Medtronic

Study Title	Multi-Center, Prospective, Observational Study of the TS (Threshold Suspend) Feature with a Sensor-Augmented Pump System in Pediatric Patients with Type 1 Diabetes
NCT Number	NCT02120794
Document Description	Study Protocol (Version C)
Document Date	17 August 2015

Title:	**Multi-Center, Prospective, Observational Study of the TS (Threshold Suspend) Feature with a Sensor-Augmented Pump System in Pediatric Patients with Type 1 Diabetes**
Protocol Number:	CEP287/Z25/C (FDA version C.3)
Sponsor:	Medtronic MiniMed, Inc. (“Medtronic”) 18000 Devonshire St Northridge, CA 91325 866.948.6633
Date of Protocol:	17 Aug 2015

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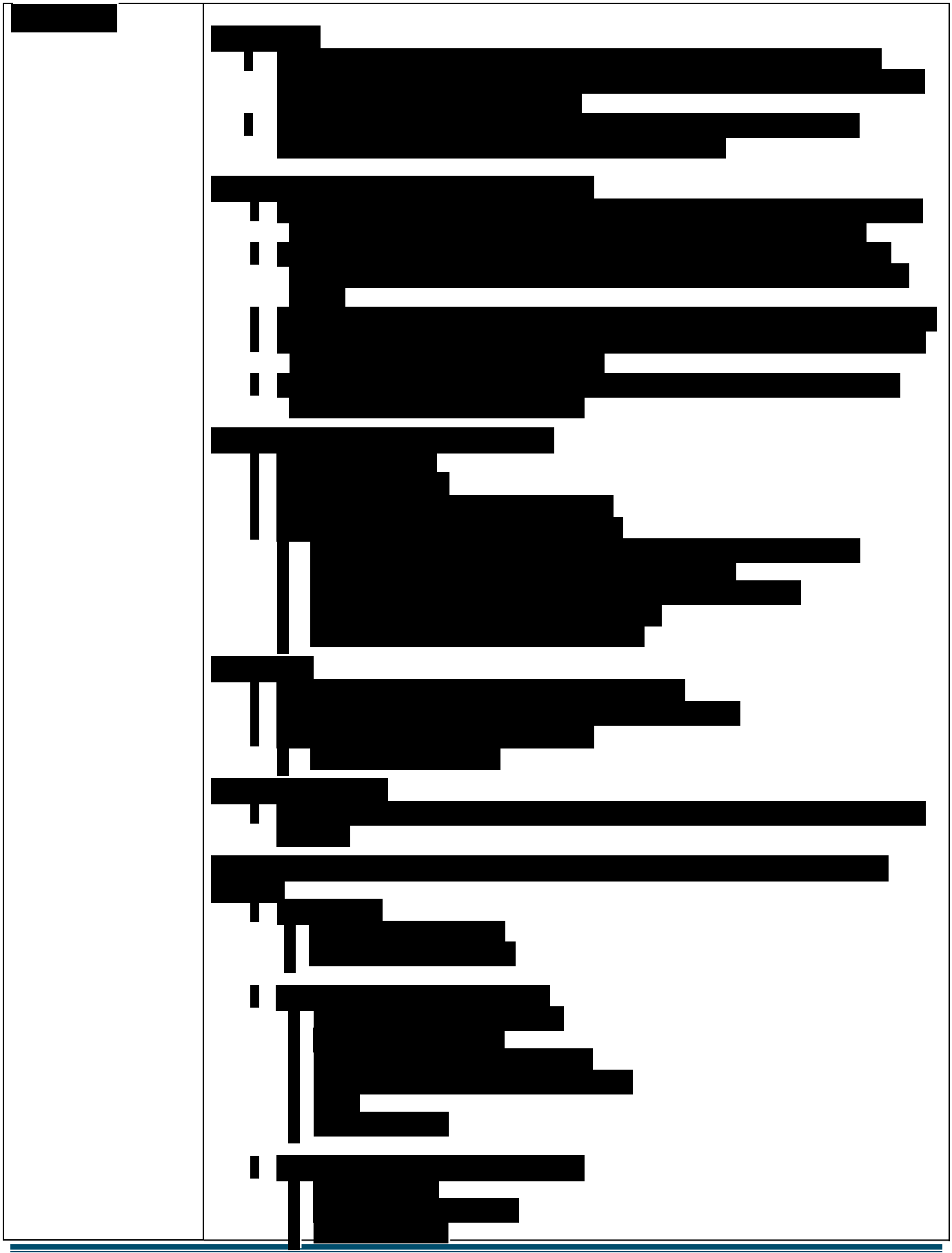
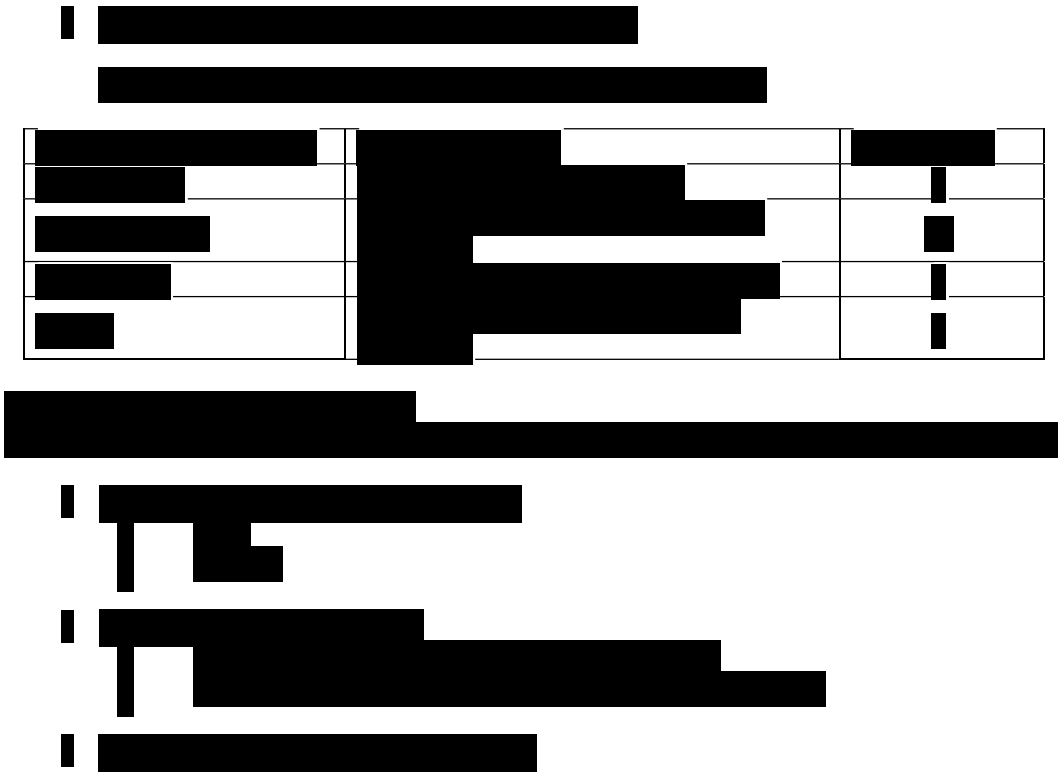
Synopsis

Study Design:	This study is a longitudinal, multi-center trial that aims to observe the Threshold Suspend (TS) feature with a sensor-augmented insulin pump in patients 7–15 years with Type 1 diabetes. The study will measure the change in A1C from baseline over a period of one year while subjects are wearing the study pump.
Devices:	***Investigational Devices*** • Medtronic MiniMed® 530G (MMT-551, MMT-751) Insulin Pump, referred to as the study pump in the protocol. • Medtronic MiniMed Enlite™ Glucose Sensor (MMT-7008), referred to as glucose sensor in the protocol • Medtronic MiniMed MiniLink® 2 REAL-Time Transmitter (MMT- 7713), referred to as MiniLink 2 throughout this protocol • Enlite™ Serter (MMT-7510), referred to as Enlite serter in the protocol • Medtronic CareLink® Therapy Management Software for Diabetes (MMT-7334) – referred to as CareLink Clinical in the protocol ***Non-Investigational Devices*** • Paradigm Remote Control/Programmer (MMT-503) - Optional • Medtronic MiniMed charger (MMT-7705) • Medtronic MiniMed CareLink® USB (MMT-7305) • Medtronic MiniMed Test Plug (MMT-7706) • Bayer CONTOUR™ Next Link RF enabled Blood Glucose Meter (HMS 9740)
Study Objective:	The study objective is to demonstrate that home use of Threshold Suspend (TS) is not associated with glycemic deterioration in pediatric patients with type 1 diabetes, as measured by change in A1C.
Primary Study Endpoint and Hypothesis:	The overall mean change in A1C from baseline will be estimated and compared by a non-inferiority test with an A1C margin of 0.4% and a significance level of 0.025 (one-sided).

Secondary Endpoint	The mean change in A1C from baseline to end of study for each individual A1C cohort
	• **Baseline A1C**
	  ○ A1C less than 7.0% (Minimum N=50)
	  ○ A1C between 7.0% to 9.0% (Minimum N=50)
	  ○ A1C greater than 9.0% (Minimum N=50)

Safety Endpoints:	***The following Safety information will be collected:*** • Serious Adverse Events (SAE) • Unanticipated Adverse Device Effects (UADE) • Incidence of Severe Hypoglycemia • Incidence of Severe Hyperglycemia • Incidence of Diabetic Ketoacidosis (DKA) • Adverse Events will be stratified by age, ethnicity, baseline BMI, gender, duration of diabetes, hypoglycemia awareness, frequency and average duration of hypoglycemic event (based on two weeks prior to the adverse event)
[redacted]	[redacted]



Number of Subjects and Study Population:	Up to 300 subjects will be enrolled so that there will be 200 subjects who are eligible to participate in the study.
	
	Up to 20 Investigational centers will be selected across the United States. Selection is based on each Investigator's experience and qualifications, availability of sufficient resources to carry out the required study procedures and the investigator's ability to recruit subjects into the study.
	
	Subjects will be grouped by baseline demographics: Baseline A1C, age, ethnicity, body mass index (BMI), gender and duration of diabetes and hypoglycemic awareness. Sponsor will oversee distribution of subjects across study sites.
	
