Medtronic

Study Title	Post Approval Study of the TS (Threshold Suspend) Feature with a Sensor-Augmented Pump System Supplemented with Commercial Patient Data
NCT Number	NCT02003898
Document Description	Study Protocol Version E (Equivalent to FDA Approved Version Q)
Document Date	10-OCT-2017

Title:	**Post Approval Study of the TS (Threshold Suspend) Feature with a Sensor-Augmented Pump System Supplemented with Commercial Patient Data**
Protocol Number:	CEP266DOC, Version E (Equivalent to FDA Approved Version Q)
Sponsor:	Medtronic MiniMed, Inc. (“Medtronic”) 18000 Devonshire St Northridge, CA 91325 866.948.6633
Date of Protocol:	10-OCT-2017

TABLE OF CONTENTS

Synopsis

Study Design:	The evaluation of Threshold Suspend(TS) feature is conducted by two sub-studies: 1) Multi-Center Trial; 2) Commercial Data Evaluation. Multi-center trial is initiated to observe the Threshold Suspend (TS) feature with a sensor-augmented insulin pump (Medtronic MiniMed® 530G insulin pump) in patients 16 and older with insulin requiring diabetes over a period of one year. In addition, additional data from commercial use will be analyzed/summarized to support the Multi-center trial as the enrolled population is lower (N=426) than the anticipated N=1000 subjects Additional dataset: • CareLink® data from the commercial MiniMed 530G users • Summary of supplementary data on hospitalized patients using the 530G system; taken from Medical Device Reporting (MDR) • Review of published data on the TS feature • Review of unpublished data on the TS feature, as available
Devices:	***Non-Investigational Devices*** • Medtronic MiniMed® 530G (MMT-551,MMT-751) Insulin Pump, referred to as 530G Insulin Pump in the protocol. • Medtronic MiniMed MiniLink® REAL-Time Transmitter (MMT-7703), referred to as MiniLink throughout this protocol • Paradigm Remote Control/Programmer (MMT-503) - Optional • Medtronic MiniMed charger (MMT-7705) • Medtronic MiniMed CareLink® USB (MMT-7305) • Watertight Tester (MMT-7726) • One-press Serter (MMT-7512), referred to as One-press Serter in the protocol • CONTOUR® NEXT LINK RF enabled Blood Glucose Meter (HMS-9740) • Medtronic MiniMed Enlite® Glucose Sensor (MMT-7008) • Enlite Serter (MMT-7510) • CONTOUR NEXT Test Strips (HMS-7309) • MICROLET® lancing device (HMS-6606) • MICROLET lancets (HMS-6586) • CONTOUR NEXT Control Solution (HMS-7314) • Medtronic CareLink® Therapy Management Software for Diabetes (MMT-7334) – referred to as CareLink Clinical in the protocol • Medtronic CareLink® Personal Therapy Management Software for Diabetes (MMT-7333)- referred to as CareLink Personal in the protocol

Study Objective:	The study objective is to demonstrate that home use of Threshold Suspend (TS) is not associated with glycemic deterioration. This objective will be demonstrated in several ways using two sub-studies: 1) **Sub-study 1:** Multi-Center Trial • Comparison of A1C measurement from baseline to end of study in the CEP266 study population 2) **Sub-study 2:** Commercial Data Evaluation • CareLink® data from the commercial MiniMed 530G users • Summary of supplementary data on hospitalized patients using the 530G system; taken from Medical Device Reporting (MDR) • Review of published data on the TS feature • Review of unpublished data on the TS feature, as available
Primary Study Endpoint and Hypothesis for CEP 266 Study population:	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) with the CEP 266 study population.

Secondary Endpoint for CEP 266 Study population	The mean change in A1C from baseline to end of study for each individual A1C cohort
	
	• **Baseline A1C**
	  ○ A1C less than 7.0%
	  ○ A1C between 7.0% to 9.0%
	  ○ A1C greater than 9.0%

Safety Endpoints for CEP 266 study population:	***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, diabetes classification, duration of diabetes, hypoglycemia awareness, frequency and average duration of hypoglycemic event (based on two weeks prior to the adverse event) The actual 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. Please note: the planned analysis may not be adequate since we did not meet the defined minimum sample size requirement.
Descriptive Endpoints for CEP 266 study population:	***Descriptive summary statistics will be provided:*** ***A1C Change:***

	• The percentages of subjects with increased A1C and decreased A1C from baseline will be presented for each baseline A1C subgroup (less than 7%, 7% – 9% and greater than 9%) and overall. • The distribution of subjects' changes in A1C will also be summarized by histogram for each baseline A1C subgroup and overall. ***Hypo/Hyperglycemia Events and TS Metrics:*** • Hypoglycemic Event Incidence, duration and percentage of time spent (SG less than or equal to 40, 50, 60, 65 and 70 mg/dL) with and without TS ON • Hyperglycemic Event Incidence, duration and percentage of time spent (SG greater than or equal to 180, 250, 300, 350 and 400 mg/dL) with and without TS ON • Hypoglycemic duration (below TS threshold setting) within 4 – 6 hours of suspend. • The data will be summarized for each baseline A1C subgroup less than 7%, 7% – 9% and greater than 9%) and overall • The data will be summarized by Day (8:00am – 10:00pm) /Night (10:00pm – 8:00am) and TS Threshold Settings. ***Device Utilization (Detail in Section 7.1.6):*** • TS Setting ON/OFF • TS Threshold Setting • Insulin Delivery Suspend (Manual vs. TS) • Subject response to TS insulin suspension o Confirmatory SMBG compliance during TS (within 2 hours of alarm) o Time it takes to respond to TS alert by day and night o Therapeutic change in basal insulin (within 2 hours of alarm) o Frequency of infusion set changes o Frequency of Infusion Set occlusion alarms o Early infusion set change (before 3 days) ***CGM Metric:*** • CGM Adherence – average sensor wear per week • Comparison between CGM data and Glucose Meter data ***Device Performance*** • All complaints that are reported to the 24-hour HelpLine will be summarized and reported. ***Effectiveness of educational materials:*** • Subject Questionnaire at Screening • Subject Questionnaire After Training Session and Device Placement

Descriptive subgroup analysis of A1C data will be performed on the following cohorts:

- **Age Groups:**
  - Adults age 22-and older
  - Adolescents age 16-21

- **Diabetes cohort based on Ethnicity**
  - Hispanic/Latino
  - Non-Hispanic/Non-Latino
  - Subject Refused

- **Diabetes cohort based on Race**
  - American Indian/Alaska Native
  - Black/African-American
  - White - anticipated maximum less than 80%
  - Native Hawaiian/Other Pacific Islander
  - Asian
  - Other
  - Subject Refused

- **Diabetes cohorts based on BMI according to WHO criteria [World Health Organization, 2011]:**

  A description of the following 5 groups will be performed:
  - Underweight subjects (BMI less than 18.5 kg/m)
  - Normal weight subjects (BMI 18.5 to 24.99 kg/m²):
  - Overweight (BMI 25.00 to 29.99 kg/m)
  - and obese subjects (BMI 30.00 to 39.99 kg/m)
  - Morbidly obese subjects (BMI greater than or equal to 40 kg/m²)

- **Diabetes cohort based on gender**
  - Male
  - Female

- **Diabetes Classification**
  - Diabetes type 1
  - Diabetes type 2
  - Other diagnosis of Diabetes

	• **Duration of diabetes cohort**
	  ○ Duration of diabetes less than 20 years
	  ○ Duration of diabetes greater than or equal to 20 years
	
	• **Hypoglycemic awareness**
	  ○ Patients with intact hypoglycemic awareness
	  ○ Patients who have impaired hypoglycemic awareness

Number of Subjects and CEP 266 Study Population:	A total of 426 subjects have been enrolled in the study
	
	40 Investigational centers were activated across the United States. Selection was based on 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, race, body mass index (BMI), gender, diabetes classification, duration of diabetes, hypoglycemic awareness and transition group. Sponsor will oversee distribution of subjects across study sites.
	
	Summary of data will include the following baseline demographic categories:
	
	• **Baseline A1C**
	  ○ A1C less than 7.0%
	  ○ A1C between 7.0% to 9.0%
	  ○ A1C greater than 9.0%
	
	• **Age Groups**
	  ○ Adults age 22-and older
	  ○ Adolescents age 16-21
	
	• **Ethnicity**
	  ○ Hispanic/Latino
	  ○ Non-Hispanic/Non-Latino
	  ○ Subject refused
	
	• **Race**
	  ○ American Indian/Alaska Native Black/African-American
	  ○ White - anticipated maximum less than 80%
	  ○ Native Hawaiian/Other Pacific Islander
	  ○ Asian Other
	  ○ Subject refused

	• **BMI according to WHO criteria [World Health Organization, 2011]:** o Underweight subjects (BMI less than 18.5 kg/m²) o Normal weight subjects (BMI 18.5 to 24.99 kg/m²) o Overweight subjects (BMI 25.00 to 29.99 kg/m²) o Obese subjects (BMI 30.00 to 39.99 kg/m²) o Morbidly obese subjects (BMI greater than or equal to 40 kg/m²) - • **Gender** o Male o Female • **Diabetes Classification** o Diabetes type 1 o Diabetes type 2 o Other diagnosis of Diabetes • **Duration of diabetes** o Duration of diabetes less than 20 years o Duration of diabetes greater than or equal to 20 years • **Hypoglycemic awareness** o Patients with intact hypoglycemic awareness o Patients who have impaired hypoglycemic awareness • **Transition Groups** The "transition" to the 530G system is based on the first time the TS (threshold suspend) feature is turned ON, outside/excluding pump training. o Naïve: Subjects who have been exposed to the 530G pump therapy with the TS feature ON for 7 days or less prior to screening. o Non-Naïve: Subjects who have been exposed to the 530G pump therapy with the TS feature ON for 8 to 365 days prior to screening.
Inclusion Criteria for CEP 266 Study population:	1. Subject is age 16 or older at time of screening 2. Subject has been diagnosed with diabetes mellitus for at least one year prior to screening. 3. Subject is currently on pump therapy. 4. Subject is transitioning to the 530G insulin pump system with the TS feature turned ON. 5. Subject is willing to complete all study related activities 6. Subject is willing to upload data every 21 days from the study pump

	7. 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. 8. Subject is able (by insurance or financial means) to cover the initial investment and ongoing cost of the 530G insulin pump and consumables, CGM, CONTOUR NEXT LINK RF enabled meter and supplies for the length of the study- 1 year.
Exclusion Criteria for CEP 266 study population:	1. Subject is actively participating in an investigational study (drug or device) wherein he/she has received treatment from an investigational study drug or investigational study devices in the last 2 weeks. 2. Subject is a woman of child-bearing potential who has a positive pregnancy test at screening or plans 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 has sickle cell disease or hemoglobinopathy 11. Subject has received red blood cell transfusion or erythropoietin within 3 months prior to time of screening or plans to receive red blood cell transfusion or erythropoietin over the course of study participation 12. Subject diagnosed with current eating disorder such as anorexia or bulimia 13. Subject has been diagnosed with chronic kidney disease that results in chronic anemia 14. Subject is on dialysis
Visit Schedule for CEP 266 study:	The study will consist of 6 visits: Enrollment Visit 0 and Visit(s) 1-5. Enrollment Visit 0 will include obtaining the ICF and completion of the screening labs. Baseline Visit 1 (Screening) will be the visit in which subject eligibility will be assessed, and if subject meets eligibility criteria, the subject will also complete all other study related activities per Visit 1. Visits 2-5 are conducted in order to collect A1C labs and review ongoing subject safety and adherence to the protocol. At Visit 5, the subject will be exited from the study.
Commercial Data Evaluation	
Commercial Data Evaluation: Primary Safety Endpoint	The difference in self-reported first A1C and subsequent A1C collected from StartRight program. The mean difference in A1C will be estimated and compared by a non-inferiority test with 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 difference in A1C is less than 0.4%

