obtaining informed consent

Reporting of all other study deviations should comply with EC policies and/or local laws and must be reported to Medtronic as soon as possible upon the center becoming aware of the deviation. Reporting of deviations must comply with EC policies, local laws, and/or regulatory agency requirements. Refer to Investigator Reports, Table 3 and Table 4 for specific deviation reporting requirements and timeframes for reporting to Medtronic and/or regulatory agency (if applicable).

9.12.3. 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. Medtronic will provide center-specific reports to investigators summarizing information on deviations that occurred at the investigational center on a periodic basis.

9.13. Subject Withdrawal or Discontinuation

Subjects may choose to withdraw from the study at any time by notifying investigational center staff of their intent. Subjects who are unwilling to participate in the follow up visits of complete study procedures should be withdrawn from the study by the investigator.

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

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

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

Lost to Follow-up

In the case that the subject is determined to be lost to follow-up, details of a minimum of two attempts and the method of attempt (e.g., one letter and one phone record or two letters) to contact the subject must be recorded. In addition, the requirements set by the governing EC for subjects lost to follow-up must be followed.

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

Upon exiting from the study, no further study data will be collected or study visits will occur for the subject. All data available through the time of the subject's exit will be used for analysis. In the event of study exit, the investigator should discuss with the subject the plans for future care and treatment. The investigator should explain that the subject will continue to receive standard medical care. Alternative treatment, such as medication options or follow-up through standard of care procedures instead of study procedures, and medical consequences should also be discussed. Source documentation of this conversation recommended. The investigator must notify the subject of any significant new findings that may become available during the course of the study, which are pertinent to the safety and well-being of the subject.

9.14. Stopping Rules

9.14.1. Subject Stopping Rules

The subject will stop the study if there is an UADE.

9.14.2. Stopping Rules for Entire Study

The study will stop if there is an UADE.

10. Risks and Benefits

10.1. Potential Risks

During the course of the study, risks will be continuously monitored, assessed and documented by the investigators.

Risk with Sensors	Prevention and Mitigation
Risks with Sensors may include: • Skin irritation or reaction to adhesives • Bruising • Discomfort • Redness • Bleeding • 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	Prevention and mitigation include: • Follow the provided user guides for insertions and care of sensors. • If a sensor site becomes infected or inflamed, the sensor should be removed and another placed in a new location • Base diabetes management on fingerstick readings
Risks with Serter	**Prevention and Mitigation**
Risks with Serters may include: • Improper insertion may lead to device performance issue or hyperglycemia	Prevention and mitigation include: • Follow the provided user guides for insertions and care of Serters. • Training on proper use of the Serter and skin preparation prior to insertion.

Risks with Finger Sticks	Prevention and Mitigation
Risks with frequent finger stick testing may include: • Potential risks associated with frequent meter testing of blood glucose include discomfort and ecchymosis at tips of fingers • Potential risks associated with drawing blood include discomfort and bruising	Prevention and mitigation include: • Follow the provided user guides for use of meter with fingerstick testing. • Training on proper use of the meter and fingerstick testing.
Risks with IV Catheter Insertion	**Prevention and Mitigation**
Risks with IV catheter insertion may include: • Pain • Bruising • Infection • Irritation • Syncopal episode secondary to catheter insertion • Swelling. • Discomfort • Anxiety	Prevention and mitigation include: • Qualified individual to perform IV catheter insertion • Sterile technique will be used to insert the IV Treatment of these risks include: • Removal of IV catheter if subject experiences significant discomfort • Removal of IV catheter if infection develops • Antibiotics should be given, if needed
Risks for indwelling IV catheter	**Prevention and Mitigation**
Risks with indwelling IV catheters may include: • Infection • irritation • swelling • thrombosis • phlebitis • bruising	Prevention and mitigation include: • Management of IV per investigational center protocol • Use of universal precautions to avoid infection • Qualified Investigator presence during experiment • Observation for redness at IV insertion site by qualified staff Treatment of these risks include: • Removal of IV catheter if infection develops and antibiotics should be given.
Risks with Blood Draw	**Prevention and Mitigation**
Risks with drawing blood may include: • Discomfort and bruising • Insertion of an IV catheter and drawing blood may also result in faintness, inflammation of the blood vessel, pain and bruising at the needle site • There is also a slight possibility of infection.	Prevention and mitigation include: • Qualified staff to perform blood draw