	• **Baseline A1C**
	  ○ A1C less than 7.0% (Minimum N=50)
	  ○ A1C between 7.0% to 9.0% (Minimum N=50)
	  A1C greater than 9.0% (Minimum N=50)
	
	• **Race**
	  ○ American Indian/Alaska Native
	  ○ Black/African-American
	  ○ White - anticipated maximum 80%
	  ○ Native Hawaiian/Other Pacific Islander
	  ○ Asian
	  ○ Subject Refused
	• **Ethnicity**
	  ○ Hispanic/Latino
	  ○ Non-Hispanic/Non-Latino
	  ○ Subject refused
	
	• **Diabetes cohorts based on BMI percentile:**

Weight Status Category	Percentile Range	N=Minimum
Underweight	Less than the 5th percentile	2
Healthy weight	5th percentile to less than the 85th percentile	30
Overweight	85th to less than the 95th percentile	4
Obese	Equal to or greater than the 95th percentile	1

BMI Percentiles according to CDC:
http://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html

- **Gender**
  - Male (minimum N=80)
  - Female (minimum N=80)

- **Hypoglycemic awareness**
  - Patients with intact hypoglycemic awareness (minimum N=60)
  - Patients who have impaired hypoglycemic awareness (minimum N=40)

Inclusion Criteria:

1. Subject is age 7 to 15 at time of screening
2. Subject has been diagnosed with type 1 diabetes mellitus and must have been diagnosed for at least one year prior to screening
3. Subject is currently transitioning from pump therapy, with or without continued glucose monitoring (CGM), to the 530G insulin pump system.
4. Subject is willing to perform greater than or equal to 4 finger stick blood glucose measurements daily
5. Subject is willing to perform required sensor calibrations
6. Subject is willing to wear the system (Pump, glucose sensors, meter) continuously throughout the study
7. Subject is willing to upload data every 21 days from the study pump
8. Subject must have Internet access and access to a computer system that meets the requirements for uploading the pumps. This may include use of family or friend's computer system with Internet access.
9. Subject is using either Humalog or Novolog at time of Screening and plans to use either of those insulins throughout the study

Exclusion Criteria:

1. Subject is actively participating in an investigational study (drug or device) wherein he/she is receiving treatment from an investigational study drug or investigational study device.
2. Women of child-bearing potential who have a positive pregnancy test at screening or plan to become pregnant during the course of the study
3. Subject is being treated for hyperthyroidism at time of screening
4. Subject has an abnormality (>1.8mg/dL) in creatinine at time of screening visit
5. Subject has an abnormality (out of reference range) in thyroid-stimulating hormone (TSH) at time of screening visit
   - If TSH is out of range, Free T3 and Free T4 will be tested
   - Subject may be included with TSH out of range as long as Free T3 and Free T4 are in normal reference range.
6. Subject has taken any oral, injectable, or IV steroids within 8 weeks from time of screening visit, or plans to take any oral, injectable, or IV steroids during the course of the study
7. Subject is currently abusing illicit drugs
8. Subject is currently abusing prescription drugs

<table>
<tr><td></td><td>
9. Subject is currently abusing alcohol
10. Subject is using pramlintide (Symlin) at time of screening
11. Subject has a sickle cell disease, hemoglobinopathy; or has received red blood cell transfusion or erythropoietin within 3 months prior to time of screening
12. Subject plans to receive red blood cell transfusion or erythropoietin over the course of study participation
13. Subject diagnosed with current eating disorder such as anorexia or bulimia
14. Subject has been diagnosed with chronic kidney disease that results in chronic anemia
15. Subject is on dialysis
16. Subject is already on a 530G system with CGM for 8 days or more.
</td></tr>
<tr><td><u>Visit Schedule:</u></td><td>
Subjects will attend 5 study visits
<table>
<tr><th>Visit 1
Day 0</th><th>Visit 2
Day 90 (±21)</th><th>Visit 3
Day 180 (±30)</th><th>Visit 4
Day 270 (±30)</th><th>Visit 5
Day 365 (+30)</th></tr>
<tr><td>Consent
Screening
A1C
Device
Disbursement
EQ5-5DYouth questionnaire
HFS Parent questionnaire
HFS Child/Teen questionnaire
Hypoglycemia Unawareness questionnaire
Study Pump training
CGM training</td><td>A1C
Device
Disbursement
CareLink upload</td><td>A1C
Device
Disbursement
CareLink upload</td><td>A1C
Device
Disbursement
CareLink upload</td><td>End of Study
CareLink upload
A1C
EQ5-5DYouth questionnaire
HFS Parent questionnaire
HFS Child/Teen questionnaire
Hypoglycemia Unawareness questionnaire
Return of Study Devices and supplies</td></tr>
</table>
The schedule for subjects is planned out as follows:
Details are in Table 1: Visit Plan and Study Activities
</td></tr>
</table>

1. Background

Continuous Subcutaneous Insulin Infusion (CSII), or pump therapy, allows for insulin to be delivered continuously into the body, as opposed to delivery at specific times. Rapid-acting insulin is infused into the body at constant/basal rates throughout a 24-hr period via the insulin pump which mimics normal insulin secretion from the pancreas. Additional rapid-acting insulin can be delivered in boluses to compensate for anticipated fluctuations in blood glucose in response to meals.

Frequent self-monitoring of blood glucose (SMBG) is also an important part of the management of Type 1 diabetes. Careful attention to blood glucose values throughout the day allows patients to more precisely adjust insulin dosages. However, because SMBG values are taken only at specific time points and measure brief instances of time within a 24-hour period, there are limits to the usefulness of this information. The "snap-shot" effect of SMBG proves to be a challenge for tracking of blood glucose (BG) trends which can be overcome through the addition of continuous interstitial glucose monitoring to the SMBG regimen.

Current methods of continuous glucose monitoring (CGM) include the use of subcutaneous glucose sensors worn by the user which convert glucose from the subject's interstitial fluid into an electronic signal, the strength of which is proportional to the amount of glucose present in the fluid. The Paradigm® System, which received market approval from FDA on April 7, 2006 (P980022/S013), combined the technology of the Paradigm Insulin Pump (Models 522/722) with that of the MiniMed Guardian® REAL-Time Clinical device. The Paradigm System represents a combination of innovative therapies for the treatment of Type 1 diabetes mellitus: Pump therapy in conjunction with continuous interstitial glucose monitoring, as well as SMBG to perfect treat-to-glycemic–target approach.

In this study, the sensor is attached to a transmitter which sends interstitial glucose information to the study Pump via radio signals. The pump screen is the data collection/user interface of the system and provides continuous real-time glucose values to the user, as well as high/low glucose alerts set according to the individual patient's needs. The Diabetes Control and Complications Trial (DCCT) convincingly established the benefits of tight glucose control in the avoidance of long-term diabetic complications. However, a pitfall of the aggressive management of diabetes using intensive insulin regimens is an increased frequency of hypoglycemia. Surveys investigating the prevalence of hypoglycemia have provided some alarming results. The DCCT reported a threefold increase in severe hypoglycemia and coma in intensively treated patients versus conventionally treated patients [DCCT Research Group, 1991].

For many individuals with diabetes, episodes of severe hypoglycemia are the major obstacle to the achievement of euglycemia and the prevention of long-term complications. Hypoglycemia is frightening to patients and their families. It has been estimated that about 55% of severe hypoglycemic episodes occur during sleep. Acutely diminished brain function during a hypoglycemic episode poses potential physical danger to the patient. In addition, recurrent hypoglycemia may impose long-lasting damaging effects on the brain, resulting in impairment of memory or other cognitive functions.

In addition to adversely affecting cognition, recurrent hypoglycemia also impairs the body's defense mechanisms against hypoglycemia, creating a vicious cycle for the patient. Normally, hypoglycemia triggers a series of hormonal and neural responses designed to restore glucose concentration towards normal, to maintain brain metabolism. A component of this counter-regulatory response is the secretion of epinephrine, which generates "neurogenic" symptoms (e.g., palpitations, sweating, and anxiety) that serve to warn the patient of the drop in blood glucose. The patient can then take action (i.e., eat) to help reverse the hypoglycemia. After an episode of severe hypoglycemia the body's natural responses are impaired further increasing the patient's risk of another hypoglycemic episode.

Terms regarding TS used in this protocol:

- Threshold Suspend (TS) refers to low glucose suspend which allows for the suspension of insulin when a preset sensor glucose threshold has been set.

- Threshold Suspend ON (TS ON) refers to low glucose suspend wherein the preset sensor glucose threshold has been set and turned ON.

- Threshold Suspend OFF (TS OFF) refers to low glucose suspend wherein the preset sensor glucose threshold is turned OFF.

- Threshold Suspend triggered (TS triggered) refers to the suspension of insulin secondary to meeting the preset sensor glucose threshold.

2. Devices and Supplies

2.1 *Names and Intended Use of Devices*

2.1.1 Medtronic MiniMed® 530G Pump (MMT-551, MMT-751) – Investigational

The Medtronic MiniMed® 530G Pump model (MMT-551, MMT-751) used in this study is an approved device in the United States. This insulin pump is equipped with a number of features to actively manage the user's glucose levels. The Threshold Suspend (TS) feature automatically stops insulin delivery based on a low Sensor Glucose Value (SGV). The TS feature is only available when the pump is used in conjunction with continuous glucose monitoring (CGM) which consists of a subcutaneous glucose sensor and transmitter to communicate sensor glucose readings to the insulin pump.

2.1.2 Paradigm Remote Control/Programmer (MMT-503) – Approved under 510(k) K001829

The Paradigm Remote Controller is a hand-held, reusable accessory device that uses radio frequency to transmit a signal to Paradigm Infusion Pumps for limited pump programming. Using this accessory, a pump user can program a normal bolus, suspend or restart the pump. The device is considered an accessory to the Paradigm Infusion Pump family

2.1.3 Medtronic MiniMed Enlite™ Glucose Sensor (MMT-7008) – Investigational

The Medtronic MiniMed Enlite Sensor is a sensor that is similar in design and materials to the Medtronic MiniMed Glucose Sof-Sensor. The sensor includes 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 smaller 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, 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.

2.1.4 Medtronic MiniMed MiniLink® 2 REAL-Time Transmitter (MMT-7713) – Investigational

The MiniLink 2 is an investigational small transmitter device. The hardware of this transmitter is identical to MiniLink transmitter approved under (PMA supplement approval number P980022/S018). The only difference between the two devices is the addition of the Artifact Detection software feature. Once the sensor has been inserted, the MiniLink 2 is connected directly to the sensor where it receives the electronic signal from the sensor electrode, converts signals into glucose data, and transmits the data to the pump. When a sensor is attached to the

MiniLink 2, it enters an initialization period. After two hours, it begins to periodically transmit glucose data to the pump, using a radio signal.

The MiniLink 2 contains a rechargeable battery, sensor electronics, and a radio frequency (RF) transmitter. A fully charged battery provides up to 14 days of transmitter use. The system includes a battery charger that will recharge the device according to the user guide. For additional information on the MiniLink 2 REAL-Time Transmitter, refer to the MiniLink REAL-Time Transmitter User Guide.