Commercial Data Evaluation: Primary Efficacy Endpoint	Two primary efficacy endpoints are defined. The study will be considered successful if both endpoints are met. Therefore alpha is kept at a significance level of 0.025 (one sided). • The difference in percent time spent <70 mg/dL using sensor glucose values from TS feature ON and TS feature OFF. The mean change in percent time spent <70 mg/dL (TS feature ON and TS feature OFF) will be estimated and compared by a superiority test with a significance level of 0.025 (one-sided). The goal is to show superiority of the TS feature ON compared to the TS feature OFF. • The difference in percent time spent >180 mg/dL using sensor glucose values from TS feature ON and TS feature OFF. The mean change in percent time spent >180 mg/dL (TS feature ON and TS feature OFF) will be estimated and compared by a non-inferiority test with a significance level of 0.025 (one-sided) and a margin of 5%. The goal is to show non-inferiority of the TS feature ON compared to the TS feature OFF
Commercial Data Evaluation: Descriptive Endpoint	• Adverse Events collected via Outreach program. Adverse events (Hospitalized High BG and Hospitalized Low BG) collected during Outreach program will be summarized and presented. Adverse event rates in 100 patient years will also be reported. Adverse events will be further stratified by device component (pump, sensor, sensor serter, infusion set, infusion set serter, reservoir or accessories), age, gender duration of diabetes and years on insulin. • The difference in estimated A1C ((average sensor glucose + 36.9) / 28.0) from TS feature ON and TS feature OFF [Nathan D, etc. 2008]. Subgroup analysis of A1c data will be performed on demographic cohorts (age, gender, duration of diabetes and years on insulin), and first A1c (less than 7.0%, 7.0-9.0%, greater than 9.0%) • TS Feature Utilization: TS feature utilization will be calculated using the available Senosr Glucose (SG) with TS feature 'turned on', divided by the period of MiniMed 530G device use (i.e. 288 * Number of days with TDD > 0 units) * 100. • Hypoglycemic Event Incidence, duration and percentage of time spent (SG less than or equal to 50 and 70 mg/dL): with and without TS feature ON, with or without fingerstick glucose. • Hyperglycemic Event Incidence, duration and percentage of time spent (SG greater than or equal to 180, 250, 300, and 400 mg/dL) with and without TS feature ON; with fingerstick or not. • CGM Adherence – average sensor wear per week • Adverse Event Reporting • Data Completeness • Sample Size Calculation • Summary of supplementary data on hospitalized patients using the 530G system; taken from Medical Device Reporting (MDR) • Review of published data on the TS feature • Review of unpublished data on the TS feature, as available

1. Background

The approval of the MiniMed® 530G Pump model (MMT-751, MMT-551) occurred on 27th September 2013. Prior to submitting the IDE for a device that incorporates the Threshold Suspend (TS) feature in the United States, Medtronic evaluated and released the Medtronic MiniMed® Paradigm Veo pump in Europe and other part of the world. One of the first steps towards approval of a similar device in the United States was taken with the CEP 235 study. The study completed in 2011 and the study report has been submitted.

2. Devices and Supplies

2.1. Names and Intended Use of Devices

2.1.1. Medtronic MiniMed® 530G Pump (MMT-551, MMT-751) – FDA approval P120010

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. Threshold Suspend is the first feature available using Medtronic SmartGuard™ technology. SmartGuard refers to all automated insulin delivery and suspension actions by Medtronic sensor-integrated insulin pump systems.

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) – FDA approval P120010

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® REAL-Time Transmitter (MMT-7703) – FDA approval P980022/S018

The MiniLink (PMA supplement approval number is P980022/S018) is a commercial device and is a small transmitter which connects directly to the sensor and is attached to the skin with tape. It contains a rechargeable battery, sensor electronics, and a radiofrequency (RF) transmitter. Once fully charged, it offers the subject up to fourteen (14) days of power to the transmitter. The system also includes a battery charger that will recharge the device according to user guide. The estimated transmitter life is two years, and it is watertight for 8 feet up to 30 minutes. The charger is powered by a AAA battery intended to last for up to four months and is designed for easy connection and disconnection from the MiniLink transmitter. When a sensor is attached to the MiniLink, it enters an initialization period. After two hours, it begins to periodically transmit glucose data to the pump, using a radio signal.

2.1.5. Medtronic CareLink® Therapy Management Software for Diabetes (MMT-7334) – 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 . A Personal Computer (PC) is used to access CareLink Clinical via the Internet, which then allows subjects 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 CareLink® Personal Therapy Management Software for Diabetes (MMT-7333) – referred to as CareLink Personal in the protocol

Carelink Personal is an Internet based software system which allows data to be viewed and is easily evaluated by the subject and his/her physician . A Personal Computer (PC) is used to access CareLink Personal via the Internet, which then allows subjects to upload data from Medtronic MiniMed insulin pumps and a range of system-supported, third-party blood glucose meters. The data contained in CareLink

Personal is accessible to users using a standard browser, e.g., Microsoft® Internet Explorer on an Internet enabled PC.

CareLink Personal 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.

The data obtained from CareLink Personal was used for the commercial data analysis.

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

This charger will used to charge the MiniLink transmitter. The MiniLink 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, 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 will fully recharge in less than 2 hours.

2.1.8. Watertight Tester (MMT-7726) - FDA approval P120010/S026 and P980022/S119

The Watertight Tester is an accessory previously approved for use with the Guardian Link Transmitter. The Watertight Tester operates as a sensor simulator creating signal current at a level that is within the range of an in-vivo sensor during normal operation.

2.1.9. Enlite Serter (MMT-7510) – FDA approval P120010

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.

2.1.10. One-press Serter (MMT-7512) – FDA approval P120010/S070 and P150001

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

2.1.11. 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.

2.1.12. CONTOUR® NEXT LINK Blood Glucose Meter (HMS-9740) – FDA approval K110894

The 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.

2.1.13. CONTOUR NEXT Test Strips (HMS-7309) and CONTOUR NEXT Control Solution (HMS-7314)

The CONTOUR NEXT blood glucose test strips and CONTOUR NEXT Control Solutions will be used in conjunction with the CONTOUR NEXT LINK Blood Glucose Meter. These may be provided between study visits to subjects who are unable to adhere to CGM or CONTOUR NEXT LINK RF enabled meter and supply study requirements due to change in insurance coverage or financial status.

2.1.14. MICROLET® lancing device (HMS-6606) and MICROLET lancet (HMS-6586)

The MICROLET lancing device is used to puncture the skin. The MICROLET lancets are coated with silicone for easier, gentler testing by reducing the surface friction of the needle.

3. Purpose of the Study

The purpose of the study is to provide ongoing surveillance of the TS feature with a sensor augmented pump system over a 12 month period.

4. Objective and Hypothesis

4.1. Study Objective

The study objective is to demonstrate that home use of Threshold Suspend (TS) is not associated with glycemic deterioration. This objective will be demonstrated in several ways using two sub-studies:

1) Sub-study 1: Multi-Center Trial
   - Comparison of A1C measurement from baseline to end of study in the CEP266 study population

2) Sub-study 2: Commercial Data Evaluation
   - CareLink® data from the commercial MiniMed 530G users
   - Summary of supplementary data on hospitalized patients using the 530G system; taken from Medical Device Reporting (MDR)
   - Review of published data on the TS feature
   - Review of unpublished data on the TS feature, as available

5. Study Design

The evaluation of Threshold Suspend(TS) feature is conducted by two sub-studies: 1) Commercial Data Evaluation; 2) Prospective Multi-Center Trial.

5.1. Multi-Center Trial

The Multi-center trial was initiated to observe the Threshold Suspend (TS) feature with a sensor-augmented insulin pump (Medtronic MiniMed® 530G insulin pump) in patients 16 and older with insulin requiring diabetes over a period of one year.

In addition, additional data from commercial use will be analyzed/summarized to support the Multi-center trial as the enrolled population is lower (N=426) than the anticipated N=1000 subjects.

5.2. Commercial Data Evaluation

Additional dataset:

- CareLink® data from the commercial MiniMed 530G users
- Summary of supplementary data on hospitalized patients using the 530G system; taken from Medical Device Reporting (MDR)
- Review of published data on the TS feature
- Review of unpublished data on the TS feature, as available

5.2.1. CareLink® data from the commercial MiniMed 530G users

Please refer to Statistical Section 7 for analysis.

5.2.2. Summary Of Supplementary Data On Hospitalized Patients Using The 530G System; Taken From MDR

- Total number of uploaded data from pumps which also have MDR data
- Total number of hospitalizations for high blood glucose will be provided regardless of whether they were felt to be device related or not
- Summary of hospitalizations for high blood glucose which are device related will be provided including number of events and summary of causes
- Summary of hospitalizations for high blood glucose which are **NOT** device related will be provided including number of events and summary of causes

5.2.3. Review Of Published Data On The TS Feature

A review and summary of the published scientific literature on the use of TS will be provided. Inclusion of "low glucose suspend" which is another term for threshold will be included. Detailed rationale and discussion on similarities and differences of low glucose suspend with Veo insulin pump versus 530G insulin pump and TS will be provided.

a. Search date
b. Period covered by the Search (e.g. There were no date limitations applied during search)
c. Search engine utilized for medical review of literature will be provided Resources will include but not limited to:
    i. http://handbook.cochrane.org/
    ii. http://prisma-statement.org/PRISMAStatement/PRISMAStatement.aspx
    iii. http://prisma-statement.org/documents/PRISMA%202009%20flow%20diagram.pdf
d. Search medium used (e.g. online)

e. Key terms used in search engine will be provided including brand names and Model numbers (e.g. TS, low glucose suspend, 530G insulin pump)
f. Total number of articles/citations found in entire search will be provided
g. Total number of articles/citations used in summary will be provided with rationale for selection criteria used to choose articles for full review (e.g. rationale for exclusion of articles if applicable)
h. Summary of data and findings will include:
    i. Title of study
    ii. Device studied
    iii. Population studied
    iv. Number of subjects
    v. Study Design
    vi. Efficacy endpoints/results
    vii. Safety which will include but not limited to adverse events or any device performance issues noted
    viii. Reference of study
    ix. Publication type
i. Summary of this review with attention to Safety results will be provided and include a discussion on the limitations from this data. Conclusion will include risk benefit statement and justification of this statement based on these findings.

5.2.4. Review Of Un-Published Data On The TS Feature, as Available

The limitation of a review for only published data is that it excludes unpublished data which may have critical safety information. For example, there could be a selection bias to only publish data which is favorable on the use of the TS feature. Therefore, a review and summary of the unpublished data on the use of TS will also be provided if available. Inclusion of "low glucose suspend" which is another term used for TS will be performed.

a. Medtronic sponsored studies (i.e. Investigator initiated grants or health care database analyses)
b. Key terms used in search will be provided including brand names and Model numbers (e.g. TS, low glucose suspend, 530G insulin pump)
    i. Characterization of how this search was performed will be provided
    ii. Number of studies where devices using an automated TS provided by MDT as an investigator initiated grant will be summarized.
    iii. Number of studies where investigator was able to be contacted on above studies to obtain unpublished data will be provided
    iv. Number of studies where investigator was able to provided unpublished data will be provided
    v. Summary of unpublished data and findings will include:
        1. Title of study
        2. Device studied
        3. Population studied
        4. Number of subjects
        5. Study Design
        6. Efficacy endpoints/results
        7. Safety which will include but not limited to adverse events or any device performance issues noted
    vi. Summary of this review will provided if data is available and will include a discussion on the limitations from this data and attention to Safety results
c. Non-Medtronic sponsored studies
    i. Search in Clintrials.gov database for studies
    ii. Search date
    iii. Period covered by the Search (i.e.,. There were no date limitations applied during search)
    iv. Key terms used in search engine will be provided including brand names and Model numbers (i.e., TS, low glucose suspend, 530G insulin pump)

v. Characterization of how this search was performed will be provided
vi. Number of studies where devices using an automated TS will be summarized.
vii. Number of studies where investigator was able to be contacted on above studies to obtain unpublished data will be provided
viii. Number of studies where investigator was able to provided unpublished data will be provided
ix. Summary of unpublished data and findings will include:
    1. Title of study
    2. Device studied
    3. Population studied
    4. Number of subjects
    5. Study Design
    6. Efficacy endpoints/results
    7. Safety which will include but not limited to adverse events or any device performance issues noted
x. Summary of this review will provided if data is available and will include a discussion on the limitations from this data and attention to Safety results. Conclusion will include risk benefit statement and justification of this statement based on these findings.

6. Study Population of Multi-Center Trial

6.1. Number of Subjects and CEP266 Study Population

A total of 426 subjects have been enrolled in the study.

40 Investigational centers were activated across the United States. Selection was based on 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, race, ethnicity, body mass index (BMI), gender, diabetes classification, duration of diabetes, hypoglycemic awareness and transition group. Sponsor will oversee distribution of subjects across study sites.