Risks with IV Saline Infusion	Prevention and Mitigation
Risks with saline infusion may include: • Edema • CHF • Third spacing	Prevention and mitigation include: • Qualified investigator presence during experiment Treatment of these risks include: • Reduction of IV fluid if subject shows signs of CHF, lower extremity edema, crackles on lung auscultation or S3 heart sound Subjects who still exhibit signs of fluid overload at time of discharge will be transported to the emergency room (ER) or follow guidelines of the local institution for the disposition of subject.
Risk with Acetaminophen Use	**Prevention and Mitigation**
Potential risks with acetaminophen may include: • False elevation of sensor glucose readings. The level of inaccuracy depends on the amount of acetaminophen active in subject's body and may be different for each subject	Prevention and mitigation include: • Follow the user guide • Where possible, subjects should avoid the use of Acetaminophen • If acetaminophen is taken, subjects should use additional BG meter readings (they are not to calibrate with those readings) to verify their glucose levels

10.2. Potential Benefits

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

10.3. Risk-Benefit Rationale

The Enlite glucose sensors and serter are new variations of the CFDA approved Sof-sensor™ and Sen-serter™. They are similar in design and function to the predecessor Medtronic Sof-sensor and Sen-serter but include several design enhancements to improve sensor performance and ease of use. Given that the investigational study devices used in the study are commercially available in other countries (e.g. USA) and used within their intended use, the anticipated risks for a patient to be in the study is not expected to be higher than in routine practice.

Although subjects are not anticipated to receive any benefit specific to use of the Enlite glucose 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.

10.4. Risk Determination

The Enlite 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 CFDA is not required.

10.5. Subject Compensation and Indemnification

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

11. Adverse Event Assessments

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

11.1. Definitions and Classification of Adverse Events

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

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

2. **Diabetic Ketoacidosis/DKA** diagnostic criteria: 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:

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

Medtronic uses the definitions provided in CFDA Order No. 25, ISO 14155:2011, 21 CFR 812 for adverse event 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.

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) (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)

An adverse event that:

- Led to death
- Led to 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
- Led to fetal distress, fetal death or a congenital abnormality or birth defect

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

Serious Adverse Event (SAE) (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.

Note: In SAE definition, the term "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. 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)

11.2. Reporting of Adverse Events

The Investigator or designee will record all AEs while the Subject is enrolled in the clinical study. This includes AE that are device or study procedure related as well as those events with no relationship to the study. Examples include:

- Device related (ADE): insertion site infection
- Serious adverse device effect (SADE): cellulitis at device insertion site requiring hospitalization
- Procedure related AE: bruising at IV insertion site

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

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 questionnaires 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 end of study participation; however, there will be no eCRF entry for the ongoing follow-up.

11.3. Notification of Adverse Events

Sponsor Notification:

As soon as possible (desired within 24 hours) of investigator or study coordinator awareness, the Investigational Center staff must report all Severe Hypoglycemia; DKA; Serious Adverse Events; Serious Adverse Device Effects and any Unanticipated Adverse Device Effect to Medtronic. For the previously mentioned events, the AE eCRF will be completed with all known details details as soon as possible (desired within 24 hours) of Investigational Center awareness – 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.

11.4. Expedited Safety Reporting Requirements

For device studies, investigators are required to submit a report of a UADE to the sponsor and the reviewing GCP office and EC as soon as possible after the investigator first learns of the event. Investigators are required to report these events details as soon as possible (desired within 24 hours) of awareness.

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.

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

Table 3. Investigator Reporting requirements for AE and Device Deficiencies

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 other Device Deficiencies**	
Investigators shall record all the adverse events 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
For the following events, reporting requirements are: • **Serious Adverse Events (SAE)** • **Device Deficiencies with SAE potential**	
Medtronic submits to:	
The food and drug regulatory authorities and health and family planning competent authorities at the same level	Within 5 working days upon being informed
Other Investigational Center and investigators participating in the study	As per local reporting requirement
EC	Timely report to EC of the clinical Research institution through management department of medical device clinical study

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.

11.5. Causality Assessment

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

Causality assessment is the determination of the relationship between an AE and the device being studied. A causal relationship is present if a determination is made that there is a reasonable possibility that the AE was caused by the study device or a study procedure. 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 based on 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 serious 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 serious 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 additional information may be obtained.