2.1.5 Medtronic CareLink® Therapy Management Software for Diabetes (MMT-7334) – Investigational – referred to as CareLink Clinical in the protocol

Carelink Clinical is an Internet based software system which allows data to be viewed and is easily evaluated by the subject and his/her physician but should not be used by research site or subject for data analysis or diabetes management. A Personal Computer (PC) is used to access CareLink Clinical via the Internet, which then allows subjects/parents/caregivers to upload data from Medtronic MiniMed insulin pumps and a range of system-supported, third-party blood glucose meters. Carelink Clinical was developed for use by clinical trial subjects only. The data contained in CareLink Clinical is accessible to users using a standard browser, e.g., Microsoft® Internet Explorer on an Internet enabled PC.

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

1. The internet to the web server;
2. Web server to the application server;
3. Application server to the database server.

This software has been developed especially for use in clinical trials.

2.1.6 Medtronic MiniMed charger (MMT-7705) – FDA approval P980022/S018

This charger will used to charge the MiniLink 2 transmitter. The MiniLink 2 contains a non-replaceable, rechargeable battery that can be recharged as needed. The charger has a green light to indicate the charging status and a red light that indicates problems during charging. Before using MiniLink 2, it must be fully charged, which will take up to 8 hours. A full charge lasts for up to 14 days of continuous use. After 14 days of use, the MiniLink 2 will fully recharge in less than 2 hours.

2.1.7 Medtronic MiniMed Test plug (MMT-7706) - FDA approval P980022/S018

The Test Plug operates as a sensor simulator creating signal current at a level that is within the range of an in-vivo sensor during normal operation.

2.1.8 Enlite™ Serter (MMT-7510) – Investigational

The Enlite Serter is an insertion device used to ensure correct placement of the Medtronic MiniMed Enlite Glucose Sensor. The Serter injects the sensor into the insertion site when the button is released.

2.1.9 Medtronic MiniMed CareLink™ USB (MMT-7305) - FDA approval K070438

The Medtronic CareLink USB (510 (k) clearance number K070438) is indicated for use commercially by patients at home and for clinicians in a medical office setting as a means of facilitating communication between Medtronic diabetes therapy management devices that use Paradigm-compatible RF telemetry and a personal computer that uses data management application software. The CareLink USB device will enable data from the Medtronic MiniMed® 530G to be uploaded to CareLink Clinical.

2.1.10 Bayer CONTOUR™ Next Link Blood Glucose Meter (HMS 9740) – FDA approval K110894

The Bayer Contour Next Link RF enabled BG Meter measures a subject's capillary blood glucose level, which is then used to calibrate the pump. The Medtronic MiniMed® 530G pump uses the calibration point in the real-time algorithm which calculates the sensor glucose values that are displayed to the subject. In a normal setting, the result of the SMBG reading is transmitted to the pump via radiofrequency (RF) and can be stored in its memory as a glucose calibration point. The pump asks the user every time if the user wants to use the linked meter BG for calibration. If accepted, the glucose value will be stored in the pump's memory as a calibration point.

3. Objective and Hypothesis

3.1. Study Objective

The study objective is to demonstrate that home use of Threshold Suspend (TS) is not associated with glycemic deterioration in pediatric patients with type 1 diabetes, as measured by change in A1C.

3.2. Study Hypothesis

Change in A1C is defined as A1C measured at the end of 12-month study period minus A1C measured at the baseline visit. The hypothesis is mathematically expressed as:

$H_o: \mu \geq 0.4\%$
$H_a: \mu < 0.4\%$

Where 0.4% is the pre-specified non-inferiority margin, μ is the mean of change in A1C (%).

4. Study Design

This study is a longitudinal, multi-center trial that aims to observe the Threshold Suspend (TS) feature with a sensor-augmented insulin pump in patients 7–15 years with Type 1 diabetes. The study will measure the change in A1C from baseline over a period of one year while subjects are wearing the study pump.

5. Study Population

5.1 Number of Subjects and Study Population:

Up to 300 subjects will be enrolled so that there will be 200 subjects who are eligible to participate in the study.

Up to 20 Investigational centers will be selected across the United States. Selection is based on each Investigator's experience and qualifications, availability of sufficient resources to carry out the required study procedures and the investigator's ability to recruit subjects into the study.

Subjects will be grouped by baseline demographics: Baseline A1C, age, ethnicity, body mass index (BMI), gender and duration of diabetes and hypoglycemic awareness. Sponsor will oversee distribution of subjects across study sites.

- Baseline A1C
  - A1C less than 7.0% (Minimum N=50)
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  - White - anticipated maximum 80%
  - Native Hawaiian/Other Pacific Islander
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  - Subject refused

- Ethnicity
  - Hispanic/Latino
  - Non-Hispanic/Non-Latino
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- Diabetes cohorts based on BMI percentile:

Weight Status Category	Percentile Range	N=Minimum
Underweight	Less than the 5th percentile	2
Healthy weight	5th percentile to less than the 85th percentile	30
Overweight	85th to less than the 95th percentile	4
Obese	Equal to or greater than the 95th percentile	1

BMI Percentiles according to CDC:
http://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html

- Gender
  - Male (minimum N=80)
  - Female (minimum N=80)

- Hypoglycemic awareness
  - Patients with intact hypoglycemic awareness (minimum N=60)
  - Patients who have impaired hypoglycemic awareness (minimum N=40)

5.2 Study Schedule / Duration

Each subject's participation in the study will be comprised of 5 scheduled office visits over approximately 12 months. The entire study is expected to be completed within approximately 24 months from approval of the study protocol and the study device.

5.3 Inclusion Criteria

1. Subject is age 7 to 15 at time of screening
2. Subject has been diagnosed with type 1 diabetes mellitus and must have been diagnosed for at least one year prior to screening
3. Subject is currently transitioning from pump therapy, with or without continued glucose monitoring (CGM), to the 530G insulin pump system.
4. Subject is willing to perform greater than or equal to 4 finger stick blood glucose measurements daily
5. Subject is willing to perform required sensor calibrations
6. Subject is willing to wear the system (Pump, glucose sensors, meter) continuously throughout the study
7. Subject is willing to upload data every 21 days from the study pump
8. Subject must have Internet access and access to a computer system that meets the requirements for uploading the pumps. This may include use of family or friend's computer system with Internet access.
9. Subject is using either Humalog or Novolog at time of Screening and plans to use either of those insulins throughout the study

5.4 Exclusion Criteria

1. Subject is actively participating in an investigational study (drug or device) wherein he/she is receiving treatment from an investigational study drug or investigational study device.
2. Women of child-bearing potential who have a positive pregnancy test at screening or plan to become pregnant during the course of the study
3. Subject is being treated for hyperthyroidism at time of screening
4. Subject has an abnormality (>1.8mg/dL,) in creatinine at time of screening visit
5. Subject has an abnormality (out of reference range) in thyroid-stimulating hormone (TSH) at time of screening visit
    - If TSH is out of range, Free T3 and Free T4 will be tested
    - Subject may be included with TSH out of range as long as Free T3 and Free T4 are in normal reference range.
6. Subject has taken any oral, injectable, or IV steroids within 8 weeks from time of screening visit, or plans to take any oral, injectable, or IV steroids during the course of the study
7. Subject is currently abusing illicit drugs
8. Subject is currently abusing prescription drugs
9. Subject is currently abusing alcohol
10. Subject is using pramlintide (Symlin) at time of screening
11. Subject has a sickle cell disease, hemoglobinopathy; or has received red blood cell transfusion or erythropoietin within 3 months prior to time of screening
12. Subject plans to receive red blood cell transfusion or erythropoietin over the course of study participation
13. Subject diagnosed with current eating disorder such as anorexia or bulimia
14. Subject has been diagnosed with chronic kidney disease that results in chronic anemia
15. Subject is on dialysis
16. Subject is already on a 530G system with CGM for 8 days or more.

6. Statistical Methods and Data Analysis

6.1. Sample Size Calculation

6.1.1 Sample Size for Primary Endpoint

The overall mean change in A1C from baseline to the end of study will be estimated and compared by a non-inferiority test with an A1C margin of 0.4%

and a significance level of 0.025 (one-sided). The null hypothesis will be rejected if the one-sided 97.5% upper confidence limit of the mean change in A1C is less than 0.4%

The hypothesis is mathematically expressed as:
Ho: μ ≥ 0.4%
Ha: μ < 0.4%

Where 0.4% is the pre-specified non-inferiority margin, μ is the mean of change in A1C (%).

Assuming the mean of change in A1C from baseline to the 12-month follow-up visit is zero, the standard deviation of change in A1C is 1%, SAS power and sample size calculator shows that a total of 100 subjects will provide over 95% power to detect the non-inferiority with a margin of 0.4% and with one-sided type I error of 0.025.

6.1.2 Overall Consideration

The above calculations suggest a sample size of 100 subjects who complete the study. For the drop-out rate, a conservative estimate of 20% is adopted (based on STAR3, IDE G060159, the percentage of subjects not completing study in the SAP group is 9.3%); assume 65% of subjects would wear the system most of the time. Then a total of 193 subjects needs to be recruited. In general, a number of 200 will be eligible to participate in the study, with up to 300 subjects enrolled.

6.2. Study Populations

6.2.1. Intention to Treat (ITT) Population

The Intention to Treat (ITT) population will include all enrolled subjects.

6.2.2 Completed Case (CC) Population

The Completed Cases (CC) population is all subjects who complete the trial.

6.2.3 Efficacy Population

The primary efficacy analysis will be performed on the CC population.

6.2.4 Safety Population

The Safety Population will be the ITT population (include all enrolled subjects).