Summary of data will include the following baseline demographic categories:

- **Baseline A1C**
    - A1C less than 7.0%
    - A1C between 7.0% to 9.0%
    - A1C greater than 9.0%
- **Age Groups**
    - Adults age 22-and older
    - Adolescents age 16-21
- **Ethnicity**
    - Hispanic/Latino
    - Non-Hispanic/Non-Latino
    - Subject refused
- **Race**
    - American Indian/Alaska Native
    - Black/African-American

- White - anticipated maximum less than 80%
- Native Hawaiian/Other Pacific Islander
- Asian
- Other
- Subject refused

- **BMI according to WHO criteria [World Health Organization, 2011]:**
  - Underweight subjects (BMI less than 18.5 kg/m²)
  - Normal weight subjects (BMI 18.5 to 24.99 kg/m²)
  - Overweight subjects (BMI 25.00 to 29.99 kg/m²)
  - Obese subjects (BMI 30.00 to 39.99 kg/m²)
  - Morbidly obese subjects (BMI greater than or equal to 40 kg/m²)
- **Gender**
  - Male
  - Female
- **Diabetes Classification**
  - Diabetes type 1
  - Diabetes type 2
  - Other diagnosis of Diabetes
- **Duration of diabetes**
  - Duration of diabetes less than 20 years
  - Duration of diabetes greater than or equal to 20 years
- **Hypoglycemic awareness**
  - Patients with intact hypoglycemic awareness
  - Patients who have impaired hypoglycemic awareness
- **Transition Groups**

  The "transition" to the 530G system is based on the first time the TS (threshold suspend) feature is turned ON, outside/excluding pump training.

  - Naïve: Subjects who have been exposed to the 530G pump therapy with the TS feature ON for 7 days or less prior to screening.
  - Non-Naïve: Subjects who have been exposed to the 530G pump therapy with the TS feature ON for 8 to 365 days prior to screening.

6.2. Study Schedule / Duration

Each subject's participation in the study will be comprised of 6 scheduled office visits over approximately 12 months. The entire study is expected to be completed within approximately 60 months from approval of the study protocol and the study device.

6.3. Inclusion Criteria for CEP 266 Study population

1. Subject is age 16 or older at time of screening
2. Subject has been diagnosed with diabetes mellitus for at least one year prior to screening.
3. Subject is currentlyon pump therapy.
4. Subject is transitioning to the 530G insulin pump system with the TS feature turned ON.
5. Subject is willing to complete all study related activities
6. Subject is willing to upload data every 21 days from the study pump
7. 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.
8. Subject is able (by insurance or financial means) to cover the initial investment and ongoing cost of the 530G insulin pump and consumables, CGM, CONTOUR NEXT LINK RF enabled meter and supplies for the length of the study- 1 year.

6.4. Exclusion Criteria for CEP 266 Study population

1. Subject is actively participating in an investigational study (drug or device) wherein he/she has received treatment from an investigational study drug or investigational study devices in the last 2 weeks.
2. Subject is a woman of child-bearing potential who has a positive pregnancy test at screening or plans 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 has sickle cell disease or hemoglobinopathy
11. Subject has received red blood cell transfusion or erythropoietin within 3 months prior to time of screening or plans to receive red blood cell transfusion or erythropoietin over the course of study participation
12. Subject diagnosed with current eating disorder such as anorexia or bulimia
13. Subject has been diagnosed with chronic kidney disease that results in chronic anemia
14. Subject is on dialysis

7. Statistical Methods and Data Analysis

7.1. Multi-Center Trial

7.1.1. Sample Size Calculation

7.1.1.1. 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) with the CEP 266 study population. 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: $\mu \geq 0.4\%$

Ha: $\mu < 0.4\%$

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.

7.1.1.2. Sample size for Adverse Event

Based on previous STAR3 IDE study (G060159), the serious adverse event rate for DKA and severe hypoglycemia was 14.79% (1.27% for DKA and 13.52% for severe hypoglycemia). Assuming a one year serious adverse event rate for DKA and severe hypoglycemia of 14.5%, a sample size of 480 would produce a one-sided 95% upper confidence limit around 17.5%.The actual one-sided 95% upper confidence limit for DKA incidence rate and severe hypoglycemia incidence rate will also be report separately.

7.1.2. Study Populations

7.1.2.1. Intention to Treat (ITT) Population

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

7.1.2.2. Completed Case (CC) Populatio

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

7.1.2.3. Efficacy Population

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

7.1.2.4. Safety Population

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

7.1.3. Analysis of Primary Endpoint for CEP 266 Study Population

7.1.3.1. Primary Efficacy Analysis

A mixed effects model will 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 with the CEP 266 study population. 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.

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

where

$Y_{ij} = (Y_{ij1}, \ldots, Y_{ij5})'$ is the A1C measurement vector for the jth subject in the ith site;

$$= \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 0 & 1 \end{pmatrix}$$ 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;

$B_i = (b_i, \ldots b_i)'$ is the random effect vector for the ith site;

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

$\varepsilon_{ij} = (\varepsilon_{ij1}, \ldots, \varepsilon_{ij5})'$ 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."

7.1.3.2. **Sensitivity Analysis**

Sensitivity analysis will be performed on the ITT population with multiple imputations. The missing data in A1C measurements will be handled by the multiple imputation approach using imputation regression method, where the independent variables in the regression model are age, gender, baseline A1C and BMI. In each imputed dataset, the missing A1C data will be imputed by $\hat{y} + z\hat{\sigma}$, where $\hat{y}$ is the predicted value from regression, z is a standard normal random variable, $\hat{\sigma}$ is the estimated standard deviation of the random residual from the regression model. The imputation

will be performed five times using the MI procedure and the analysis results will be combined to form one inference using the MIANALYZE procedure in SAS 9.3.

7.1.3.3. Descriptive Statistics

The primary endpoint will also be summarized (descriptive statistics) and stratified by:

- Investigational Site
- Age
  - Adults age 22 and older
  - Adolescents age 16-21
- Ethnicity
  - Hispanic/Latino
  - Non-Hispanic/Non-Latino
  - Subject refused
- Race
  - American Indian/Alaska Native
  - Black/African-American
  - White - anticipated maximum less than 80%
  - Native Hawaiian/Other Pacific Islander
  - Asian
  - Other
  - Subject refused
- Baseline BMI according to WHO criteria [World Health Organization, 2011]
  - Underweight subjects (BMI less than 18.5 kg/m
  - Normal weight subjects (BMI 18.5 to 24.99 kg/m²):
  - Overweight subjects (BMI 25.00 to 29.99 kg/m)
  - Obese subjects (BMI 30.00 to 39.99 kg/m)
  - Morbidly obese subjects (BMI greater than or equal to 40 kg/m²)
- Gender
  - Male
  - Female
- Diabetes Classification
  - Diabetes type 1
  - Diabetes type 2
  - Other diagnosis of Diabetes
- Duration of Diabetes
  - Duration of diabetes less than 20 years
  - Duration of diabetes greater than or equal to 20 years
- Hypoglycemic Unawareness Questionnaire
  - Patients with intact hypoglycemic awareness (95% confidence interval will be provided)

- Patients who have impaired hypoglycemic awareness (95% confidence interval will be provided)

- Transition Groups
  - Subjects who have been exposed to the 530G pump therapy with the TS feature ON for 7 days or less prior to screening
  - Subjects who have been exposed to the 530G pump therapy with the TS feature ON for 8 to 365 days prior to screening

7.1.4. Safety Analysis for Multi-Center Trial

All adverse events reported by the site per protocol 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 to be collected include the following:

- Adverse Events related to the study device
- Adverse Events related to study procedures
- 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
  - Adults age 22 and older
  - Adolescents age 16-21
- Ethnicity
  - Hispanic/Latino
  - Non-Hispanic/Non-Latino
  - Subject refused
- Race
  - American Indian/Alaska Native
  - Black/African-American
  - White - anticipated maximum less than 80%
  - Native Hawaiian/Other Pacific Islander)
  - Asian
  - Other

- Subject Refused

- Baseline BMI according to WHO criteria [World Health Organization, 2011]
  - Underweight subjects (BMI less than 18.5 kg/m)
  - Normal weight subjects (BMI 18.5 to 24.99 kg/m²)
  - Overweight subjects (BMI 25.00 to 29.99 kg/m)
  - Obese subjects (BMI 30.00 to 39.99 kg/m)
  - Morbidly obese subjects (BMI greater than or equal to 40 kg/m²)
- Gender
  - Male
  - Female
- Diabetes Classification
  - Diabetes type 1
  - Diabetes type 2
  - Other diagnosis of Diabetes
- Duration of Diabetes
  - Duration of diabetes less than 20 years
  - Duration of diabetes greater than or equal to 20 years
- Hypoglycemic Unawareness 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 actual 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. Please note: the planned analysis may not be adequate since we did not meet the defined minimum sample size requirement.

7.1.5. Secondary Endpoint for Multi-Center Trial

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%

7.1.6. Descriptive Endpoints for Multi-Center Trial

Descriptive Summary Statistics will be provided.

A1C Change:

- The percentages of subjects with increased A1C and decreased A1C from baseline will be presented for each baseline A1C subgroup (less than 7%, 7% – 9% and greater than 9%) and overall.
- The distribution of subjects' changes in A1C will also be summarized by histogram for each baseline A1C subgroup and overall.

TS Metrics – Hypoglycemia Endpoints:

Hypoglycemic Event Incidence, where an event is identified by the following criteria within 4 hours that TS is activated:

- CGM value less than or equal to 70 mg/dL continuously for greater than 20 minutes
- The rate of change (defined by the change between two consecutive sensor glucose measurements) will be examined during the 10 minute time interval before reaching a sensor glucose value of less than or equal to 70 mg/dL. If any rate of change in sensor glucose is >5 mg/dl/minute, the event will not be counted
- When the time between two successive events is less than 30 minutes, they will be combined as one event

The above information will be repeated for hypoglycemia threshold at 40, 50, 60, 65 and 70 mg/dL with and without TS activation and will be summarized by Day (8:00am – 10:00pm) /Night (10:00pm – 8:00am) and TS Threshold Settings.

The hypoglycemic event incidence, duration and the percentage of time spent (below TS threshold setting) within 4-6 hours of suspend will also be summarized. The hypoglycemic event is identified as:

- CGM value below the TS threshold continuously for at least 20 minutes
- No evidence of patient intervention which includes meter BG, meal marker and insulin delivery change during the first 20 minutes when CGM value is below the TS threshold.
- When the time between two successive events is less than 30 minutes, they will be combined as one event

Data will be summarized for each baseline A1C subgroup (less than 7%, 7%-9% and greater than 9%) and overall.

TS Metrics – Hyperglycemia Endpoints:

Hyperglycemic Event Incidence, where an event is identified by the following criteria within 4 hours that TS is activated:

- CGM value greater than or equal to 180 mg/dL continuously for greater than 20 minutes.
- The rate of change (defined by the change between two consecutive sensor glucose measurements) will be examined during the 10 minute time interval before reaching a sensor glucose value of greater than or equal to 180 mg/dL. If any rate of change in sensor glucose is >5 mg/dl/minute, the event will not be counted
- When the time between two successive events is less than 30 minutes, they will be combined as one event

The above information will be repeated for hyperglycemia threshold at 180, 250, 300, 350 and 400 mg/dL with and without TS activation and will be summarized by Day (8:00am – 10:00pm) /Night (10:00pm – 8:00am) and TS Threshold Settings. The hypoglycemic event incidence, duration and the percentage of

time spent (below TS threshold setting) within 4-6 hours of suspend will also be summarized. The data will be summarized for each baseline A1C subgroup (less than 7%, 7%-9% and greater than 9%) and overall.