- **Possible:** the relationship with the use of the investigational device is weak but cannot be ruled out completely. 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 were relatedness cannot be assessed or no information has been obtained 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, but additional information may be obtained.

- **Causal relationship:** the serious 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 serious 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 serious event (when clinically feasible);
  - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
  - harm to the subject is due to error in use;
  - the event depends on a false result given by the investigational device used for diagnosis, when applicable;
  - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

11.6. Anticipated or Unanticipated

If the adverse event is determined to be related to the study device or study procedure the Investigator must then assess the event to determine if it is anticipated or unanticipated.

- **Anticipated:** the event is identified in the CIP; labeling; Investigator's Brochure or user guide.
- **Unanticipated:** the event has not been previously identified in the CIP; labeling; Investigator's Brochure or user guide.

11.7. Severity of Event

A clinical determination of the severity of the event will be made. The following guidelines should be used:

- **Mild:** transient, needing no special treatment, and/or does not interfere with the subject's daily activity.
- **Moderate:** low level of inconvenience or concern to the subject and may interfere with daily activities, but is usually improved by simple therapeutic remedy.
- **Severe*:** interrupts a subject's daily activity and typically requires intervening treatment.

*Please Note: In the classification of AEs, the term "**severe**" is not the same as "**serious**." The term "**severe**" relates to an indication of the intensity of a specific event (as in mild, moderate, or severe chest pain). The term "**serious**" relates to a participant/event outcome or action criteria, usually associated with events that pose a threat to a participant's life or functioning.

11.8. Skin Assessment: Glucose Sensor Insertion Sites

Skin irritation may be associated with the insertion procedure or device wear and may be associated with the adhesives and tapes used to secure the study devices. The area of skin associated with glucose sensor insertion & wear will be assessed following the removal of each glucose sensor by Investigational Center staff.

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 classification per the skin assessment case report form (for example: bruising 8 cm in diameter; rash that requires prescription medication)

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

11.9. Documentation of Symptoms During YSI FST

During YSI FST it is expected that subjects may experience minor symptoms that are related to the procedure requirement of driving glucose levels high and low. All symptoms experienced by the subject must be recorded on the appropriate log. Those symptoms that are minor and directly associated with the requirements of the FST would be recorded on the log only. Examples include:

- Headache
- Shakiness/tremors
- Discomfort associated with iv insertion

- Shortness of breath

Events that are more serious or those events which have an intensity of moderate or severe should be noted on the log and reported as AEs. This would include:

- Severe Hypoglycemia
- DKA
- Seizure
- Vomiting
- Chest pain
- Syncope/Fainting

12. Data Review Committees

A clinical events committee (CEC) consisting of external physicians with an expertise in Endocrinology and the management of diabetes including Insulin Pumps and CGM will be convened. The CEC will review all reports of:

- SAE
- SADE
- UADE
- Severe Hypoglycemia
- DKA

The CEC will assess these events to determine agreement or disagreement with the Investigator classification of the event. The sponsor will notify the Investigator of any disagreement in assessment of an event by the CEC.

13. Device Deficiencies and Troubleshooting

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

All device deficiencies (per definitions in table below) reported directly to the Investigational Center staff by a subject and those experienced by the Investigational Center staff will be reported on the appropriate eCRF.

Device Deficiency	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)

	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. (CFDA Order No.25 Article 93)

Investigators shall record and report all the identified device deficiencies occurred during the study, analyze the reasons for the events jointly with sponsor, form written analysis report and propose the comments of continuing, suspending or terminating trials, which shall be reported to EC through management department of medical device clinical trials in investigational centers for review. See Table 3 for device deficiencies reporting requirements.

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

It is the responsibility of the Investigator to follow their EC reporting requirements for device deficiencies.

14. Statistical Design and Methods

14.1. General Considerations

All data collected from the time of screening until the end of the study will be collected either on eCRFs or electronically by downloading the various devices. Data and analysis will be summarized in a Clinical Study Report.

14.2. Subject Disposition

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

14.3. Sensor Disposition

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

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

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

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

14.4. Subject Demographics and Baseline Characteristics

Subject characteristics, including age, gender, race, ethnicity, medical diagnosis, height, weight, BMI, CGM experience, and baseline A1C will be summarized by descriptive statistics (mean, standard deviation, minimum, median, and maximum) for continuous variables and by counts and percentages for categorical variables.