6.3 Analysis of Primary Endpoint

6.3.1 Primary Efficacy Analysis

A mixed effects model be used to produce the estimate and confidence interval of the overall mean change in A1C while accounting for inter-site variability. The 97.5% upper confidence interval of A1C will be calculated and compared to the 0.4% non-inferiority margin. As for endpoint analysis, the proposed mixed effects model using all A1C measurements has more power than the model only using Change in A1C from baseline to one-year visit.

$$\Gamma_{ij} = X_{ij}\beta + B_i + B_{ij} + \varepsilon_{ij}$$

where

$Y_{ij} = (Y_{ij1}, \ldots, Y_{ijP})'$ is the A1C measurement vector for the jth subject in the ith site;

$$X_{ij} = \begin{pmatrix} 1 & C & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 \\ 1 & C & 1 & 0 & 0 \\ 1 & C & 0 & 1 & 0 \\ 1 & C & 0 & 0 & 1 \end{pmatrix}$$ is a the covariate vector for the jth subject in the ith site;

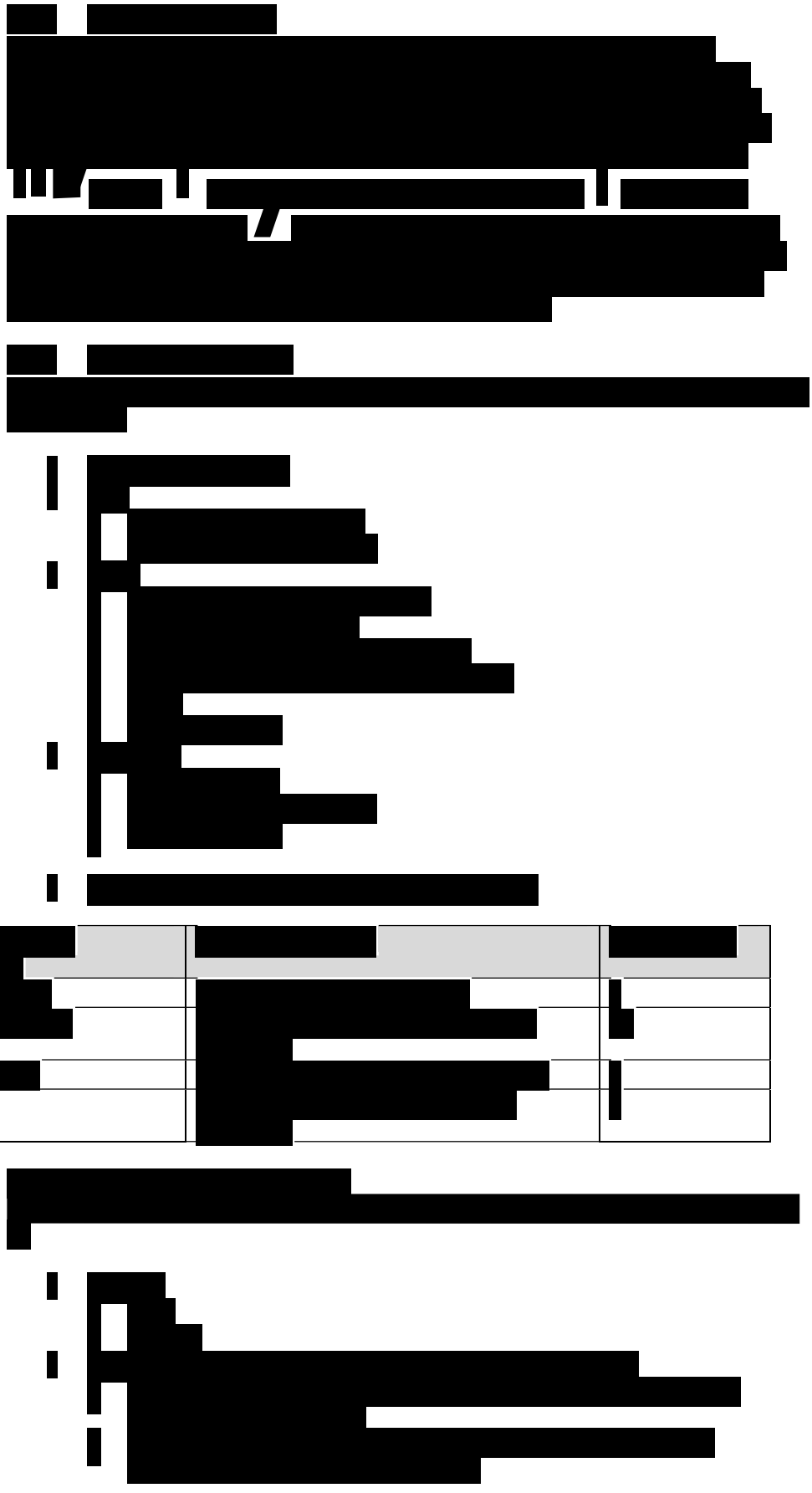
$$\beta = \begin{pmatrix} \beta_0 \\ \beta_1 \\ \beta_2 \\ \beta_3 \\ \beta_4 \end{pmatrix}$$ is the coefficient vector, β_0 estimate the mean A1C at baseline, β_4 estimate the mean change of A1C from baseline to one-year visit;

$b_i = (b_{i1}, \ldots b_{iq})'$ is the random effect vector for the ith site;

$b_{ij} = (b_{ij1}, \ldots b_{ijq})'$ is the random effect vector for the jth subject in the ith site;

$\varepsilon_{ij} = (\varepsilon_{ij1}, \ldots, \varepsilon_{ijP})'$ is the random error term;

"The mean of baseline A1C measurement is estimated by β_0, mean of 3-month A1C measurement estimated by $\beta_0 + \beta_1$, …, mean of 12-month A1C measurement estimated by $\beta_0 + \beta_4$, i.e., β_4 estimate the mean change of A1C from baseline to one-year visit; the 97.5% upper confidence interval of β_4 will be calculated and compared the 0.4% non-inferiority margin."



6.4 Safety Analysis

All site reported adverse events for enrolled subjects will be summarized. The summary will include all adverse events and adverse events by: Insulin Pump Infusion set; Insulin administration and pump use; Sensor Use; Severe Hypoglycemia; Severe Hyperglycemia; Diabetic Ketoacidosis; Adverse Device Event; Serious Adverse Event and Unanticipated Adverse Device Effect. Adverse Events by Investigator will also be provided. No formal statistical analysis will be carried out.

In addition, data will be collected for a descriptive summary of device disposition; adverse events; device performance and user acceptance. Safety analysis will include a summary of the following:

All adverse events including

- Serious Adverse Events (SAE)
- Unanticipated Adverse Device Effects (UADE)
- Incidence of Severe (clinical) Hypoglycemia
- Incidence of Severe Hyperglycemia
- Incidence of Diabetic Ketoacidosis (DKA)

Adverse Events will be stratified by

- **Age**
  - Children age 7-12 years
  - Children age 13-15 years
- **Race**
  - American Indian/Alaska Native
  - Black/African-American
  - White - anticipated maximum 80%
  - Native Hawaiian/Other Pacific Islander
  - Asian
  - Subject Refused
- **Ethnicity**
  - Hispanic/Latino
  - Non-Hispanic/Non-Latino
  - Subject Refused

- **Diabetes cohorts based on BMI percentile:**

Weight Status Category	Percentile Range	N=Minimum
Underweight	Less than the 5th percentile	2
Healthy weight	5th percentile to less than the 85th percentile	30
Overweight	85th to less than the 95th percentile	4
Obese	Equal to or greater than the 95th percentile	2

BMI Percentiles according to CDC:
http://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html

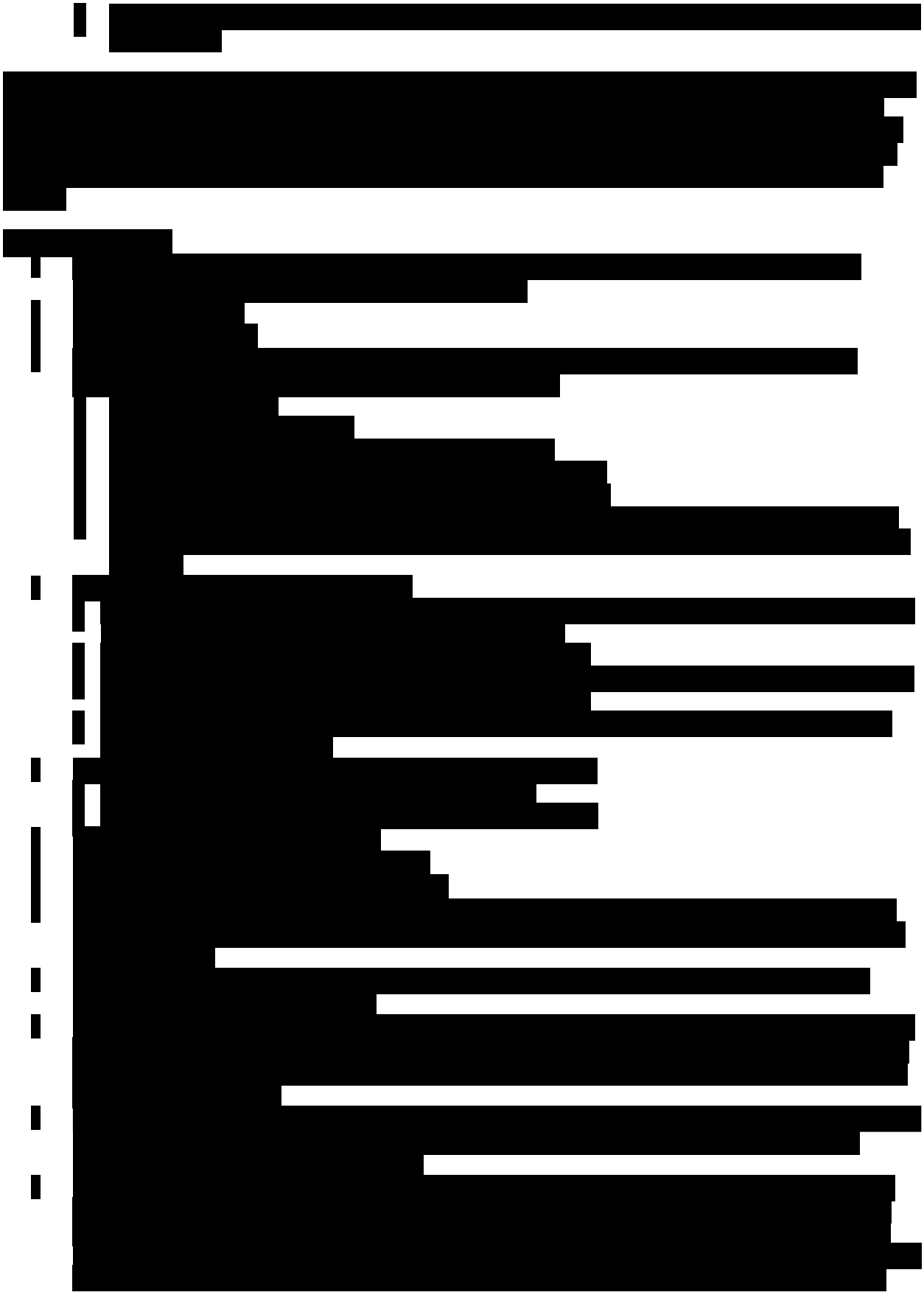
- **Gender**
  - Male
  - Female
- **Hypoglycemic awareness at Baseline Questionnaire**
  - Patients with intact hypoglycemic awareness (95% confidence interval will be provided)
  - Patients who have impaired hypoglycemic awareness (95% confidence interval will be provided)
- Frequency and average duration of hypoglycemic event (based on two weeks prior to the adverse event)