Device Utilization:

- We will provide descriptive summary statistics of suspend event including frequency, mean change of SG values before and after the suspense.
- TS Setting ON/OFF
- TS Threshold Setting
- Number of occurrences and time of Insulin Delivery Suspension by TS suspension/manual suspension (unrelated to the threshold suspend feature)
    - Manual suspension
    - Temporary basal set to zero
    - Threshold Suspend without user acknowledgement
    - Threshold Suspend acknowledged by user and cancelled
    - Threshold Suspend acknowledged by user and confirmed
    - Threshold Suspend first acknowledged by subject and confirmed, the followed by a second Threshold suspend not acknowledged by the subject after the hypoglycemia repeat time has elapsed.
- Subject response to insulin suspension
    - Confirmatory SMBG compliance during TS (within 2 hours of alarm) by length of time after the alarm (every 30 min up to 4 hours from TS activation)
    - Length of time to acknowledge TS alert by day and night
    - Comparison of time of alarm, time to SMBG and effects on glycemia
- Therapeutic change in basal insulin (within 2 hours of alarm)
    - Frequency of basal increase/decrease/no change;
    - Summary statistics of amount of basal increase/decrease
- Frequency of Sensor Dislodgement / Suspected Occlusion
- Early infusion set change (before 3 days)
- Frequency of infusion set changes
- Frequency of Infusion Set occlusion alarms
- Total suspend time including manual suspends, times when the subject sets a temporary basal rate of zero, and threshold suspends separately and together during the nighttime, daytime, and 24 hour periods.
- Frequency of repeated threshold suspends with 1) ≤15 minutes and 2) ≤60 minutes of basal insulin delivery between suspends.
- Repeated threshold suspends with total suspend durations of ≤1 hour, 1-≤2 hours, 2-≤4 hours, 4-≤6 hours, etc. Please calculate “total suspend durations” as the sum of the durations of repeated suspensions with 1) ≤15 and 2) ≤ 60 minutes between suspends (intervening basal delivery time should not be included).

CGM Metric*:*

- CGM Adherence – average sensor wear per week
- Comparison between CGM data and Glucose Meter data

Device Performance

- All complaints that are reported via the 24-hour HelpLine will be summarized and reported.

Effectiveness of educational materials

- Subject Questionnaire at Screening
- Subject Questionnaire After Training Session and Device Placement

Human Factors:

- Frequency of subject acknowledging the alarm and continuing the suspend, when the suspend occurred automatically (without subject interaction)
- Frequency of subject not continuing the Threshold Suspend and instead manually suspending insulin delivery or setting a temporary basal rate of zero

Questionnaires:

The following will be performed on each questionnaire:

1) EQ-5D and EQ-5D-Y
    - Summary of changes in score from baseline to end of study will be performed.
2) Low Blood Sugar Survey (Adult, Parent and Child)
    - Summary of changes in score from baseline to end of study will be performed.
3) Subject Questionnaire at Screening and Subject Questionnaire after Training Session and Device Placement (training evaluation questionnaire)
    - Summary of answers that will be provided no more than 2 hours before and 2 hours after placement of 530 G pump in order to assess effectiveness of training materials.
4) Hypoglycemia Unawareness Questionnaire
    - Summary of changes in score from baseline to end of study will be performed.

7.2. Commercial Data Evaluation: Carelink Database Analysis

Analysis from the Carelink database with patients on the MiniMed 530G system intends to provide a large heterogeneous source of data taken from the actual commercial use with MiniMed 530G. The focus of this analysis is to provide a robust data set on the safety of this system. To this end, our analysis will not only provide a summary of glucose control and correlation with the use of the Threshold Suspend (TS) feature but will provide a focused analysis on key aspects of the MiniMed 530G system as it relates to the safety of the system.

Datasets will come from MiniMed 530G patients and insulin pumps sold and uploaded within date windows.

7.2.1. Primary Safety Endpoint

The difference in self-reported first A1C and subsequent A1C collected from StartRight program. The mean difference in A1C will be estimated and compared by a non-inferiority test with a significance level of 0.025 (one-sided).

The overall difference in A1C 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 difference in A1C is less than 0.4%

The hypothesis is mathematically expressed as:

Ho: $\mu \geq 0.4\%$

Ha: $\mu < 0.4\%$

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

Primary safety endpoint will be presented and tested using pair t-test on those subjects with both first and subsequent A1c.

Descriptive subgroup analysis of A1c data will be performed on demographic cohorts (age, gender, duration of diabetes and years on insulin), and first A1c (less than 7.0%, 7.0-9.0%, greater than 9.0%)

This analysis addresses the primary and secondary safety endpoint per conditions of approval in FDA 530G approval letter

7.2.2. Primary Efficacy Endpoint

Two primary efficacy endpoints are defined below (see sections 7.2.2.1 and 7.2.2.2). The study will be considered successful if both endpoints are met. Therefore alpha is kept at a significance level of 0.025 (one sided).

Primary efficacy endpoint will be presented and tested using pair t-test on those subjects with both TS feature ON and TS feature OFF within date windows.

7.2.2.1. Co-Primary Efficacy Endpoint:

The difference in percent time spent <70 mg/dL using sensor glucose values from TS feature ON and TS feature OFF. The mean change in percent time spent <70 mg/dL (TS feature ON and TS feature OFF) will be estimated and compared by a superiority test with a significance level of 0.025 (one-sided). The goal is to show superiority of the TS feature ON compared to the TS feature OFF.

The hypothesis is mathematically expressed as:

$H0: \mu_{\text{TS Feature ON}} \geq \mu_{\text{TS Feature OFF}}$

$Ha: \mu_{\text{TS Feature ON}} < \mu_{\text{TS Feature OFF}}$

where μ (TS feature ON) is the subject mean of percent time with SG below 70 mg/dL during TS feature ON, μ (TS feature OFF) is the subject mean of percent time with SG below 70 mg/dL during TS feature OFF.

7.2.2.2. Co-Primary Efficacy Endpoint:

The difference in percent time spent >180 mg/dL using sensor glucose values from TS feature ON and TS feature OFF. The mean change in percent time spent >180 mg/dL (TS feature ON and TS feature OFF) will be estimated and compared by a non-inferiority test with a significance level of 0.025 (one-sided) and a margin of 5%. The goal is to show non-inferiority of the TS feature ON compared to the TS feature OFF.

The hypothesis is mathematically expressed as:

H0: $\mu_{TS\ Feature\ ON} \geq \mu_{TS\ Feature\ OFF} + 5\%$

Ha: $\mu_{TS\ Feature\ ON} < \mu_{TS\ Feature\ OFF} + 5\%$

where μ (TS feature ON) is the subject mean of percent time with SG > 180 mg/dL during TS feature ON, μ (TS feature OFF) is the subject mean of percent time with SG > 180 mg/dL during TS feature OFF.

7.2.3. Descriptive Endpoint

- Adverse Events collected via Outreach program. Adverse events (Hospitalized High BG and Hospitalized Low BG) collected during Outreach program will be summarized and presented. Adverse event rates in 100 patient years will also be reported. Adverse events will be further stratified by device component (pump, sensor, sensor serter, infusion set, infusion set serter, reservoir or accessories), age, gender duration of diabetes and years on insulin.

- The difference in estimated A1C ((average sensor glucose + 36.9) / 28.0) from TS feature ON and TS feature OFF [Nathan D, etc. 2008]. Subgroup analysis of A1c data will be performed on demographic cohorts (age, gender, duration of diabetes and years on insulin), and first A1c (less than 7.0%, 7.0-9.0%, greater than 9.0%). This analysis addresses the primary and secondary safety endpoint per conditions of approval in FDA 530G approval letter

- TS Feature Utilization: TS feature utilization will be calculated using the available SG with TS feature 'turned on', divided by the period of MiniMed 530G device use (i.e. 288 * Number of days with TDD > 0 units) * 100.

Validation of correct TS feature activation (i.e., insulin suspension) with fingerstick when available will be provided including:

1. Total number of insulin suspensions from TS feature activations
2. Total number of insulin suspensions which were accompanied by fingerstick glucose. (fingerstick glucose needs to be within 30 minutes from the Threshold Suspend activation or while the TS is active)
3. Total number of insulin suspensions with fingerstick glucose, categorized by three groups: 1) within ±20%, 2) above 20% and 3) below 20% from the sensor glucose value. If SMBG is less than 75 mg/dl, 15 mg/dl will be used to determine which group it belongs to.

- Hypoglycemic Event Incidence, duration and percentage of time spent (SG less than or equal to 50 and 70 mg/dL): with and without TS feature ON, with or without fingerstick glucose. A hypoglycemic event is defined by SG less than the defined threshold for at least 20 minutes. Validation of CGM with fingerstick when available will be provided including:

1. Total number of hypoglycemic events
2. Total number of hypoglycemic events that were accompanied by fingerstick glucose (fingerstick glucose needs to be within 30 minutes from the Threshold Suspend activation or while the TS is active)
3. Total number of hypoglycemic event with fingerstick glucose, categorized by three groups: 1) within ±20%, 2) above 20% and 3) below 20% from the sensor glucose value. If SMBG is less

than 75 mg/dl, 15 mg/dl will be used to determine which group it belongs to.

- Hyperglycemic Event Incidence, duration and percentage of time spent (SG greater than or equal to 180, 250, 300, and 400 mg/dL) with and without TS feature ON; with fingerstick or not. A hyperglycemic event is defined by SG greater than the defined threshold for at least 20 minutes. Provision of fingerstick data when available will provide a separate and important reference to CGM data. Validation of CGM with fingerstick when available will be provided including:

  1. Total number of hyperglycemic events
  2. Total number of hyperglycemic events that were accompanied by fingerstick glucose (fingerstick glucose needs to be within 30 minutes from the Threshold Suspend activation or while the TS is active)
  3. Total number of hyperglycemic event with fingerstick glucose, categorized by three groups: 1) within ±20%, 2) above 20% and 3) below 20% from the sensor glucose value. If SMBG is less than 75 mg/dl, 15 mg/dl will be used to determine which group it belongs to.

- Characteristics of patient behavior for each cohort (e.g. Cohort 1-5 below) will be provided. The provision of this data will help to better understand the profile of patients using this device.

Cohort Description:
- Cohort 1: 0-24% TS feature utilization
- Cohort 2: 25-49% TS feature utilization
- Cohort 3: 50-74% TS feature utilization
- Cohort 4: 75-100% TS feature utilization
- Cohort 5: Data from all 530G uploads regardless of TS feature utilization

7.2.3.1. CGM Adherence – average sensor wear per week

Logic used: sensor utilization will be calculated using the available SG, divided by the period of 530G device use (i.e. 288 * Number of days with TDD > 0 units) * 100

In studies such as the JDRF1, higher utilization was associated with improved glucose control. Compliance to sensor wear or fingerstick testing gives insight into the type of patient using the system. However this assessment is limited by the fact that patient may not be wearing a sensor because they have a change in insurance or financial status that does not allow them to wear sensor.

CGM adherence will be stratified by

- Age:
  - Adults age 22-and older
  - Adolescents age 16-21
- Gender
  - Male
  - Female
- Years on Insulin
  - Years on Insulin less than 20 years
  - Years on Insulin greater than or equal to 20 years
- Age at diabetes onset or Duration of Diabetes:
  - Duration of diabetes less than 20 years

- Duration of diabetes greater than or equal to 20 years

- Baseline A1c
  - < 7%
  - 7-9%
  - >9%

7.2.3.2. Fingerstick monitoring

In the DCCT2,3 the higher amount of times the patient checked their glucose was correlated with overall glucose control. For example, if the patient checked glucose more frequently they had better glucose control. Compliance to sensor wear or fingerstick testing gives insight into the type of patient using the system. However this assessment is limited by the fact that a patient may not be checking their glucose because their insurance limits the amount of fingerstick glucose strips or their copays have increased.

Logic used: Fingerstick utilization will be calculated using the number of available SMBGs, divided by the period of 530G device use (i.e. Number of days with TDD > 0 units) * 100

7.2.3.3. Infusion set changes – how often

Compliance to infusion set changes gives insight into the type of patient using the system. However, this assessment is limited by the patient's ability to pay (copay) for their infusion sets and extends the wear of the infusion set.

Logic used: Infusion set utilization will be calculated using the average days between available infusion set change surrogate (i.e., rewind event to rewind event).

7.2.4. Adverse Event Reporting

Adverse events (Hospitalized High BG and Hospitalized Low BG) collected during Outreach program will be summarized and presented. Adverse event rates in 100 patient years will also be reported.

Adverse events will be further stratified by device component (pump, sensor, sensor serter, infusion set, infusion set serter, reservoir or accessories), age, gender duration of diabetes and years on insulin.

7.2.5. Data Completeness

Missing demographic measures (Age, gender, Age at Diabetes Onset, Years on Insulin and baseline A1C at entry) for Carelink dataset will be summarized and presented.