14.5. Sample Size and Power

The sample size selected is based on the primary analysis of the primary effectiveness endpoint (i.e., accuracy), agreement in comparative readings of paired sensor and YSI glucose readings.

Bases on pervious study, using one sample T test (formula provided below) with α level of 0.975 (one sided), β of 0.8, $\boldsymbol{\mu_0}$ is 0.6, $\boldsymbol{\mu_\alpha}$ is 0.72 and $\boldsymbol{\sigma}$ is 0.32:

$$\boldsymbol{n = \sigma^2 \frac{(t_\alpha + t_\beta)^2}{(\mu_0 - \mu_\alpha)^2}}$$

it is indicated that a sample size of 58 will have power greater than or equal to 80% to demonstrate that the overall agreement rate is greater than 0.6. Considering 20% drop out, we need to enroll 72 subjects.

14.6. Analysis Populations, handling of missing data, error

Data entry error or non-reasonable values will be cleaned before data analysis. No imputations will be done for missing data. All enrolled subjects who have at least one paired Enlite Sensor and YSI measurement will be included in the efficacy analysis population. All enrolled subjects who have a Enlite Sensor inserted will be included in the safety analysis population.

14.7. Assignment to Day of YSI FST

Adult subjects and subjects with age of 14 - 21 will be required to attend 7-hour sessions of frequent sampling in which agreement between YSI and Enlite Sensors connected to the iPro2 will be evaluated.

14.8. General Considerations for Data Analysis

14.8.1. Data Collection

Primary endpoint, secondary endpoints, and other descriptive endpoints will be based on retrospective data collected from primary sensor. Precision analysis will be based on data collected from both sensors.

14.8.2. Pairing Scheme

All YSI and fingerstick values collected will be presented. , Most of descriptive analyses will include all YSI values, such as those less than (<) 40 mg/dL, or greater than (>) 400 mg/dL as long as Enlite Sensor values are greater than or equal to (>=) 40 mg/dL or less than or equal to (<=) 400 mg/dL (displayed to users as Low or High without numerical numbers). Reference glucose values (YSI values or fingerstick values) will be paired with the closest Enlite Sensor value between [0, 5) minutes. The primary Enlite Sensor will be used as a reference for precision analysis. Clarke EGA will be restricted to YSI values of 40-400 mg/dL. The same pairing scheme will be utilized.

14.8.3. YSI Retention

All YSI values will be captured and retained in OC-RDC database. However, if the difference between Result A (black) and Result B (white) is greater than (>) 5%, the YSI values will not be included in the analysis dataset.

14.9. Statistical Model and Analyses of Primary Endpoint

Sensor values from primary sensor 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 Reference BG less than or equal to (≤) 80 mg/dL (4.4 mmol/L) between Enlite Sensor values and YSI plasma glucose values during YSI FST days defined as μ will be evaluated against the null Hypothesis:

H0: $\mu \leq 60\%$

H1: $\mu > 60\%$

- Statistical testing

One sample T test will be used for the analysis of the primary endpoint. The 97.5% lower confidence limit of the mean agreement rate will be tested against corresponding threshold.

- Missing data

  No imputation for missing data will be performed.

- Pass/Fail Criteria

  The study pass/fail criteria is based on statistical hypothesis of the primary endpoint. If the 97.5% lower confidence limit is greater than 60%, the study will be considered as success.

- Justification for Exclusion of Particular Information from the testing of the Hypothesis

  Not Applicable

14.10. Analyses of Secondary Endpoints

Sensor values from primary sensor will be compared to YSI plasma glucose values during YSI FSTs. And the 95% Confidence Interval of MARD, mean rate in Zone A+B of Clarke Error Grid and Consensus Error Grid will be provided.

14.11. Numbers of Reading in the Low and High Ranges

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

14.12. Other Descriptive Endpoints

Other descriptive endpoint analysis will be repeated for each dataset under 14.8

14.12.1. Difference Tables Comparing Sensor and Reference Readings

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

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

14.12.2. Sensor Calibration

Characteristics of Enlite Sensor calibration will be evaluated by:

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

14.12.3. Clarke Error Grid Analysis (EGA) of Paired Sensor and YSI and Reference Values

1) Description
Clarke 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 provide form YSI glucose ranges of 40-80 mg/dL, greater than (>) 80-120 mg/dL, greater than (>)120-240 mg/dL, and greater than (>) 240 mg/dL.