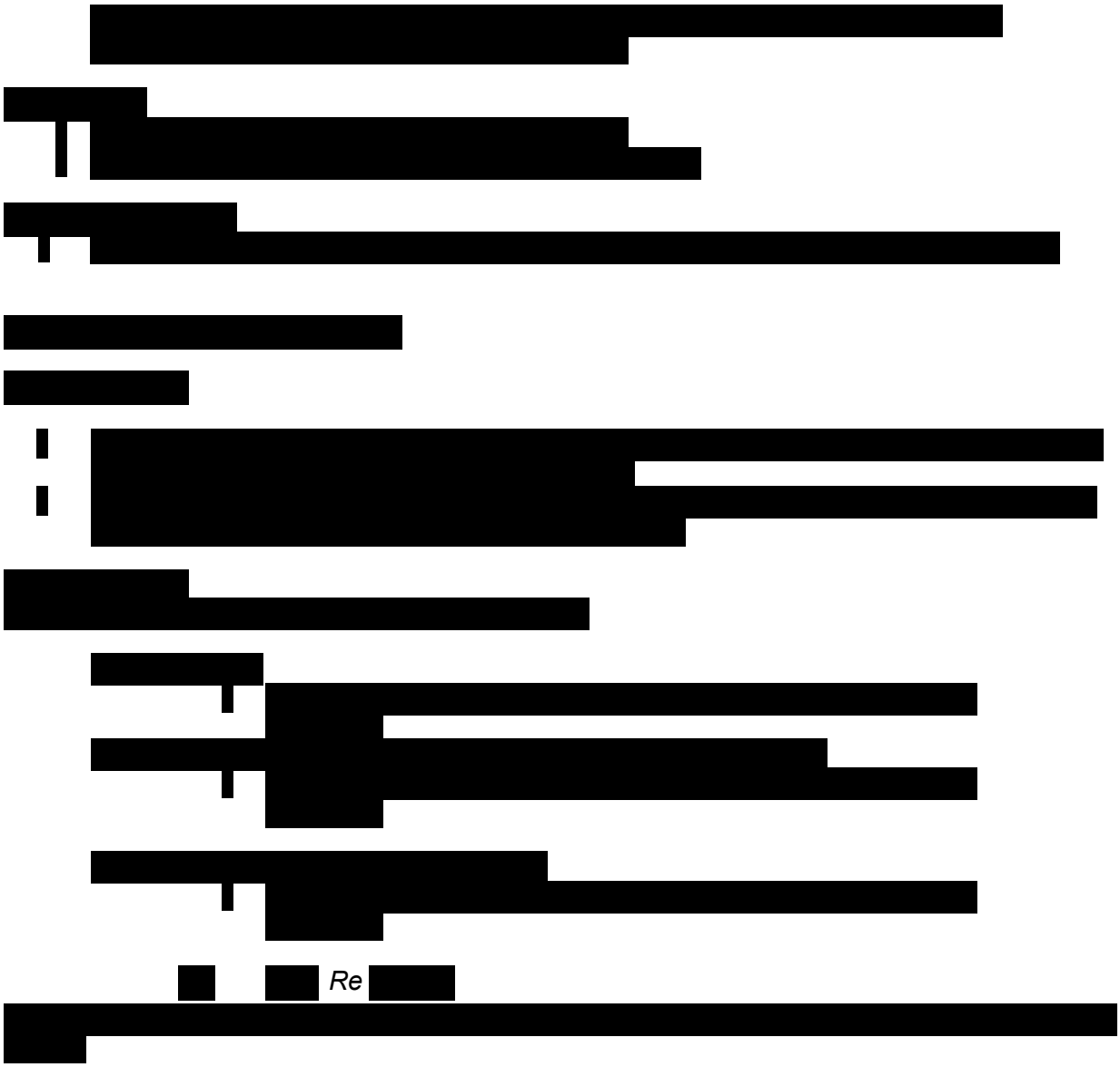
- The one-sided 95% upper confidence limit of severe adverse event incidence rate (DKA and severe hypoglycemia) will be calculated. Individual one-sided 95% confidence limit for DKA only and severe hypoglycemia only will also be provided.

6.5 Secondary Endpoint

The mean change in A1C from baseline to 3-month, 6-month, 9-month and 12-month will be summarized individually for each of the three baseline A1C cohorts:

- A1C less than 7.0%;
- A1C between 7.0% to 9.0;
- A1C greater than 9.0%





7. Institutional Review Board

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

8. Subject Confidentiality

8.1 Subject Identification

The identity of the subjects may not be disclosed, unless required by law, to any persons not immediately involved in the study or the study procedures. All correspondence between the Investigational Center and Medtronic that refers to individual study subjects will use unique identifiers that are specific to each

subject in lieu of subject names. Furthermore, all subject names will be redacted from reports, safety updates, and source documents that are forwarded to the Medtronic.

8.2 Subject Database Assignment

In the Oracle Clinical database, the Investigational Centers will be identified numerically, i.e. from 01 to 25 (depending on center number). At the Screening visit, Investigational Center staff will assign each subject a sequential ID number that corresponds to a pre-defined casebook in the Oracle database.
Each case book will contain all relevant Case Report Forms for each subject. Subjects will be assigned a unique 9-digit identifier that will be structured such that the first 3 digits correspond to the study number (287), the next 3 digits correspond to the Investigational Center number, and the final 3 digits correspond to the subject number. An example of a typical subject's unique identifier is shown in the following example: The numerical sequence 287001001 translates into: Study number (287), Investigational Center number (001), Subject number (001).

All study documents, eCRFs and correspondence will use this identifier sequence in lieu of a subject's name or initials.

8.3 Informed Consent

Informed Consent/ Assent will be obtained in accordance with the Code of Federal Regulations (CFR) Title 21, Part 50. Prior to entry into the study the California Experimental Subject's Bill of Rights (if applicable), the IRB- and Medtronic-approved Informed Consent Form (ICF)/Assent, and the HIPAA Authorization Form will be given to each subject. Subjects/parents/caregivers will be offered the opportunity to review these documents away from the Investigational Center. Pediatric subjects 7-15 years of age should provide informed assent to participate in this research even if their parents or guardians have given permission for their participation through informed consent. A subject's participation in study procedures cannot start before the consent process has been properly executed.

9. Investigator Responsibilities

This study will be conducted at up to 20 Investigational Centers where all study-related activities will take place; at each center, the study will be led by a principal Investigator. Per 21 CFR 56.102, an Investigator is "an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject) or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team." Specific responsibilities of the principal investigator are described in 21 CFR 812.100 and in the FDA guidance document dated October, 2009 (see Regulatory Binder).

10. Study Visits

Chart 1: Visit 1-5

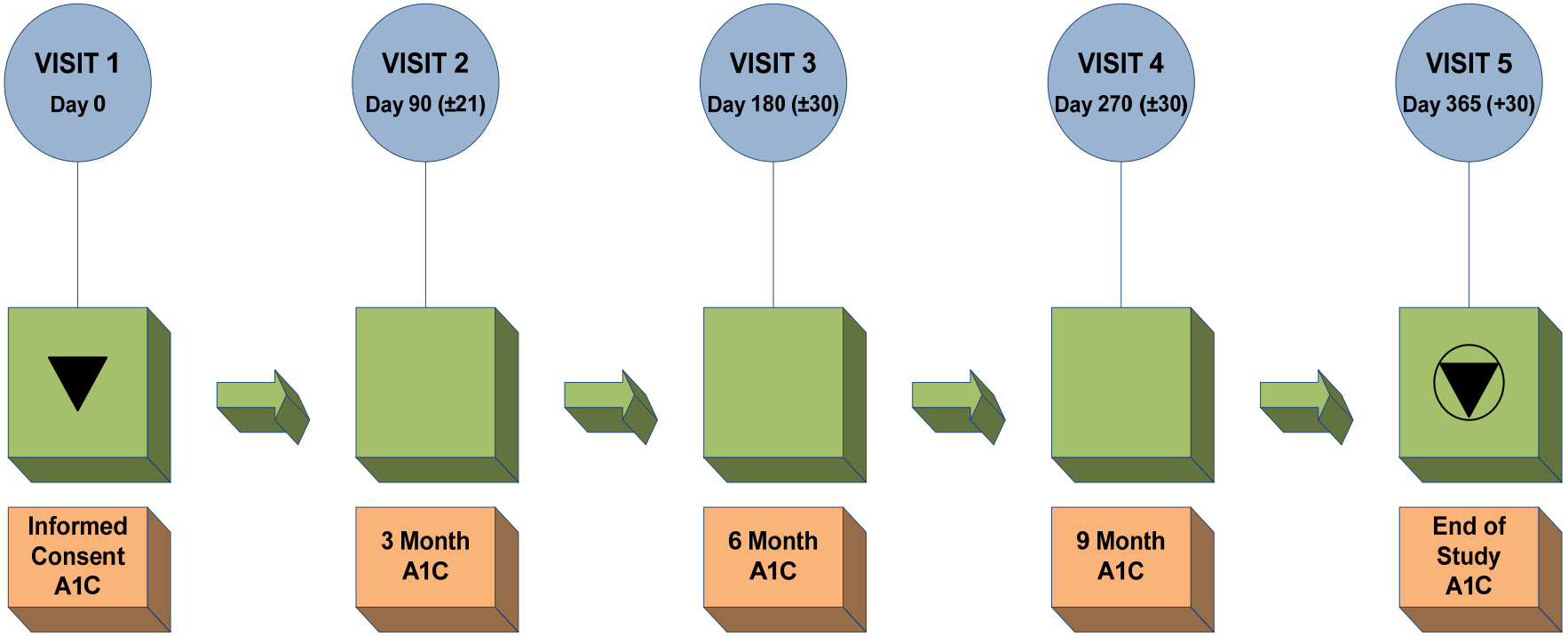


Table 1: Visit Plan and Study Activities

	Visit 1 Screening	Visit 2 90 Day A1C	Visit 3 180 Day A1C	Visit 4 270 Day A1C	Visit 5 365 Day A1C End of Study
Study Activities at Site during visit	Informed Consent Eligibility Assessment Subject Demography Record Concomitant medications Screening A1C Lab Draw Administer Questionnaires Case Report Forms Distribute devices and supplies (e.g., pump, transmitter, Bayer meter, glucose sensors, meter strips, ketone strips) to each subject Dislodgement Subject Diary Study Pump Training CareLink Registration Help Line Training Case Report Forms EQ5-5DYouth questionnaire HFS Parent questionnaire HFS Child/Teen questionnaire Hypoglycemia Unawareness questionnaire Upload insulin pump Instruct subjects to use either Humalog or Novolog insulins Instruct Subjects to use the Bayer Contour Link meter for all calibrations	Adverse Event Check CareLink Upload A1C Test Case Report Forms Distribute devices and supplies (e.g., glucose sensors, meter strips, ketone strips) that need replenishing to each subject Review Sensor Dislodgement Diary Distribute Urine Ketone Test strips Remind subjects to use either Humalog or Novolog insulin Remind Subjects to use the Bayer Contour Link meter for all calibrations	Adverse Event Check CareLink Upload A1C Test Case Report Forms Distribute devices and supplies that need replenishing (e.g., glucose sensors, meter strips, ketone strips) to each subject Review Sensor dislodgement Diary Distribute Urine Ketone Test strips Remind subjects to use either Humalog or Novolog insulin Remind Subjects to use the Bayer Contour Link meter for all calibrations	Adverse Event Check CareLink Upload A1C Test Case Report Forms Distribute devices and supplies that need replenishing (e.g., glucose sensors, meter strips, ketone strips) to each subject Review Sensor dislodgement Diary Distribute Urine Ketone Test strips Remind subjects to use either Humalog or Novolog insulin Remind Subjects to use the Bayer Contour Link meter for all calibrations	Adverse Event Check CareLink Upload A1C Test Case Report Forms EQ5-5DYouth questionnaire HFS Parent questionnaire HFS Child/Teen questionnaire Hypoglycemia Unawareness questionnaire Review Sensor dislodgement Diary Return of Study Devices and supplies