7.2.6. Sample Size Calculation

7.2.6.1. Sample Size for Primary Safety Endpoint

The difference in self-reported first A1C and subsequent A1C collected from StartRight program. The mean difference in A1C will be estimated and compared by a non-inferiority test with a significance level of 0.025 (one-sided).

The overall 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). The null hypothesis will be rejected if the one-sided 97.5% upper confidence limit of the mean difference in A1C is less than 0.4%

The hypothesis is mathematically expressed as:

Ho: $\mu \geq 0.4\%$

Ha: $\mu < 0.4\%$

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

Assuming the mean different in A1C from baseline to subsequent is zero, the standard deviation of change in A1C is 1%, SAS power and sample size calculator shows that a total of 200 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.

7.2.6.2. Sample Size for Co-Primary Efficacy Endpoint

The difference in percent time spent <70 mg/dL using sensor glucose values from TS feature ON and TS feature OFF. The mean difference in percent time spent <70 mg/dL (TS feature ON and TS feature OFF) will be estimated and compared by a superiority test with a significance level of 0.025 (one-sided). The goal is to show superiority of the TS feature ON compared to the TS feature OFF.

The hypothesis is mathematically expressed as:

H0: $\mu_{\text{TS Feature ON}} \geq \mu_{\text{TS Feature OFF}}$

Ha: $\mu_{\text{TS Feature ON}} < \mu_{\text{TS Feature OFF}}$

Sample size estimates for time in hypoglycemic range is based on paired t test with a one-sided type I error rate of 2.5%. Assume in TS feature ON, the mean is 5% with standard deviation of 4%, In TS feature OFF, mean is 9% with standard deviation of 6%, SAS power and sample size calculator shows that a total of 200 subjects will provide over 90% power to detect the superiority of TS feature ON compared to TS feature OFF.

7.2.6.3. Sample Size for Co-Primary Efficacy Endpoint

The difference in percent time spent >180 mg/dL using sensor glucose values from TS feature ON and TS feature OFF. The mean difference in percent time spent >180 mg/dL (TS feature ON and TS feature OFF) will be estimated and compared by a non-inferiority test with a significance level of 0.025 (one-sided) and a margin of 5%. The goal is to show non-inferiority of the TS feature ON compared to the TS feature OFF.

The hypothesis is mathematically expressed as:

H0: $\mu_{\text{TS Feature ON}} \geq \mu_{\text{TS Feature OFF}} + 5\%$

Ha: $\mu_{\text{TS Feature ON}} < \mu_{\text{TS Feature OFF}} + 5\%$

Sample size estimates for time in hyperglycemic range is based on paired t test with a one-sided type I error rate of 2.5%. Assume in TS feature ON, the mean is 21% with standard deviation of 9%, In TS feature OFF, mean is 25% with standard deviation of 10%, SAS power and sample size calculator shows that a total of 200 subjects will provide over 90% power to detect the non-inferiority of TS feature ON compared to TS feature OFF, with a margin of 5%.

7.3. FDA Reporting

An interim report will be submitted to the FDA at 4 month intervals during the first year of the study. During the second year, the reporting frequency will be reduced to 6 month intervals, i.e. semi-annually. For subsequent years, reports will be submitted annually. No hypothesis test will be included in the interim reports.

8. 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.

9. Subject Confidentiality

9.1. 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.

9.2. 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 Enrollment Visit 0, 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 (266), 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 266001001 translates into: Study number (266), 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.

9.3. 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 will be offered the opportunity to review these documents away from the Investigational Center. Pediatric subjects 16-17 years of age must 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.

10. Investigator Responsibilities

This study will be conducted at up to 50 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 Subpart E and in the FDA guidance document dated October, 2009 (see Regulatory Binder).

11. Study Visit Windows

Table 1: Visit Activity Schedule

Study Activities	**Enrollment Visit 0**	**Baseline Visit 1- Screening** (Day 0) Up to 90 days from Enrollment Visit 0	**Visit 2** (Day 90 ±30 days)	**Visit 3** (Day 180 ±30 days)	**Visit 4** (Day 270 ±30 days)	**Visit 5** (Day 365 +30 days)
Informed Consent/Assent Process	X					
Screening Labs[1]	X					
Adverse Events Training	X					
Subject Demography		X				
Assess Labs for Eligibility[2]		X				
Assess Inclusion/Exclusion Criteria		X				
Confirm/Arrange for Subject Device Training		X				
Remind Subject to Bring 530G Pump to Visit		X	X	X	X	X
Collect all Medications		X				
Subject Questionnaire at Screening		X				
Subject Questionnaire after Training Session		X				
Hypoglycemia Unawareness Questionnaire		X				X
EQ-5Dand EQ-5D-Y		X				X
Low Blood Sugar Survey (Adult/Parent/Child)		X				X
Record device information on the Site Device Accountability		X	X	X	X	X
Distribute Sensor Dislodgement/Suspected Infusion Set Occlusion (without Occlusion Alarm) Subject Log	X[3]	X	X	X	X	
Distribute Wallet Card	X[3]	X				
Distribute EZ Reference Guide		X				

Study Activities	Enrollment Visit 0	Baseline Visit 1- Screening (Day 0) Up to 90 days from Enrollment Visit 0	Visit 2 (Day 90 ±30 days)	Visit 3 (Day 180 ±30 days)	Visit 4 (Day 270 ±30 days)	Visit 5 (Day 365 +30 days)
Distribute Telephone Service Instructions		X				
Distribute CareLink Clinical Subject Instructions		X				
A1C Labs		X	X	X	X	X
Upload Insulin Pump into CareLink Clinical		X	X	X	X	X
Distribute 1 Sensor		X	X	X	X	
Distibute urine ketone strips		X				
CareLink Clinical Registration and Training		X				
HelpLine Training/Discussion	X[3]	X	X	X	X	
Review HelpLine Report	X[3]	X	X	X	X	X
Adverse Event Review/Inquiry		X	X	X	X	X
Record Adverse Events	X	X	X	X	X	
Sensor Dislodgement Review		X[3]	X	X	X	X
Case Report Form Completion	X	X	X	X	X	X
Schedule Next Visit	X	X	X	X	X	
Notify Sponsor of Subject Device Assistance[4]		X[5]	X[5]	X[5]	X[5]	
Discharge Subject						X

[1] Screening labs include: Creatinine, TSH, Free T3, Free T4, Pregnancy test (urine/serum)

[2] Assessment of the labs will be reviewed prior to Baseline Visit 1 (Screening). If subject does not meet lab screening assessments, they do not need to meet inclusion/exclusion criteria and should be exited from the trial.

[3] These activities will only be performed at this visit if the subject is a Non-Naïve subject (already using the 530G pump with TS feature turned on).

[4] If, after the Baseline Visit 1 (Screening) , a subject is no longer able to afford the study related supplies, the site staff will communicate this to the sponsor. At this point, the sponsor will be able to supply the necessary study related supplies to the subject for the length of the need but no longer than the subjects study participation.

[5] The site is only required to notify the sponsor once per subject but this can be completed at any point in which the need becomes necessary.

Table 2: Milestone Table

Major Milestone	Estimated time required to achieve milestone (from study protocol approval and device launch)
Protocol Approval	**September 26, 2013**
First site activated	**30 days**
First subject completed	**13 months**
Last site activated	**24 months**
Last subject enrolled	**48 months**
Last subject completed	**60 months**
Last site closed	**62 months**
Final report submitted	**3 months after Last Subject Completion Date**

The above table lists the major milestones that are expected to be met for this study. Actual start and completion dates for the study are based on study approval date as well as commercial availability of the study device.

Chart 1: Actual Site Activation

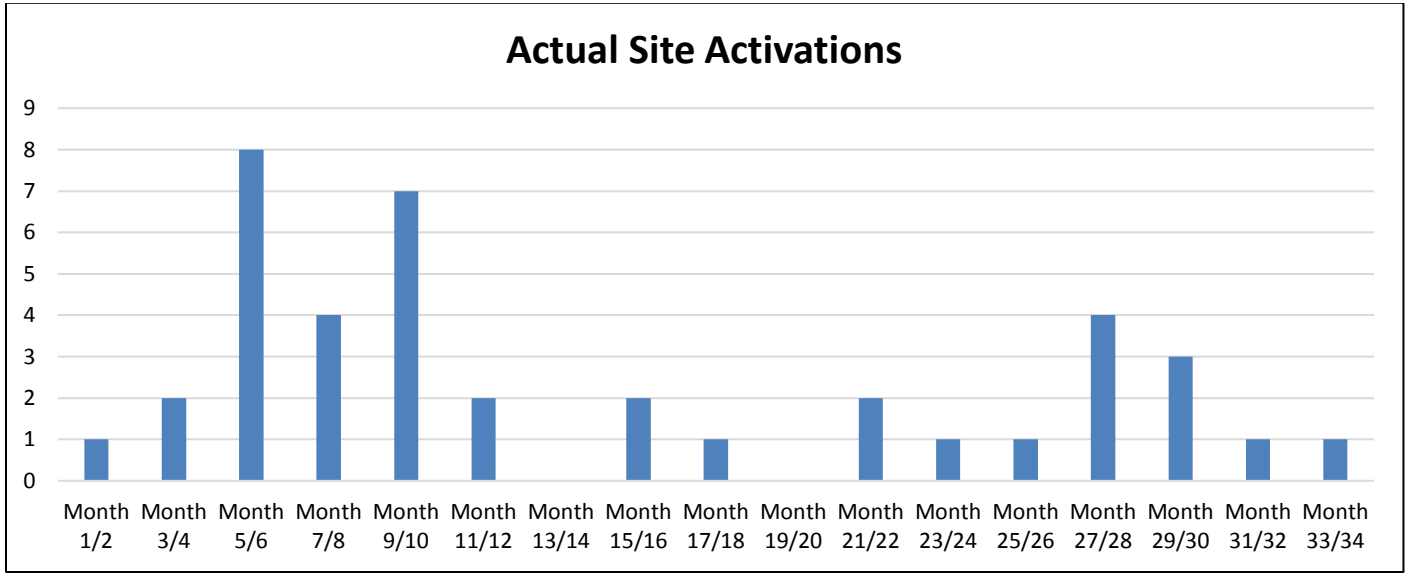


Table 3: Actual Site Activation at 2 month intervals

	Month 1/2	Month 3/4	Month 5/6	Month 7/8	Month 9/10	Month 11/12	Month 13/14	Month 15/16	Month 17/18	Month 19/20	Month 21/22	Month 23/24	Month 25/26	Month 27/28	Month 29/30	Month 31/32	Month 33/34
Site Activations	1	2	8	4	7	2	0	2	1	0	2	1	1	4	3	1	1