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

14.12.4. Precision Analysis

Precision analysis will be performed for the two sensors worn by the same subject in the same location. The recorder connected to the Enlite sensor will be re-analyzed using the exact calibration SMBG used in iPro2 Device.

14.12.5. Other Accuracy Analyses

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

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

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

Descriptive subgroup analysis of Enlite Sensor performance (20% mean agreement rate (±20 mg/dL (1.1 mmol/L) when Reference BG less than or equal to (≤) 80 mg/dL (4.4 mmol/L))) will be performed in the following cohorts:

- **FST:**
  - Day 1
  - Day 3-4
  - Day 6

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

14.12.6. Home-Use Portion Data Analysis

Data from the home-use portion will be described. Analysis will include but not be limited to: 20% mean agreement rate (±20 mg/dL (1.1 mmol/L) when Reference BG less than or equal to (≤) 80 mg/dL (4.4 mmol/L)) for all fingersticks (capillary SMBG) collected, Clarke Error Grid, other accuracy analysis, ARE, bias, correlation between Enlite Sensor and SMBG and Bland-Altman plots. In addition, 20% mean agreement rate (±20 mg/dL (1.1 mmol/L) when Reference BG less than or equal to (≤) 80 mg/dL (4.4 mmol/L)) will be described by subgroups of YSI FST. The number of actual calibrations performed per day by study subjects will be tabulated and presented:

- **FST:**
  - Day 1
  - Day 3-4

- Day 6

14.13. Safety

For Safety analysis, no formal hypothesis testing will be performed. Descriptive analytics will be used to summarize safety events. Safety events which will be characterized include:

- Skin assessment of Enlite Sensor insertion sites
- All AEs to include but not limited to:
  - Device Related AE
  - Procedure Related AE
  - SAE
  - SADE
  - UADE
  - Severe Hypoglycemia
  - DKA

14.14. Device Deficiencies

Descriptive summary will be used to characterize device deficiencies

14.15. Subject Feedback

Descriptive summary will be used to characterize study questionnaire results. The questionnaire will use a Likert scale rating to assess their Enlite Sensor experience.

14.16. Clinical Study Report

The Clinical Study Report will be compliant with CFDA 2016 No. 58 Announcement Annex 5 "Template of Clinical Trial Report of Medical Devices". Any deviations from original statistical plan and the rationale will be described in the Clinical Study Report.

There will be no interim analysis perform during the study so therefore there are no criteria and/ reasons for trial termination based on statistics.

15. Ethics

15.1. Statement(s) of Compliance

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.

This protocol, any subsequent amendments to this protocol, the Informed Consent/Assent form, subject material and any form of subject recruitment information (e.g. advertisements) relating to this study will be approved by the responsible EC in accordance with CFDA Order No. 25 and local regulatory requirements as applicable. The study will not start until 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. Copies of all relevant correspondence between the investigational center and the EC will be retained at investigational center with copies forwarded to the Sponsor for their files.

Regulatory Compliance

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 Good Clinical Practice for Medical Devices (CFDA Order No. 25), Announcement of CFDA 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.

The principles of the Declaration of Helsinki have been implemented through the patient informed consent process, EC approval, study training, clinical trial registration, preclinical testing, risk-benefit assessment and publication policy.The clinical trial filing will be completed prior to conduct of this study per the requirement of the Announcement of CFDA on Filing of the Medical Device Clinical Trial (2015, No. 87).

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

Regulatory Submission

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.

Sponsor's Support

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 representatives may provide support as required for the study, including 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.