	Visit 1 Screening	Visit 2 90 Day A1C	Visit 3 180 Day A1C	Visit 4 270 Day A1C	Visit 5 365 Day A1C End of Study
Study Activities at Home between visits		Upload the Pump every 21 days Change Sensors as required Test urine ketones daily and enter test results into CareLink Clinical Call the study doctor and his staff if you are experiencing any medical problem either related to your diabetes or unrelated to your diabetes Call the Medtronic 24 Hr helpline if you have a device problem Fill out a Sensor Dislodgement Diary as needed	Upload the Pump every 21 days Change Sensors as required Test urine ketones daily and enter test results into CareLink Clinical Call the study doctor and his staff if you are experiencing any medical problem either related to your diabetes or unrelated to your diabetes Call the Medtronic 24 Hr helpline if you have a device problem Fill out a Sensor Dislodgement Diary as needed	Upload the Pump every 21 days Change Sensors as required Test urine ketones daily and enter test results into CareLink Clinical Call the study doctor and his staff if you are experiencing any medical problem either related to your diabetes or unrelated to your diabetes Call the Medtronic 24 Hr helpline if you have a device problem Fill out a Sensor Dislodgement Diary as needed	

10.1 Visit 1 - Day 0: Consent and Screening

General
Eligibility:
This study is open to all individuals who meet the eligibility criteria. Subjects will be considered enrolled after they have signed the Informed Consent form. The Investigational Center will be responsible for making adequate source documentation available to the sponsor to verify subject eligibility.

General
Standard Care:
It is expected that subjects will continue to undergo their routine diabetes care as per clinic standard. During routine quarterly visits data collection for the study will be obtained by the designated staff.

General
Investigational Center staff will:

- Obtain informed consent/Assent from subject/parent/caregiver
    - Subjects 7-15 years should provide assent in addition to Informed Consent from parent/caregiver
- Assess eligibility of subjects to participate in the study
- Collect demographic information and baseline characteristics, including age, gender, race, ethnicity and medical diagnosis, duration of diabetes (Screening eCRF).
- Record concomitant medications on appropriate CRF
- Obtain blood sample(s) to complete required screening A1C test, if all eligibility criteria (excluding those involving blood test results) are met: **Note: All collected blood specimens will be sent to and tested by a NGSP certified Central Laboratory. A1C testing must follow National Glycohemoglobin Standardization Program (NGSP) standards. This A1C will be used for data analysis.**
- Obtain blood samples to complete required screening tests, i.e.TSH (also T3, T4 if TSH is abnormal), Creatinine
- Perform screening labs including urine or serum pregnancy test
- Subjects may be rescreened up to a maximum of two times if they do not meet inclusion/exclusion criteria at the time of their original screening
- Register subjects in CareLink Clinical (see Investigator/Coordinator binder for details) and **upload insulin pump**
- Disburse devices and supplies (e.g., pump, transmitter, glucose sensors, Bayer meter, meter strips, ketone strips) to each study subject
- Administer the following questionnaires:
    - Hypoglycemia awareness questionnaire
        - Score of 4 or more is impaired awareness. It means that subjects with this score will be assigned to the impaired hypoglycemic awareness cohort.
        - Score of 3 or less is aware. It means that subjects with this score will be assigned to the intact hypoglycemic awareness cohort.
    - EQ-5D Youth
    - Hypoglycemia Fear Scale (HFS) – Child/Teen
    - Hypoglycemia Fear Scale (HFS) – Parent

- Tell subject/parent/caregiver that they should call site as soon as possible with any changes to their health status (adverse events)
- Schedule the next visit date and time.
- Enter eCRFs into the study database as appropriate.

Device Disbursement
Investigational Center staff will:

- Disburse devices and supplies (e.g., pump, transmitter, glucose sensors, Bayer meter, meter strips, ketone strips)

Training and Instructions
Notes:

1. **All device training for this study should be consistent with the training plan in place for patients who receive a new study pump system through commercial channels.**
    a. **Subjects should only use the Bayer meter**
2. **Training on study procedures will be performed**

Designated Training staff will:

- Train subject/parent/caregiver on the use of the Medtronic study pump.
    - Subject/parent/caregiver will be instructed to record carbohydrate intake and exercise into the insulin pump as part of the study requirements
- Train subject/parent/caregiver on how to upload the pumps as part of study requirements.
    - Uploads of all study pumps into CareLink Clinical should occur every 21 days throughout the study.
    - Subject/parent/caregiver will receive an automated reminder (e-mail, text, or voice message) twice a month to remind them to upload pumps.
    - In addition to the 21 day upload requirement, subject/parent/caregiver will be instructed to upload the pumps prior to each study visit. Investigational Center staff will again upload pump data at the time of the visit.
- Instruct subject/parent/caregiver per User Guide to calibrate the study pump at least every 12 hours after the second calibration. For best calibration results per User Guide, subject/parent/caregiver will be instructed to calibrate 3-4 times, spread throughout the day.
- Instruct subject/parent/caregiver to use the Bayer Contour Link meter for all calibrations
- Instruct subject/parent/caregiver to test blood glucose per User Guide at least 4 times per day
    - Although the pump has multiple safety alarms, it cannot notify the subject if the set is leaking or the insulin has lost its potency. It is essential, therefore, that the subject test his or her blood glucose levels at least 4 times per day. If the subject's blood glucose is out of range, he/she should check the pump and the infusion set to ensure that the necessary amount of insulin is being delivered.
- Instruct subject/parent/caregiver on the use of the Sensor dislodgement Diary
    - Subject/parent/caregiver will be instructed to record sensor dislodgement occurrences in the Sensor dislodgement Diary.
- Discuss glucose sensor wear requirement.
    - Glucose sensors should be worn throughout the course of the study
- Train subject/parent/caregiver on the use of CareLink Clinical which includes that this application should only be used to upload the study pump and not for data analysis or diabetes management.
- Instruct subject/parent/caregiver to use either Humalog or Novolog insulin

- Instruct subject/parent/caregiver to contact the Medtronic 24hr HelpLine in the event they experience problems with their study devices.
- Instruct subject/parent/caregiver to test for urine ketones daily and to record results in CareLink Clinical.
    - Urine ketone test strips will be provided by sponsor free of charge to subjects.
    - The urine ketone strips will not be tracked by sponsor.
- Instruct subject/parent/caregiver to report all adverse events as soon as possible. This would include any new medical problem or deterioration of an existing medical problem, such as sickness or glycemic problems. If necessary refer subject/parent/caregiver to the subject's own providers or an emergency facility for treatment.

10.2 Visit 2 - Day 90 (± 21 days): 90 Day A1C Test

General
Investigational Center staff will:

- Ask subject/parent/caregiver about the occurrence of adverse events
- Record adverse events on the appropriate eCRF, if subject/parent/caregiver reports health status changes that result in a new medical condition or deterioration of an existing medical condition
- Review the Sensor Dislodgement Diary
- Upload pump into CareLink Clinical.
- Sponsor will provide surveillance report on device uploads.
- Collect blood sample for A1C.
  Note: All collected blood specimens will be sent to and tested by a NGSP certified Central Laboratory. A1C testing must followNational Glycohemoglobin Standardization Program (NGSP) standards. This A1C will be used for data analysis.
- Provide subject/parent/caregiver with the opportunity to bring up study-related questions and concerns.
- Remind subject/parent/caregiver about the need to wear glucose sensors consistently.
- Remind subject/parent/caregiver to use the Bayer Contour Link meter for all calibrations
- Remind subject/parent/caregiver to use either Humalog or Novolog insulin
- Remind subject/parent/caregiver to upload the pump every 21 days
- Perform accuracy testing with study meter
- Enter eCRFs into the study database as appropriate.
- Schedule the next visit date and time. Disburse devices and supplies (e.g., glucose sensors, meter strips, ketone strips) that need replenishing
- Remind subject/parent/caregiver to record carbohydrate intake and exercise into the insulin pump as part of the study requirements.

10.3 Visit 3 - Day 180 (± 30 days): 180 Day A1C Test

General
Investigational Center staff will:

- Ask subject/parent/caregiver about the occurrence of adverse events
- Record adverse events on the appropriate eCRF, if subject/parent/caregiver reports health status changes that result in a new medical condition or deterioration of an existing medical condition.
- Review the Sensor Dislodgement Diary
- Upload pump into CareLink Clinical.
- Sponsor will provide surveillance report on device uploads.
- Collect blood sample for A1C.

Note: All collected blood specimens will be sent to and tested by a NGSP certified Central Laboratory. A1C testing must follow National Glycohemoglobin Standardization Program (NGSP) standards. This A1C will be used for data analysis.

- Provide subject/parent/caregiver with the opportunity to bring up study-related questions and concerns.
- Remind subject/parent/caregiver about the need to wear glucose sensors consistently.
- Remind subject/parent/caregiver to use the Bayer Contour Link meter for all calibrations
- Remind subject/parent/caregiver to use either Humalog or Novolog insulin
- Remind subject/parent/caregiver to upload the pump every 21 days
- Perform accuracy testing with study meter
- Enter eCRFs into the study database as appropriate.
- Schedule the next visit date and time. Disburse devices and supplies (e.g., glucose sensors, meter strips, ketone strips) that need replenishing
- Remind subject/parent/caregiver to record carbohydrate intake and exercise into the insulin pump as part of the study requirements.