Chart 2: Actual Subject Enrollment

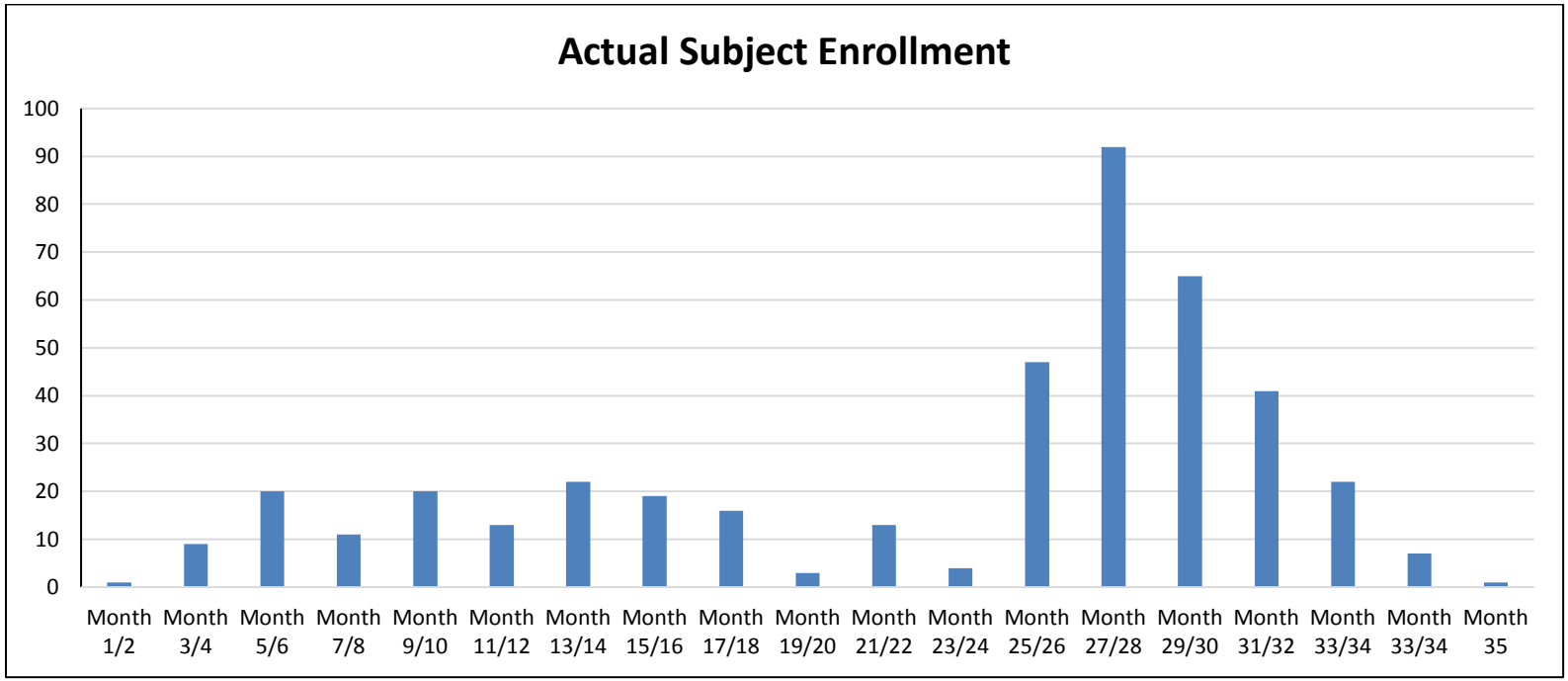


Table 4: Actual Subject Enrollment at 2 month intervals

	Month 1/2	Month 3/4	Month 5/6	Month 7/8	Month 9/10	Month 11/12	Month 13/14	Month 15/16	Month 17/18	Month 19/20	Month 21/22	Month 23/24	Month 25/26	Month 27/28	Month 29/30	Month 31/32	Month 33/34	Month 33/34	Month 35
Subject Enrollment	1	9	20	11	20	13	22	19	16	3	13	4	47	92	65	41	22	7	1

11.1. General Visit Considerations

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. As screening for potential subjects, please complete Pre-Screening/Enrollment Log.

Sponsor will provide a surveillance report on pump uploads into CareLink Clinical. This data will be visible to the sites via the Surveillance eCRF. In order for data to be pulled in to the Surveillance eCRF, it is critical that the subject be registered into CareLink Clinical, that the subject upload their study pump(s) as required by protocol and that the site have the Site Device Accountability eCRF updated. Data will be processed and pulled into the Surveillance eCRF bi-weekly. As a result, please be aware that you may not see the data immediately following a pump upload.

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.

11.2. Enrollment Visit 0: Consent and Labs

This visit will be used to obtain informed consent and complete the screening labs. If the subject does not yet have the 530G pump, the site will work with the subject to ensure that they receive the pump prior to the Baseline Visit 1 (Screening).

11.2.1. Study Procedures:

At this visit, the Investigational center staff will:

- Obtain informed consent/assent from subjects
    - Confirm that the subject/legal guardian has signed and dated all pages of the informed consent/assent as necessary.
    - Confirm that the person obtaining informed consent has signed and dated all pages necessary.
    - Confirm that the informed consent process is documented appropriately in the subject's source.
    - Subject received a copy of the signed Informed Consent.
- Perform screening labs: ***<u>These lab/urine screening tests may only be performed after the subject has been consented/assented</u>***
    - Creatinine
    - TSH
    - Free T3
    - Free T4
    - Pregnancy test (either Serum or Urine)
        - Pregnancy test will be performed for all women subjects of child bearing potential. It is expected that if they are not of child bearing potential that this is documented within the source.
- Adverse Event Collection Training

- Once a subject signed Informed Consent, they are considered enrolled in the trial. At this point, it is expected that adverse events will be collected. Train the subject on the expectation for the collection of adverse events.
- Instruct subjects 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 subjects to their own providers or an emergency facility for treatment.

- Record adverse events on the appropriate eCRF, if subject reports health status changes that result in a new medical condition or deterioration of an existing medical condition.

Naïve Subjects:

If the subject has not yet received the 530G pump or has not yet turned on the Threshold Suspend (TS) feature, instruct the subject to **not** turn on the TS feature until the Baseline Visit 1 Screening). This is in effort to ensure these subjects are enrolled as Naïve.

Non-Naïve Subjects:

If the subject is already using the 530G pump as of the Enrollment Visit 0, you will also complete the following:

- Distribute Sensor Dislodgement/Suspected Infusion Set Occlusion (without Occlusion Alarm) Subject Log
- Distribute Wallet Card
- HelpLine Training/Discussion
  - Remind subjects to contact the Medtronic 24hr HelpLine in the event the subject has any devices issues or complaints/deficiencies. Subject should also contact the site within any changes to their health status (potential adverse events)

11.3. Baseline Visit 1- Screening (Day 0):

Prior to the Baseline Visit 1 (Screening), the screening labs will need to be reviewed. If the screening labs do not meet exclusion criteria, the subject will not be required to come in for Baseline Visit 1 (Screening) and can be discontinued over the phone. Potential Adverse Events should be reviewed over the phone. For subjects that screen fail at this point, complete the Informed Consent, Inclusion/Exclusion, Screening Laboratory Test, Exit and Adverse Event eCRF as necessary. In the event that the subject has a sensor dislodgement to report, the site will document the event in the source and complete the Subject Log eCRF.

Enrollment Visit 0 and Baseline Visit 1(Screening) may be within 90 days of one another.

11.3.1. Study procedures:

- Make sure that all subjects bring the 530G pump to Baseline Visit 1 (Screening)
  - If the subject has not yet turned on the TS feature, instruct the subject to do so at this visit.
- Assess eligibility of subjects to participate in the study
- Confirm/Arrange for Subject Device Training
- Adverse Event Review/Inquiry
- Record adverse events on the appropriate eCRF, if subject reports health status changes that result in a new medical condition or deterioration of an existing medical condition.

- 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 blood sample will be sent to Central lab (Quest Diagnostics) and used for data analysis.

- Collect demographic information including age, gender, race, ethnicity and medical diagnosis, duration of diabetes
- Collect all the medications (e.g. prescriptions, over the counter, vitamins, topical and supplements) that are being used by the subject at the time of screening.
- Register subjects in CareLink Clinical (see Coordinator binder for details) and upload insulin pump.
- Distribute questionnaires to the subject for completion
    - Subject Questionnaire at Screening:
        - This should be completed no more than 2 hours before placement of 530G pump in order to assess effectiveness of training materials. Subjects who have already transitioned to the 530G system should be asked to complete this questionnaire on the basis of their memory regarding the experience they had with previous insulin pump and CGM use, and training for the previous system prior to switching to the 530G system.
    - Subject Questionnaire after Training Session and Device Placement:
        - This should be completed no more than 2 hours after placement of 530G pump in order to assess effectiveness of training materials. Subjects who have already transitioned to the 530G system should be asked to complete this questionnaire on the basis of their memory regarding the 530G system training experience.
    - Hypoglycemia Unawareness Questionnaire
    - EQ-5D: Adult or Youth
    - Low Blood Sugar Survey (Adult or Parent and Child/Teen)
- Record device information on the Site Device Accountability worksheet (to be entered into the Site Device Accountability eCRF)
    - Should the subject get a new pump at any point during their study participation, the pump will need to be added to the Site Device Accountability and uploaded into CareLink Clinical under the same account they were originally registered under.
- Provide subjects with the opportunity to bring up study-related questions and concerns.
- Disburse 1 Glucose sensor to each study subject
    - Site staff is to notify Medtronic if subjects become unable to adhere to CGM or CONTOUR Next Link RF enabled meter and supply study requirements due to change in insurance coverage or financial status, wherein they are unable to obtain sensors or CONTOUR Next Link RF enabled meter and supplies. If a subject is not able to obtain sensors or meter and supplies via insurance coverage or loses such benefit, additional sensors or meter and supplies will be provided to cover the time period between study visits.
- Disburse urine ketone strips to each study subject for use in occurrance of hyperglycemic event.

- Distribute Subject Materials:
    - Wallet Card
        - This includes contact information for the study doctor /staff as well as the 24Hr Helpline.
    - Sensor Dislodgement/Suspected Infusion Set Occlusion (without Occlusion Alarm) Subject Log
    - EZ Reference Guide
    - Telephone Service Instructions
    - CareLink Clinical Subject Uploading and Logbook Entry Instructions
- HelpLine Training/Discussion
    - Remind subjects to contact the Medtronic 24hr HelpLine in the event the subject has any devices issues or complaints/deficiencies. Subject should also contact the site within any changes to their health status (potential adverse events).
- Instruct subjects 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 subjects to their own providers or an emergency facility for treatment.
- Remind subjects about the need to wear sensors consistently
- Remind subjects to upload the pump every 21 days
- Schedule the next visit date and time
- Enter eCRFs into the study database as appropriate

11.3.2. 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 530G System through commercial channels.**
    - **Subjects should only use the CONTOUR NEXT LINK RF enabled meter**
2) **Site trainers who train PAS subjects should hold the same qualifications as the trainers employed for routine commercial training.**
3) **No additional training on the commercial devices should be provided to the study staff or to subjects beyond the training they would receive in the context of routine commercial training.**
4) **Training on study procedures will be performed**

Designated Training staff will:

- Train subjects on the use of the Medtronic MiniMed 530G insulin pump.
    - Subjects will be instructed to record carbohydrate intake and exercise into the insulin pump as part of the study requirements
- Train subjects 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.

- Subjects will receive an automated reminder (e-mail, text, or voice message) twice a month to remind them to upload pumps.
- In addition to the subject 21 day upload requirement,the Investigational Center staff will again upload pump data at the time of the visit.

- Instruct subjects per User Guide to calibrate the 530G pump at least every 12 hours after the second calibration. For best calibration results per User Guide, subjects will be instructed to calibrate 3-4 times, spread throughout the day.
- Instruct subjects to test their 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 tests 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 subjects on the use of the Sensor Dislodgement / Suspected Occlusion Subject Diary
  - Subjects will be instructed to record Sensor Dislodgement / Suspected Occlusion occurrences in the Sensor Dislodgement / Suspected Occlusion Subject Diary.
- Discuss sensor wear requirement.
  - Sensors should be worn throughout the course of the study
- Train subjects on the use of CareLink Clinical which includes that this should only be used to upload the study pump and not for data analysis or diabetes management.
- Instruct subjects to contact the Medtronic 24hr HelpLine in the event they experience problems with their study devices.
- In the event of hyperglycemia, urine ketone test strips will be provided by sponsor free of charge to subjects for use.
- Instruct subjects 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 subjects to their own providers or an emergency facility for treatment.

11.4. Visit 2 - Day 90 (± 30 days):

11.4.1. Study procedures:

- Remind Subject to Bring 530G Pump to visit
- Adverse Event Review/Inquiry
- Record adverse events on the appropriate eCRF, if subject reports health status changes that result in a new medical condition or deterioration of an existing medical condition.
- 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 blood sample will be sent to Central lab (Quest Diagnostics) and used for data analysis.
- Record device information on the Site Device Accountability worksheet (to be entered into the Site Device Accountability eCRF)

- Should the subject get a new pump at any point during their study participation, the pump will need to be added to the Site Device Accountability and uploaded into CareLink Clinical under the same account they were originally registered under.

- Upload Insulin Pump into CareLink Clinical.
- Provide subjects with the opportunity to bring up study-related questions and concerns.
- Disburse 1 Glucose sensor to each study subject
    - Site staff is to notify Medtronic if subjects become unable to adhere to CGM or CONTOUR Next Link RF enabled meter and supply study requirements due to change in insurance coverage or financial status, wherein they are unable to obtain sensors or CONTOUR NEXT LINK RF enabled meter and supplies. If a subject is not able to obtain sensors or meter and supplies via insurance coverage or loses such benefit, additional sensors or meter and supplies will be provided to cover the time period between study visits.
- Review/Distribute Subject Materials:
    - Sensor Dislodgement/Suspected Infusion Set Occlusion (without Occlusion Alarm) Subject Log
- HelpLine
    - Remind subjects to contact the Medtronic 24hr HelpLine in the event the subject has any devices issues or complaints/deficiencies. Subject should also contact the site within any changes to their health status (potential adverse events).
    - Review HelpLine calls since last visit
- Instruct subjects 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 subjects to their own providers or an emergency facility for treatment.
- Remind subjects about the need to wear sensors consistently
- Remind subjects to upload the pump every 21 days
- Schedule the next visit date and time
- Enter eCRFs into the study database as appropriate

11.5. Visit 3 - Day 180 (± 30 days):

11.5.1. Study procedures:

- Remind Subject to Bring 530G Pump to visit
- Adverse Event Review/Inquiry
- Record adverse events on the appropriate eCRF, if subject reports health status changes that result in a new medical condition or deterioration of an existing medical condition.
- 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 blood sample will be sent to Central lab (Quest Diagnostics) and used for data analysis.