15.2. Investigator's Responsibilities

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

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

- Conduct of the investigation in accordance with the CIP, the regulations as outlined in CFDA that apply to this study and other applicable regulations, and any conditions of approval imposed by the reviewing EC
- Conduct of investigation in accordance to regulations from CFDA to meet responsibilities with respect to protect human subjects and ensuring the integrity of the data from clinical investigations. The regulations is also intended to clarify CFDA's expectations concerning the investigator's responsibility:
    1) to supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other third parties, and
    2) to protect the rights, safety, and welfare of study subjects.
- Supervision of all testing of the device involving human subjects
- Ensuring that the requirements for obtaining informed consent are met in accordance with CFDA
- Allowing study devices to be used only with subjects under the investigator's supervision and to supply study devices only to persons authorized to receive it
- Ensuring that investigational center staff are adequately trained to perform their assigned duties
- Maintenance of accurate, complete, and current records relating to the investigator's part of an investigation, to include
    - all relevant correspondence with Medtronic and EC
    - records of receipt, use, or disposition of a device
    - records of each subject's case history and exposure to the device
    - the CIP, with documents showing the dates of and reasons for each deviation from the CIP

- Preparation and submission to Medtronic and, when required, the reviewing EC, the following complete, accurate, and timely reports:
    - any reportable AEs (see Section 11) occurring during an investigation
    - progress reports on the investigation as required by the EC
    - protocol deviation that may affect the subjects' rights and interests, safety, health or the scientificity of clinical trials, including deviation regarding requests and reports
    - any use of the device without obtaining informed consent
    - any further information requested by the EC about any aspect of the investigation
- Meeting with the monitor to discuss study progress and findings
- Ensuring that investigational center resources are adequate to fulfill the obligations of the study
- Ensuring completion of eCRF to include: entry and addressing discrepancies in a timely fashion and approving selected eCRFs. It is expected that data is entered into OC-RDC. Failure to keep up with entry of study data may result in study payment delay.

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

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

16. Study Administration

16.1. Training of Clinical Staff

Training of the Investigational Center staff on the conduct of the study and system being studied will be initiated prior to enrollment of the first study subject. All participating physicians and coordinators will be familiarized with the system being studied. Other members of the Investigational Center staff may require training depending on their role listing in the Delegation of Authority Log. Training may contain both lecture and hands-on experience.

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

16.2. Monitoring

Monitoring visits will be conducted at the start, during and at the closure of the clinical study in accordance with Medtronic Standard Operating Procedure (SOP)s and the Monitoring Plan. At minimum, it will be verified whether signed and dated ICFs have been obtained from each subject at the point of enrollment and that AEs discussed in Section 11 were reported via completion of the Adverse Event eCRFs. More details regarding the monitoring activities (frequency of monitoring visits, planned extent of source data verification) are described in the Monitoring Plan.

16.2.1. Accessibility of Investigational Center Staff and Study Materials

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

16.2.2. Audits and Investigational Center Inspections

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

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

16.2.3. Investigational Center Disqualification

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

- Unsatisfactory subject enrollment with regard to quality and quantity.
- Deviations from CIP, without prior notification and approval from Medtronic.
- Inaccurate, incomplete, and/or untimely data recording on a recurrent basis.

- The incidence and/or severity of adverse experiences in this or other studies indicating a potential health hazard caused by the device.
- Unsatisfactory accountability of study devices.

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

16.3. Data Management

16.3.1. Data collection

16.3.2. Electronic Case Report Forms (eCRFs)

The investigator must ensure accuracy, completeness and timeliness of the data reported in the eCRFs and in all other required reports. Data reported on the eCRFs which are derived from source documents must be consistent with the source documents and discrepancies need to be justified in a documented rationale, signed and dated by the (principal) investigator, and filed in the patient medical file.

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

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

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

16.3.3. CareLink iPro

During the course of the study, subject's SG values will be collected and assessed from the iPro2. The iPro2 data needs to be downloaded in CareLink iPro desktop database by the investigator or designated Investigational Center staff. The Study Meter data from the Patient Log Sheet needs to be obtained by the investigator or designated Investigational Center staff and entered into CareLink iPro.

The data in the different databases are linked to each other via the SIDs, which is a 9-digit code (313XXXXXX) to prevent subject identification by the sponsor.

16.3.4. Patient Log Sheet & Subject Questionnaires

The Patient Log Sheet and subject questionnaires will be collected on paper that will be kept at the Investigational Center. The investigator, or designated Investigational Center staff, will then copy the data from the Patient Log Sheet and answers of the subject on the paper questionnaires into OC-RDC

system. It is important that the investigator or designated Investigational Center staff verifies questionnaires for completeness.