10.4 Visit 4 - Day 270 (± 30 days): 270 Day A1C Test

General

Investigational Center staff will:

- Ask subject/parent/caregiver about the occurrence of adverse events
- Record adverse events on the appropriate eCRF, if subject/parent/caregiver reports health status changes that result in a new medical condition or deterioration of an existing medical condition.
- Review the Sensor Dislodgement Diary
- Upload pump into CareLink Clinical.
- Sponsor will provide surveillance report on device uploads.
- Collect blood sample for A1C.
  Note: All collected blood specimens will be sent to and tested by a NGSP certified Central Laboratory. A1C testing must follow National Glycohemoglobin Standardization Program (NGSP) standards. This A1C will be used for data analysis.
- Provide subject/parent/caregiver with the opportunity to bring up study-related questions and concerns.
- Remind subject/parent/caregiver about the need to wear glucose sensors consistently.
- Remind subject/parent/caregiver to use the Bayer Contour Link meter for all calibrations
- Remind subject/parent/caregiver to use either Humalog or Novolog insulin
- Remind subject/parent/caregiver to upload the pump every 21 days
- Perform accuracy testing with study meter
- Enter eCRFs into the study database as appropriate.
- Schedule the next visit date and time. Disburse devices and supplies (e.g., glucose sensors, meter strips, ketone strips) that need replenishing
- Remind subject/parent/caregiver to record carbohydrate intake and exercise into the insulin pump as part of the study requirements.

10.5 Visit 5 – Day 365 (+ 30 days): End of study; 365 Day A1C Test

General

Investigational Center staff will:

- Ask subject/parent/caregiver about the occurrence of adverse events

- Record adverse events on the appropriate eCRF, if subject/parent/caregiver reports health status changes that result in a new medical condition or deterioration of an existing medical condition.
- Upload pump into CareLink Clinical.
- Sponsor will provide surveillance report on device uploads.
- Collect blood sample for A1C.
  Note: All collected blood specimens will be sent to and tested by a NGSP certified Central Laboratory. A1C testing must follow National Glycohemoglobin Standardization Program (NGSP) standards. This A1C will be used for data analysis.
- Provide subject/parent/caregiver with the opportunity to bring up study-related questions and concerns.
- Administer the following questionnaires:
  - Hypoglycemia awareness questionnaire
    - Score of 4 or more is impaired awareness.
    - Score of 3 or less is aware.
  - EQ-5D Youth
  - Hypoglycemia Fear Scale (HFS) Child Teen
  - Hypoglycemia Fear Scale (HFS) Parent
- Review the Sensor Dislodgement Diary
- Enter eCRFs into the study database as appropriate
- **"Remove and return all study devices and supplies from subjects per Section 11 of the protocol."**
- Discharge subject from the study
- Return or Disposal of Study Devices

At the end of Visit 5, the investigational center is expected to accept and retain all devices as described in Table 2 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 devices, as described in table 2, will be returned by subjects to the investigational center and then to the sponsor. Devices provided to the investigational center may be returned as subjects complete the study, at the end of study 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 devices in the eCRF.

Used glucose sensors are not expected to be returned by subjects to the investigational center and therefore are not expected to be returned to the sponsor.

Other consumable devices (i.e., reservoirs, infusion sets, 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 glucose sensors, meter testing strips and supplies, reservoirs, infusion sets and adhesive overtape.

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

10.6 Minimizing subject withdrawal

It may be reasonable to expect that subjects will not consistently comply with study requirements during the study. In this study, continuous sensor wear is a key component in the collection of TS safety data. For this reason, the strategy will be to select investigational centers that have the experience and expertise to manage subjects for an extended period of time in the context of a clinical study. Furthermore, as a means of providing encouragement to study subjects, the following will be implemented:

Subjects will be provided devices and supplies (e.g., glucose sensors, meter strips, ketone strips) that need replenishing free of charge at every study visit.

10.7 Subject Withdrawal

Subject/parent/caregiver may choose to withdraw from the study at any time by notifying Investigational Center staff of their intent.

If a subject chooses to end his or her study participation or if a subject is removed from the study at the Investigator's discretion, the reason for termination must be documented both in source documents and on the appropriate eCRF.

A subject will be withdrawn from the study by the investigator if:

- In the opinion of the Investigator, the subject's health or safety would be compromised by continuing in the study
- In the opinion of the Investigator, it is in the subject's best interest to discontinue participation in the study
- During the course of the study, subject has 2 episodes of DKA (see definition in section 14.4)
- During the course of the study, subject experiences 2 episodes of severe hypoglycemia
- During the course of the study, subject begins abusing illicit drugs.
- During the course of the study subject begins abusing prescription drugs.
- During the course of the study subject begins abusing alcohol.
- During the course of the study subject begins using pramlintide (Symlin).
- During the course of the study, subject receives red blood cell transfusion or erythropoietin.
- During the course of the study, subject takes any oral, injectable, or IV steroids.

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

10.8 Study Closure

Upon completion of the study, when all subjects have completed their visit schedules, all eCRFs have been entered and all related queries have been resolved, Medtronic and/or its designees will notify the Investigational Center of its intention to close out the study and a close-out visit will be conducted. The Monitor will ensure that the Investigator's regulatory files are up-to-date and complete and that any outstanding issues from previous visits have been resolved. Other issues that will be reviewed at this visit include discussing retention of study files, possibility of Investigational Center audits, and notifying the IRB of study closure.

11. Devices and Supplies

Subjects will be given all study devices and supplies at each scheduled visit (except final study visit). Investigational sensors that are provided by the sponsor will be tracked from Sponsor to investigational center.

11.1 Investigational Devices

Investigational devices to be used in this study include:

- Minimed MM530G Pump (labeled as Medtronic MiniMed Paradigm® Insulin Pump, MMT-751); referred to as study pump in the protocol
- Medtronic CareLink® Therapy Management Software for Diabetes (MMT-7334) –referred to as CareLink Clinical in the protocol
- Medtronic MiniMed Enlite™ Glucose Sensor (MMT-7008); referred to as glucose sensor in the protocol
- Medtronic MiniMed MiniLink® 2 REAL-Time Transmitter (MMT-7713)
- Enlite™ Serter (MMT-7510)

11.2 Non-Investigational Devices

- Medtronic MiniMed charger (MMT-7705)
- Medtronic MiniMed CareLink® USB (MMT-7305)
- Test Plug (MMT-7706)
- Bayer CONTOUR™ Next Link Blood Glucose Meter.

11.3 Non-Investigational Supplies

- Urine Ketone sticks
- Infusion Sets
- IV3000 tape
- Lancet device
- Lancets
- Batteries for Meter
- Alcohol swabs
- AAA Energizer batteries

11.4 Study Materials

- User Guides for study devices
- Study instructions
- Subject Questionnaires

Study supplies must be securely stored during the study.

11.5 Device Accountability

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

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

- Center receipt and inventory management
- Storage

- Subject disbursement
- Return (by subjects and center) and/or disposal

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

Table 2: List of Study Devices

Device	Center Receipt (Packing Slip)	Disbursement to Site (eCRF)	Site Return to MDT (eCRF)	Center Return to Sponsor (eCRF, Packing Slip)
Medtronic MiniMed 530G Insulin Pump (MMT-551, MMT-751)	Yes	Yes	Yes	Yes
Medtronic MiniMed Enlite Glucose Sensor (MMT-7008)	Yes	Yes	Unused Yes	Unused Yes
Enlite Serter (MMT-7510)	Yes	Yes	Yes	Yes
Medtronic MiniMed MiniLink 2 REAL-Time Transmitter (MMT-7713)	Yes	Yes	Yes	Yes
Paradigm Remote Control/Programmer (MMT-503)	Yes	Yes	Yes	Yes
Charger (MMT-7705)	Yes	Yes	Yes	Yes
Bayer CONTOUR Next Link RF-Enabled Blood Glucose Meter (HMS 9740)	Yes	Yes	Yes	Yes
Medtronic MiniMed CareLink USB (MMT-7305)	Yes	Yes	Yes	Yes
Medtronic MiniMed Test Plug (MMT-7706)	Yes	Yes	Yes	Yes

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

Please note that study devices which were provided to subjects through commercial channels (ie. Early protocol version which allowed study devices through commercial channels) do not apply to device accountability section.

12. Quality Assurance and Control

12.1 Monitoring Plan

Monitoring will be conducted to ensure the protection and safety of human subjects, the quality and integrity of the clinical data, and compliance with the protocol. The Monitoring Plan will be updated and revised as needed due to changes in documents or processes. The review of processes and documents will be ongoing throughout the course of the study. The most recent version of the Monitoring Plan will take precedence over any previous versions.

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

Site Qualification and Initiation Visits will be completed prior to enrollment of the first subject. Interim study monitoring activities will include an inspection of completed study documents, source document verification and reporting, verification of database accuracy and completeness. All subjects enrolled in the trial will be monitored and the eCRF data verified against the subjects' source documents. Following each monitoring visit, a report will be prepared and submitted to the Sponsor. From initiation of the study to the final close out visit, the Study Monitor(s) will assume primary responsibility for communications between the Study Investigators and the Sponsor.

The Principal Investigator is responsible for ensuring that Investigational Center staff is appropriately trained to manage the protocol. Initial and ongoing Investigational Center training will be provided during the Site Initiation Visit, subsequent monitoring visits, and regular Investigational Center contact. All Investigational Center staff must complete and sign the Study Training Record(s) and maintain the record(s) in the Investigational Center regulatory binder. Prior to enrollment of the first subject, all Investigators and study coordinators who will be participating in enrollment, eCRF completion, device insertion/application, device training, and consenting subjects must complete the Sponsor-required training.

All monitoring visits and visits from the Sponsor to the Investigational Center will be recorded using the Site Visit Sign-In Log and co-signed by Investigational Center staff. The log will be kept in the Investigational Center regulatory binder and the original will collected at the end of the study and submitted to the sponsor.

12.2 Quality Audits

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

12.3 Investigational Center Disqualification

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

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

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

12.4 Protocol Deviations

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

- observation in the monitoring report
- deviation to document the event
- corrective action plan

- site disqualification
- notification to the regulatory authorities depending on the severity of the deviation

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

Compliance with Protocol:

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

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

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

(a) To the IRB/IEC for review and approval/favorable opinion;
(b) To the sponsor for agreement and, if required;
(c) To the regulatory authority(ies).