- Record device information on the Site Device Accountability worksheet (to be entered into the Site Device Accountability eCRF)
    - Should the subject get a new pump at any point during their study participation, the pump will need to be added to the Site Device Accountability and uploaded into CareLink Clinical under the same account they were originally registered under.
- Upload Insulin Pump into CareLink Clinical.
- Provide subjects with the opportunity to bring up study-related questions and concerns.
- Disburse 1 Glucose sensor to each study subject
    - Site staff is to notify Medtronic if subjects become unable to adhere to CGM or CONTOUR NEXT LINK RF enabled meter and supply study requirements due to change in insurance coverage or financial status, wherein they are unable to obtain sensors or CONTOUR NEXT LINK RF enabled meter and supplies. If a subject is not able to obtain sensors or meter and supplies via insurance coverage or loses such benefit, additional sensors or meter and supplies will be provided to cover the time period between study visits.
- Review/Distribute Subject Materials:
    - Sensor Dislodgement/Suspected Infusion Set Occlusion (without Occlusion Alarm) Subject Log
- HelpLine
    - Remind subjects to contact the Medtronic 24hr HelpLine in the event the subject has any devices issues or complaints/deficiencies. Subject should also contact the site within any changes to their health status (potential adverse events).
    - Review HelpLine calls since last visit
- Instruct subjects 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 subjects to their own providers or an emergency facility for treatment.
- Remind subjects about the need to wear sensors consistently
- Remind subjects to upload the pump every 21 days
- Schedule the next visit date and time
- Enter eCRFs into the study database as appropriate

11.6. Visit 4 - Day 270 (± 30 days):

11.6.1. Study procedures:

- Remind Subject to Bring 530G Pump to visit
- Adverse Event Review/Inquiry
- Record adverse events on the appropriate eCRF, if subject reports health status changes that result in a new medical condition or deterioration of an existing medical condition.
- 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 blood sample will be sent to Central lab (Quest Diagnostics) and used for data analysis.

- Record device information on the Site Device Accountability worksheet (to be entered into the Site Device Accountability eCRF)
    - Should the subject get a new pump at any point during their study participation, the pump will need to be added to the Site Device Accountability and uploaded into CareLink Clinical under the same account they were originally registered under.
- Upload Insulin Pump into CareLink Clinical.
- Provide subjects with the opportunity to bring up study-related questions and concerns.
- Disburse 1 Glucose sensor to each study subject
    - Site staff is to notify Medtronic if subjects become unable to adhere to CGM or-CONTOUR NEXT LINK RF enabled meter and supply study requirements due to change in insurance coverage or financial status, wherein they are unable to obtain sensors or CONTOUR NEXT LINK RF enabled meter and supplies. If a subject is not able to obtain sensors or meter and supplies via insurance coverage or loses such benefit, additional sensors or meter and supplies will be provided to cover the time period between study visits.
- Review/Distribute Subject Materials:
    - Sensor Dislodgement/Suspected Infusion Set Occlusion (without Occlusion Alarm) Subject Log
- HelpLine
    - Remind subjects to contact the Medtronic 24hr HelpLine in the event the subject has any devices issues or complaints/deficiencies. Subject should also contact the site within any changes to their health status (potential adverse events).
    - Review HelpLine calls since last visit
- Instruct subjects 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 subjects to their own providers or an emergency facility for treatment.
- Remind subjects about the need to wear sensors consistently
- Remind subjects to upload the pump every 21 days
- Schedule the next visit date and time
- Enter eCRFs into the study database as appropriate

11.7. Visit 5 – Day 365 (+ 30 days): End of study

11.7.1. Study procedures:

- Remind Subject to Bring 530G Pump to visit
- Adverse Event Review/Inquiry
- Record adverse events on the appropriate eCRF, if subject reports health status changes that result in a new medical condition or deterioration of an existing medical condition.
- 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 blood sample will be sent to Central lab (Quest Diagnostics) and used for data analysis.

- Upload Insulin Pump into CareLink Clinical.
- Provide subjects with the opportunity to bring up study-related questions and concerns.
- Review Subject Materials:
    - Sensor Dislodgement/Suspected Infusion Set Occlusion (without Occlusion Alarm) Subject Log
- Record device information on the Site Device Accountability worksheet (to be entered into the Site Device Accountability eCRF)
    - Should the subject get a new pump at any point during their study participation, the pump will need to be added to the Site Device Accountability and uploaded into CareLink Clinical under the same account they were originally registered under
- Distribute questionnaires to the subject for completion
    - Hypoglycemia Unawareness Questionnaire
    - EQ-5D and EQ-5D-Y
    - Low Blood Sugar Survey (Adult or Parent and Child/Teen)
- Helpline
    - Review HelpLine calls since last visit
- Enter eCRFs into the study database as appropriate
- Discharge subject from study

11.8. Minimizing Subject Withdrawal

It may be reasonable to expect that subjects will not consistently comply with study requirements during post market surveillance studies. 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 1 sensor free of charge at every study visit.
- Site staff is to notify Medtronic if subjects become unable to adhere to CGM or CONTOUR NEXT LINK RF enabled meter and supply study requirements due to change in insurance coverage or financial status, wherein they are unable to obtain sensors or CONTOUR NEXT LINK RF enabled meter and supplies. If a subject is not able to obtain sensors or meter and supplies via insurance coverage or loses such benefit, additional sensors or meter and supplies will be provided to cover the time period between study visits.

11.9. Subject Withdrawal, Screen Failures and Data Censure

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

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

Subjects may also be withdrawn from the study at the discretion of the Investigator. 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

A subject's data may be subject to censure if any of the following occurs:

- During the course of the study, subject begins participation in another investigational study (drug or device).
- 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.

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

Should a subject fail to meet inclusion/exclusion criteria, theirstudy participation will end and the subject will exit the study as a screen failure. The criterion not met should be documented.

Subjects may be rescreened after a minimum of three monthsif they do not meet inclusion/exclusion criteria at the time of their original screening. Rescreening may occur up to two times.

11.10. 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.

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 and regulatory documents, and

verification of original and/or certified copies of original source data/documents against the database (Oracle RDC data entries) for 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, 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. 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

Deviations from the protocol and/or applicable regulatory requirement(s) by an Investigator/institution should lead to action by the Sponsor to secure compliance. Measures taken to secure compliance may include identifying appropriate corrective actions or additional training.

Any deviation from the procedures laid out in the protocol must be identified and documented on an eCRF. Medtronic retains the right to require the withdrawal of any subject or Investigator/Investigational Center that violates the protocol.

If monitoring and/or auditing identify serious and/or persistent non-compliance on the part of an Investigator/Investigational Center, the Sponsor should terminate the Investigator/institution's participation

in the trial. When an Investigational Center's participation is terminated because of non-compliance, the sponsor should promptly notify the IRB and the FDA.

13. Device Performance Issues & Complaints for the 530G Insulin Pump and CGM System

The Medtronic 24 Hour Help Line (HL) will be consulted for device troubleshooting; they should be contacted immediately in the event of device performance problems. Subject will be instructed to notify the HL that they are currently participating in the study. All device complaints that are reported to the HL staff by the Subject will be documented by the HL staff.

The 24-Hour Helpline is responsible for handling customer complaints/customer inquiries for all approved product. The Helpline will be notified of a customer complaint/inquiry via phone, email, letter or fax. If the customer complaint/inquiry did not originate via phone then the customer service representative may initiate a follow up call with the customer as necessary.

Helpline Customer Service Representatives will receive training from the clinical study team to ensure that study subjects will be identified appropriately.

Once the complaint is received the customer service representative will identify the customer using a SA&P (Systems Application & Products - integrated software system used by Medtronic Diabetes that stores all of Medtronic Diabetes' electronic data and enables data to be shared and accessed by multiple departments) transaction and verify/update customer's information. The customer service representative will also obtain any additional information to ensure accurate documentation and to meet regulatory requirements.

The customer service representative will obtain all details of the customer's complaint/inquiry and document those details in a service notification. The representative will also select a reason code in the SA&P transaction that matches the customer complaint or inquiry. The code will also be linked to any potential product return.

In addition, the customer service representative will troubleshoot the customer's complaint or product issue according to established and validated guides. The results of troubleshooting will be documented in the service notification. Trouble shooting by Helpline will follow the standard commercial process.

The customer service representative will explain and document the outcome of troubleshooting and will advise the customer to monitor or return the product. The customer will be advised to monitor if no issue is found or be advised to replace the product if troubleshooting indicates a possible product issue.

If a return is required a return sales order will be created and return materials sent to the customer along with a replacement product (if necessary).

Information received from study subjects during Helpline calls will be provided to study doctors for review of adverse events.

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 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 and mitigations for young adult subject population

The young adult subject population (16-21 years of age) has an increased risk for hypoglycemia, including severe hypoglycemia.

Standard mitigations in both young adult and adult 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 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'.

14.2.1. Adverse Events Reported to Sponsor:

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

- Adverse Events related to the study device
- Adverse Events related to study procedures
- Serious Adverse Events (SAE)
- Unanticipated Adverse Device Effects (UADE)
- Incidence of Severe Hypoglycemia
- Incidence of Severe Hyperglycemia
- Incidence of Diabetic Ketoacidosis (DKA)

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. CEC Review of Events

Severe hypoglycemia, Severe Hyperglycemia, DKA and SADE 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) (ISO14155-2)

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)

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 14155-2)

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 14155-2)
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 to actively administer carbohydrate, glucagon, or other resuscitative actions. 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. **(American Diabetes Association Workgroup on Hypoglycemia, Diabetes Care 28:1245-1249, 2005)**

"Severe Hyperglycemia" is defined as Hyperglycemia (blood glucose >300 mg/dL**)** with blood glucose ketones >0.6mmol/L, urine ketones moderate or large, 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 diabetes that is insulin requiring 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 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:

- Causal relationship – 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
- Unknown – not enough information exists to determine

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.

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 Medtronic MiniMed ® 530G 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 study procedures will be initiated before the protocol is implemented.