16.3.5. Time windows for completion and submission of eCRFs

It is expected that eCRFs are completed in a timely manner with the exception of reportable AEs (see Section 11.3), which need to be recorded within 24 hours in the eCRF after awareness of the investigator or Investigational Center staff to the event. Most eCRFs should be submitted in final form, i.e. saved as complete, upon data entry, so that Monitors can proceed with data verification without delay. Exceptions to this rule may apply to eCRF that need to be accessed on multiple occasions before they can be finalized (e.g. Device Accountability eCRF).

16.3.6. Data review and processing

The leading investigational center will be accountable for data management and analysis about the data from each clinical research institution in a centralized manner according to local regulations and study requirements. Medtronic will oversee all data management functions and provide support if necessary. 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.

16.4. Direct Access to Source Data/Documents

The patient's hospital/clinic file, CareLink iPro data, laboratory reports, and data collected on the Patient Log Sheets and questionnaires are handled as source data.

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

Medtronic clinical representatives or delegates, will be granted access by the Investigational Center to all source documents including electronic source documents, if applicable, purposes of monitoring, audit or inspection. Where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the Investigational Center team with a statement that it is a true and complete reproduction of the original source document.

16.4.1. Quality Audits

Medtronic reserves the right to conduct quality audits at the investigational center in order to verify adherence to external regulations and internal policies and procedures; assess adequacy and effectiveness of clinical policies and procedures; assure compliance with critical study requirements;

confirm integrity and accuracy of clinical study data; and protect the safety, rights and welfare of study subjects.

16.5. Confidentiality

All records and other information about subjects participating in this clinical study will be treated as confidential.

Subject confidentiality will be maintained throughout the clinical study to the extent permitted by law. That is, every attempt will be made to remove subject identifiers from clinical study documents. For this purpose, a unique SID code (study - investigational center - subject number) will be assigned and used to allow identification of all data reported for each subject.

This will also ensure that the information can be tracked back to the source data.

Study data may be made available to third parties, e.g., in the case of an audit or inspection performed by regulatory authorities, provided the data are treated confidentially and that the subject's privacy is guaranteed. The identity of a subject will never be disclosed in the event that study data are published. Only anonymized data will be analyzed and published.

16.6. Liability

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.

If the investigational devices have caused any damage to the testing subjects, the sponsor will compensate in accordance with the contract of clinical trials.

Finance information will be documented in Clinical Trial Agreement.

16.7. Probability analysis of success

Since the Enlite Sensor has been evaluated in previous clinical studies and has demonstrated a within 20% agreement rate, significantly higher than 60% the probability that the acceptance criteria of 60% will be met within this study is extremely rather high.

16.8. Probability analysis of failure

Since the Enlite Sensor has been evaluated in previous clinical studies and has demonstrated a within 20% agreement rate, significantly higher than 60% the probability of failure is extremely low.

16.9. Responsibilities of all parties

Investigator responsibilities will be included in clinical trial agreement and subject responsibilities will be available in Informed Consent Form (ICF). Sponsor will undertake all the responsibilities of the sponsor as required per CFDA regulations.

16.10. 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.

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

16.11. Records and reports

16.11.1. 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
- Investigator's Brochure and/or user guide
- Medtronic and EC-approved Patient ICF
- EC and Regulatory authority approval or notification
- Fully signed clinical study agreements (i.e. including Investigator Statement and Signature Page, Clinical Trial Agreement and Confidential Disclosure Agreement)
- Completed Delegation of Authority Log
- Training documentation of all investigational center staff
- Subject screening log and/or SID log
- Signed, dated and fully executed Patient ICFs
- Source document requirements
- 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

16.11.2. Investigator reporting responsibilities

Table 4. Investigator Reporting Requirements

Report	Submit to	Description/Constraints
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 deviation 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	Sponsor and EC	Informed consent shall be obtained in writing and documented before a subject is enrolled into the clinical investigation. *(ISO 14155:2011)*
Progress report	Management department of medical device clinical study then they will submit to Sponsor and EC	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.
Final report	• Management department of medical device clinical study then they will submit to Sponsor and EC (if needed per EC requirements) • CFDA	Upon completion of multi-center clinical trials, investigators of all investigational centers shall issue brief summary of clinical trials, respectively, and submit it to coordinating investigator together with eCRFs upon review as required for coordinating investigator to summarize and complete summary report. *(CFDA order No.25 Article 29（7）)* Investigators should, in accordance with the design requirements of the clinical trial protocol, verify and validate the safety and effectiveness of investigational medical devices, and complete the Clinical Trial Report. As for multi-center clinical trials, the Clinical Trial Report should contain the Summaries of Clinical Trial of all sub-centers.