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

Emergency deviations must be reported to the sponsor and IRB within 5 days. The following examples are deviations that could impact subject safety, affect the integrity of study data and/or affect subject's willingness to participate in the study. 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 IRB
- Failure to report serious adverse event to the IRB and sponsor
- Investigational study device dispensed without obtaining informed consent

13. Device Complaints and Troubleshooting

The Medtronic 24 Hour Help Line (HL) or appropriate investigational center staff will be consulted for device troubleshooting (e.g. assistance is needed by subject to operate their device(s)). If subject/parent/caregivers call the HL, they are instructed to notify the HL operator that they are currently participating in a clinical research study. All device complaints that are reported to the HL will be documented by the HL staff.

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

All device deficiencies reported directly to the investigational center staff by a subject should either be reported to the HL by the subject or investigational center staff. A device deficiency is any communication that alleges 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.

All Device returns will follow the 24 HL procedures. To return a study device as part of a complaint the investigational center and or subject are to call the 24 HL.

Descriptive discussion of device performance issues and complaints will be performed.

It is the responsibility of the Investigator to abide by the device malfunction & complaint reporting requirements stipulated by the reviewing IRB and the sponsor.

14. Safety

14.1 Potential Risks

14.1.1 Potential side effects related to insulin pump infusion set may include

- Infection
- Skin irritation/ Redness
- Bruising
- Discomfort/ Pain
- Bleeding
- Irritation
- Rash

Investigational Centers and subjects/parents/caregivers will be instructed to follow the provided user guides for insertions and care of infusion sets. If an infusion site becomes irritated or inflamed, the infusion set should be removed and another placed in a new location.

14.1.2 Potential risks with insulin administration and pump use

Due to the use of insulin, there is a potential for adverse events related to the infusion of insulin and the potential interruptions of insulin delivery. These risks all may include:

- Hypoglycemia
- Diabetic Ketoacidosis (DKA)
- Hyperglycemia
- Severe Hypoglycemia with or without associated seizure, coma or death.

14.1.3 Potential risks with sensor use

Potential risks include the following:

- 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

14.1.4 Potential adverse events with serter use:

- Skin infection around area where serter is used

14.1.5 Potential risks specific to TS Feature:

- When TS is turned ON, the feature may not activate when the blood sugar is low.
- When TS is turned ON, the feature may falsely activate when the subject's blood sugar is not low.
- The TS feature is not intended to prevent or treat hypoglycemia.

14.1.6 Potential risks related to frequent finger stick testing

- Potential risks associated with frequent meter testing of blood glucose and ketones include discomfort and bruising at tips of fingers.

14.1.7 Potential risks related to venous blood sampling

- Potential risks associated with drawing blood include discomfort and bruising.
- Syncopal episode can occur secondary to needle insertion.

14.1.8 Potential risks and mitigations for pediatric subject population

The pediatric subject population has an increased risk for hypoglycemia, including severe hypoglycemia.

Standard mitigations in pediatric subjects include:

- Training of primary caregivers will be conducted in addition to subject training.
- Subject instruction to test BG via finger stick testing 4-6 times a day.
- Subject instruction to adhere to 100% sensor wear.
- Subject instruction to use the bolus wizard when determining meal or correction bolus.

14.2 Reporting of Adverse Events

The Medtronic Clinical Research Department, in conjunction with the Medtronic Regulatory Affairs Department, in Northridge, California will monitor and manage adverse event reporting for the study.

A complete description of the event including treatment and interventions provided by medical professionals will be included on the AE eCRF. It is expected that the investigator will provide the sponsor with the necessary medical records to support the adverse event.

Throughout the course of the study, Investigational Center staff will make all efforts to remain alert to possible reportable adverse events or untoward findings. Reports of adverse events will be requested from subjects/parents/caregivers at each visit and adverse event eCRFs will be completed as required. Investigational Center staff will assess the intensity of each adverse event and its relationship to study procedures or devices.

Adverse events that are assessed to have a relationship to a study procedure or study device will be analyzed by the Human Factors group at Medtronic Diabetes to determine whether or not there is a connection to mis-use of the device(s) or user error.

Events that are moderate and severe in intensity, all SAE, SADE and UADE that have not resolved at the time of the subject's discontinuation or completion of the study will be followed until the medical outcome is determined or until no further change in the condition is expected. All adverse events that have not resolved will have a final status of 'ongoing'.

Adverse Events reported to sponsor:

The Investigator or designee will report all adverse events to the sponsor:

- Adverse Events not related to the study device or study procedure
- Adverse Events related to the study device
- Adverse Events related to study procedures
- UADE (Unanticipated Adverse Device Effect)
- All SAE (Serious Adverse Events)
- Severe Hypoglycemia
- DKA (Diabetic Ketoacidosis)

A pre-existing medical condition will only be documented as an adverse event if the condition worsens during the course of the subject's participation in the study. Non-serious Adverse events should be entered on the appropriate Electronic Case Report Form (eCRF) within 14 days of subject report to the site. For serious adverse events, reporting is required to sponsor within 24 hours of site awareness.

14.3 Review of Severe Hypoglycemia and DKA.

Severe hypoglycemia, and DKA will be adjudicated by the Clinical events committee (CEC) comprised of external physicians. The adjudication will include device relatedness and whether the event was considered to be serious or not. The CEC may use Carelink reports, medical records and information on CRF to make determination.

14.4 Definitions

Adverse Event (AE) (ISO14155: 2011)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.
Note 1: This definition includes events related to the investigational medical device or the comparator.
Note 2: This definition includes events related to the procedures involved.
Note 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse Device Effect (ADE) (ISO 14155: 2011)
Any untoward and unintended response to a medical device.

Note 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the medical device.

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

Serious Adverse Event (SAE) (ISO 14155: 2011)
An adverse event that

(a) Led to a death

(b) Led to a serious deterioration in the health of the subject that

- resulted in life threatening illness or injury,
- resulted in a permanent impairment of a body structure or a body function
- required in-patient hospitalization* or prolongation of existing hospitalization
- resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function

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

**Inpatient Hospitalization is defined as: 24 hour acute admission to the hospital based on urgent medical need rather than elective admission.*

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

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.

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 the American Diabetes Association Workgroup on Hypoglycemia, 2005)**

"Severe Hyperglycemia" is defined as Hyperglycemia (blood glucose >300 mg/dL**)** with blood glucose ketones >0.6mmol/L or accompanied by symptoms of nausea, vomiting or abdominal pain.

"Diabetic Ketoacidosis/DKA" is defined as: Hyperglycemia (blood glucose greater than 250 mg/dL or greater than 13.9 mmol/L) with either low serum bicarbonate (less than 15 mEq/L) and/or low pH (less than or equal to 7.24) Anion gap (greater than 12) and either ketonemia or ketonuria and requiring treatment within a health-care facility. (**American Diabetes Association-Diabetes Care, Volume 27, Supplement 1, January 2004**)

14.5 Device or Procedure Relatedness:

The relatedness of the event to the study device or procedures will be determined for each adverse event. Subjects participating in this study have type 1 diabetes and it is expected that due to the disease subjects will have adverse events that are part of their disease. It is expected that the investigator will assess all events to determine if the event was related to the disease or if the event was related to the device or study procedure. An adverse event 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.

The investigator will review all elements surrounding the event to properly determine relatedness – this would include the subjects/parents/caregivers description of the event, study device downloads and medical records (if applicable) from the treating facility. These records will be made available to the

sponsor and the Clinical Events Committee at the request of the sponsor. The following definitions should be considered when determining the relationship of the event to the device or study procedure:

Definite – clearly related to the device or procedure
Probable – likely related to the device or procedure
Possible – may be related to the device or procedure
Unlikely – doubtfully related to the device or procedure
Not Related – clearly not related to the device or procedure

If the investigator determines the event meets the definition of definite, probable or possible the event should be considered related and the Yes box on the AE eCRF would be checked for the question related to. If the investigator determines the event meets the definition of unlikely, not related or unknown the event should be considered unrelated and the NO box would be checked on the AE eCRF for the question was the event related to.

14.6 Event Intensity (severity):

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*: The terms "serious" and "severe" are not synonymous. Severe is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is NOT the same as "serious" which is based on the definition of "serious criteria" which have been provided.

14.7 Clinical Events Committee

A clinical events committee consisting of external physicians with an expertise in Endocrinology and the management of Type 1 diabetes including CGM will be convened. The CEC will review all reports of:

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

The CEC will assess these events to determine agreement or disagreement with the investigator determination of the event. The investigator will be notified of any disagreement in assessment of an event by the CEC.

[redacted]

15. Administrative Considerations

15.1 Document Storage and Retention

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

15.2 Data Handling

All data required for analysis will be captured on electronic Case Report Forms (eCRFs) using Oracle Clinical's 21 CFR Part 11 compliant Remote Data Capture (RDC) module. Original eCRFs will not be used as source data and supporting documentation will be required. Electronic device data will be collected from the study pump using Medtronic CareLink Clinical, which is 21 CFR Part 11 compliant.

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 CRF completion. In the event of data discrepancies, Investigational Centers will be asked to resolve queries electronically in the RDC system; otherwise, irresolvable data-related issues will be routed to the Sponsor for review and final disposition. An audit trail is maintained in Oracle Clinical to capture any corrections or changes of the eCRFs. System backups for data stored in the Oracle Clinical system will be consistent with Medtronic standard procedures.

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

15.3 Data Preparation

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

15.4 Training of Clinical Staff

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

15.5 Study Binders

A Regulatory Binder and an Investigator/Coordinator Manual will be provided by the Sponsor to be maintained by Investigational Center staff. At a minimum, each Regulatory Binder will include:

- Study Contact Sheet
- Clinical Study Agreement(s)
- Signed/dated CV of Investigator(s)
- IRB Correspondence
- IRB-approved Protocol(s) and Informed Consent Form(s), including all amendments
- Clinical Bulletins- A brief official update or summary of current study news on a matter of immediate interest and high importance to Investigational Center surrounding the study protocol.
- Site Visit Sign-In Log
- Study Correspondence
- Site Signature and Study Delegation Log
- Training Records
- Sound Bites

At a minimum, the Investigator/Coordinator Manual will include:

- Sample Coordinator Worksheets
- User Guide(s), Instructions for Use, and/or User Manual as applicable
- Quick Reference Guide
- Training materials

15.6 Publication Policy

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

16. Sponsor Contact Information

	Sponsor
	Medtronic MiniMed, Inc. ("Medtronic") 18000 Devonshire St Northridge, CA 91325 866.948.6633

17. References

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Streja D. Can continuous glucose monitoring provide objective documentation of hypoglycemia unawareness? Endocr Pract. 2005;11(2):83-90.

Juvenile Diabetes Research Foundation, Continuous Glucose Monitoring Study Group. The Effect of Continuous Glucose Monitoring in Well-Controlled Type 1 Diabetes. Diabetes Care, Volume 32, Number 8, August 2009: 1378-1383

18. Appendices

None