Report	Submit to	Description/Constraints
		(CFDA order No.25 Article 83) The Clinical Trial Report should be signed and dated by the investigators, and submitted to the sponsor after being reviewed, commented, dated and sealed by medical device clinical trial administration department of clinical trials institutions. For multi-center clinical trial, the clinical trial summary of each center should be signed and dated by the investigators of respective center, and submitted to the leading investigational center after being reviewed, dated and sealed by the investigational center's clinical trial administration department. *(CFDA order No.25 Article 86)*
Other	EC and CFDA	An investigator shall, upon request by a reviewing EC, CFDA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation.

16.12. Record Retention

The sponsor and investigator will retain all records and documents pertaining to this study. They will be available for inspection by the appropriate regulatory agencies. In addition, the investigator will retain the source documents from which the information entered on the eCRF was derived. These records are to be retained in a secure storage facility maintained by the investigational center for 10 years after completion of the study or termination of the study, whichever is longer. The investigator should not dispose of these records without the approval of the sponsor. The investigator should take measures to prevent accidental or early destruction of the clinical study related materials.The sponsor shall keep the clinical data indefinitely and till no such medical device is used.

16.13. Suspension or Early Termination of Clinical Study

16.13.1. Investigational Center suspension or termination

Medtronic, EC, or a regulatory authority may decide to suspend or prematurely terminate an Investigational Center (e.g. if information becomes available that the risk to study subject is higher than initially indicated, business decision, in case of expiring approval of the reviewing EC, non-compliance to

the CIP or lack of enrollment). The medical device clinical trial management departments of clinical trial institutions should be notified within 5 days with the rationale in writing. If an Investigational Center is suspended or prematurely terminated, Medtronic 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 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 the sponsor, EC, and department of food and drug administration of the concerned province, region and municipality.

The suspended clinical studies cannot be resumed without permission from EC. Upon completion of clinical studies, the applicant shall send written notice to the management of food and drug administration of the concerned province, autonomous region and municipality

16.13.2. 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 (unless subject is allowed to keep them per country requirement), receive appropriate treatment and follow-up.

16.14. Study close out

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

16.15. Publication and Use of Information

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

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

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

The identity of the subjects may not be disclosed, unless required by law, to any persons not immediately involved in the study or the study procedures.

17. References

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Medtronic, MMT-7340 CareLink iPro Software Purchasing Specification for Acceptance. 10572826DOC, 2016

18. Appendices

18.1. Appendix A: Contact Information

18.1.1. Names and addresses of Investigational Centers

Table 5: Investigational Centers and Investigators List

Investigational Center Number	Name of Investigational Center	Investigator	Title	Contact information
001	Shanghai Sixth People's Hospital	Jian Zhou	Chief Physician	N. 600 Yishan Road, Shanghai 20023
002	PLA Army General Hospital	Xiaofeng Lv	Professor, Chief Physician, and Director of Endocrinology Department	No.5 Nanmencang, Donsi Shitiao, Dongcheng District, Beijing, China, 100700
003	Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University,	Hong Li	Chief Physician and Director of Endocrinology Department	No.3 East Qingchun Road, Hangzhou, Zhejiang, China, 310016

18.1.2. 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.

18.2. Appendix B

Comments of the Sponsor Signature (stamp) Date: MM/DD/YYYY

Comments of the Investigator: Signature: Date: MM/DD/YYYY

Comments of medical device clinical trial institution Signature (stamp) Date: MM/DD/YYYY

18.3. Appendix C: Relevant qualification document(s) of the Sponsor/Local Sponsor(Agent)

Relevant qualification document(s) of the Sponsor/Local Sponsor(Agent) will be provided under a separate cover.

18.4. Appendix D: Informed Consent Form Template

The ICF template will be provided under a separate cover.

19. Version History

Version	Summary of Changes	Author(s)/Title
A	○ Not Applicable, New Document.	[redacted]
B	○ See "CIP313 Summary of Protocol Changes_ Version A to B"	[redacted]