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. Investigator / Sponsor Contact Information

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

17. References

Ly T, Davis E, Gallego P, and Jones T. Impaired Awareness of Hypoglycemia in a Population-Based Sample of Children and Adolescents With Type 1 Diabetes. Diabetes Care Diabetes Care 2009; 32:1802–1806

Clarke WL, Cox DJ, Gonder-Frederick LA, et al. Reduced awareness of hypoglycemia in adults with IDDM: a prospective study of hypoglycemic frequency and associated symptoms. Diabetes Care 1995; 18:517–522

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

Nathan D, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine R. Translating the A1C Assay Into Estimated Average Glucose Values, Diabetes Care 2008 Aug; 31(8): 1473-1478

18. Appendices

18.1. Validated Study Questionnaires

18.1.1. Hypoglycemia Unawareness Questionnaire

1. Check the category that best describes you: (check one only)

   _____I always have symptoms when my blood sugar is low (A)

   _____I sometimes have symptoms when my blood sugar is low (R)

   _____I no longer have symptoms when my blood sugar is low (R)

2. Have you lost some of the symptoms that used to occur when your blood sugar was low?

   _____yes (R) _____ no (A)

3. In the past six months how often have you had moderate hypoglycemia episodes? (Episodes where you might feel confused, disoriented, or lethargic and were unable to treat yourself)

   _____Never (A) _____Once or twice (R) _____Every other month (R)

   _____Once a month (R) _____More than once a month (R)

4. In the past year how often have you had severe hypoglycemic episodes? (Episodes where you were unconscious or had a seizure and needed glucagon or intravenous glucose)

   _____Never (A) _____1 time (R) _____ 2 times (R) _____3 times (R)

   _____5 times (R) _____6 times (R) _____7 times (R) _____8 times (R)

   _____9 times (R) _____10 times (R) _____11 times (R)

   _____12 or more times (U)

5. How often in the last month have you had readings <70 mg/dl with symptoms?

   ___Never ____1 to 3 times ___1 time/week ____2 to 3 times/week ____4 to 5 times/week

   ___Almost daily

6. How often in the last month have you had readings <70 mg/dl without any symptoms?

   _____Never _____1 to 3 times _____1 time/week _____2 to 3 times/week

   _____4 to 5 times/week _____Almost daily

   (R = answer to 5 > answer to 6, A = answer to 6 > answer to 5)

7. How low does your blood sugar need to go before you feel symptoms?

   _____60-69 mg/dl (A) _____50-59 mg/dl (A) _____40-49 mg/dl (R)

   _____<40 mg/dl (R)

8. To what extent can you tell by your symptoms that your blood sugar is low?

   _____Never (R) _____Rarely (R) _____Sometimes (R) _____Often (A)

   _____Always (A)

18.1.2. **EQ-5D Questionnaire**

Adult Health Questionnaire

(English version for the US)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

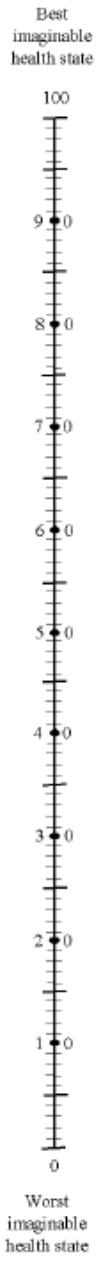
Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



18.1.3. **HFS Questionnaire**

Study ID: *Subject ID:*

Adult Low Blood Sugar Survey
(University of Virginia)

I. Behavior: Below is a list of things people with diabetes sometimes do in order to avoid low blood sugar and its consequences. Circle one of the numbers to the right that best describes what you have done during the last 6 months in your daily routine to AVOID low blood sugar and its consequences. (**Please do not skip any!**).

To avoid low blood sugar and how it affects me, I ...	Never	Rarely	Some-times	Often	Almost Always
1. Ate large snacks.	0	1	2	3	4
2. Tried to keep my blood sugar above 150.	0	1	2	3	4
3. Reduced my insulin when my blood sugar was low.	0	1	2	3	4
4. Measured my blood sugar six or more times a day.	0	1	2	3	4
5. Made sure I had someone with me when I go out.	0	1	2	3	4
6. Limited my out of town travel.	0	1	2	3	4
7. Limited my driving (car, truck or bicycle).	0	1	2	3	4
8. Avoided visiting friends.	0	1	2	3	4
9. Stayed at home more than I liked.	0	1	2	3	4
10. Limited my exercise/physical activity.	0	1	2	3	4
11. Made sure there were other people around.	0	1	2	3	4
12. Avoided sex.	0	1	2	3	4
13. Kept my blood sugar higher than usual in social situations.	0	1	2	3	4
14. Kept my blood sugar higher than usual when doing important tasks.	0	1	2	3	4
15. Had people check on me several times during the day or night.	0	1	2	3	4

II. Worry: Below is a list of concerns people with diabetes sometimes have about low blood sugar. Please read each item carefully (do not skip any). Circle one of the numbers to the right that best describes how often in the last 6 months you WORRIED about each item because of low blood sugar.

	Never	Rarely	Some-times	Often	Almost Always
Because my blood sugar could go low, I worried about...					
16. Not recognizing/realizing I was having low blood sugar.	0	1	2	3	4
17. Not having food,fruit, or juice available.	0	1	2	3	4
18. Passing out in public.	0	1	2	3	4
19. Embarrassing myself or my friends in a social situation.	0	1	2	3	4
20. Having a hypoglycemic episode while alone.	0	1	2	3	4
21. Appearing stupid or drunk.	0	1	2	3	4
22. Losing control.	0	1	2	3	4
23. No one being around to help me during a hypoglycemic episode.	0	1	2	3	4
24. Having a hypoglycemic episode while driving.	0	1	2	3	4
25. Making a mistake or having an accident.	0	1	2	3	4
26. Getting a bad evaluation or being criticized.	0	1	2	3	4
27. Difficulty thinking clearly when responsible for others.	0	1	2	3	4
28. Feeling lightheaded or dizzy.	0	1	2	3	4
29. Accidently injuring myself or others.	0	1	2	3	4
30. Permanent injury or damage to my health or body.	0	1	2	3	4
31. Low blood sugar interfering with important things I was doing.	0	1	2	3	4
32. Becoming hypoglycemic during sleep.	0	1	2	3	4
33. Getting emotionally upset and difficult to deal with.	0	1	2	3	4

II. Worry: Below is a list of concerns people with diabetes sometimes have about low blood sugar. Please read each item carefully (do not skip any). Circle one of the numbers to the right that best describes how often in the last 6 months you WORRIED about each item because of low blood sugar.

	Never	Rarely	Some-times	Often	Almost Always
Because my blood sugar could go low, I worried about...					
16. Not recognizing/realizing I was having low blood sugar.	0	1	2	3	4
17. Not having food,fruit, or juice available.	0	1	2	3	4
18. Passing out in public.	0	1	2	3	4
19. Embarrassing myself or my friends in a social situation.	0	1	2	3	4
20. Having a hypoglycemic episode while alone.	0	1	2	3	4
21. Appearing stupid or drunk.	0	1	2	3	4
22. Losing control.	0	1	2	3	4
23. No one being around to help me during a hypoglycemic episode.	0	1	2	3	4
24. Having a hypoglycemic episode while driving.	0	1	2	3	4
25. Making a mistake or having an accident.	0	1	2	3	4
26. Getting a bad evaluation or being criticized.	0	1	2	3	4
27. Difficulty thinking clearly when responsible for others.	0	1	2	3	4
28. Feeling lightheaded or dizzy.	0	1	2	3	4
29. Accidently injuring myself or others.	0	1	2	3	4
30. Permanent injury or damage to my health or body.	0	1	2	3	4
31. Low blood sugar interfering with important things I was doing.	0	1	2	3	4
32. Becoming hypoglycemic during sleep.	0	1	2	3	4
33. Getting emotionally upset and difficult to deal with.	0	1	2	3	4

18.1.4. **EQ-5D Youth Proxy Questionnaire**

Study ID: *Subject ID:*

Health Questionnaire

Proxy Version for EQ-5D-Y

The purpose of this questionnaire is to explore how a care-giver or someone who knows the child well (proxy), thinks that the child would rate his/her own health. The proxy should answer as he/she thinks that the child would respond if he/she were able to fill in the questionnaire for him/herself.

EQ-5D-Y

Describing the child's health today

PLEASE ANSWER ON BEHALF OF THE CHILD: Under each heading, please tick the ONE box that you think **the child** would tick to describe his/her own health **TODAY** if **he/she** were able to do so.

Mobility *(walking about)*

He/she has no problems walking about ❑
He/she has some problems walking about ❑
He/she has a lot of problems walking about ❑

Looking after myself

He/she has no problems washing or dressing him/herself ❑
He/she has some problems washing or dressing him/herself ❑
He/she has a lot of problems washing or dressing him/herself ❑

Doing usual activities (*for example. going to school, hobbies, sports, playing, doing things with family or friends)*

He/she has no problems doing his/her usual activities ❑
He/she has some problems doing his/her usual activities ❑
He/she has a lot of problems doing his/her usual activities ❑

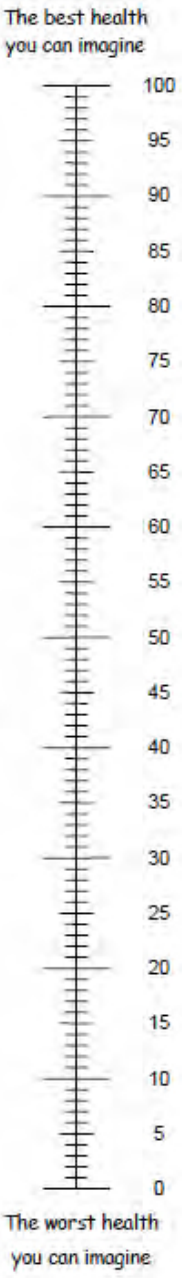
Having pain or discomfort

He/she has no pain or discomfort ❑
He/she has some pain or discomfort ❑
He/she has a lot of pain or discomfort ❑

Feeling worried, sad or unhappy

He/she is not worried, sad or unhappy ❑
He/she is a bit worried, sad or unhappy ❑
He/she is very worried, sad or unhappy ❑

How good is your health TODAY



- We would like to know how good or bad your health is TODAY.
- This line is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the line to show how good or bad your health is TODAY.

3

18.1.5. **HFS Parent Questionnaire**

Study ID: *Subject ID:*

Today's Date: _____ Study ID #_____

University of Virginia
Parent Low Blood Sugar Survey

This survey is intended to find out more about how low blood sugar makes people feel and behave. Please answer the following questions as frankly as possible.

I. Below is a list of things parents of children with diabetes sometimes DO IN ORDER TO AVOID LOW BLOOD SUGAR and related problems in their children. Read each item carefully. Circle one of the numbers that best describes YOU.

0 = NEVER 1 = RARELY 2 = SOMETIMES 3 = OFTEN 4 = ALMOST ALWAYS

1.	Have my child eat large snacks at bedtime.	0	1	2	3	4
2.	Avoid having my child being alone when his/her sugar is likely to be low.	0	1	2	3	4
3.	Allow my child's blood sugar to be a little high to be on the safe side.	0	1	2	3	4
4.	Keep my child's sugar higher when he/she will be alone for awhile.	0	1	2	3	4
5.	Have my child eat something as soon as he/she feels the first sign of low blood sugar.	0	1	2	3	4
6.	Reduce my child's insulin when I think his/her sugar is too low.	0	1	2	3	4
7.	Keep my child's blood sugar higher when he/she plans to be away from me for awhile.	0	1	2	3	4
8.	Have my child carry fast-acting sugar.	0	1	2	3	4
9.	Have my child avoid a lot of exercise when I think his/her sugar is low.	0	1	2	3	4
10.	Check my child's sugar often when he/she plans to go on an outing.	0	1	2	3	4
11.	Get up in the middle of the night to check on my child or check my child's blood sugar levels.	0	1	2	3	4

II Worry: Below is a list of concerns parents of children with diabetes sometimes have. Read each item carefully. Circle one of the numbers that best describes HOW OFTEN YOU WORRY ABOUT EACH ITEM.

0 = NEVER 1 = RARELY 2 = SOMETIMES 3 = OFTEN 4 = ALMOST ALWAYS

12.	Child not recognizing/realizing that he/she is having a low.	0	1	2	3	4
13.	Child not having food, fruit, or juice with him/her.	0	1	2	3	4
14.	Child feeling dizzy or passing out in public.	0	1	2	3	4
15.	Child having a low while asleep.	0	1	2	3	4
16.	Child embarrassing self or friends/family in a social situation.	0	1	2	3	4
17.	Child having a low while alone.	0	1	2	3	4
18.	Child appearing to be "stupid" or clumsy.	0	1	2	3	4
19.	Child losing control of behavior due to low blood sugar.	0	1	2	3	4
20.	No one being around to help my child during a low.	0	1	2	3	4
21.	Child making a mistake or having an accident at school.	0	1	2	3	4
22.	Child getting a bad evaluation at school because of something that happens when his/her sugar is low.	0	1	2	3	4
23.	Child having seizures or convulsions.	0	1	2	3	4
24.	Child developing long term complications from frequent low blood sugar.	0	1	2	3	4
25.	Child feeling light-headed or faint.	0	1	2	3	4
26.	Child having a low.	0	1	2	3	4

18.1.6. **HFS Child Questionnaire**

Study ID: *Subject ID:*

Today's Date: _____ Study ID # _____

University of Virginia

Child/Teen Low Blood Sugar Survey

We want to find out more about what low blood sugar makes young people feel and do. Please answer the questions below as honestly as you can.

I. Below is a list of things young people with diabetes sometimes DO TO KEEP FROM HAVING LOW BLOOD SUGAR. Circle the number that best describes YOU.

0=NEVER 1=RARELY 2=SOMETIMES 3=OFTEN 4=ALMOST ALWAYS

1.	Eat large snacks at bedtime	0	1	2	3	4
2.	Try not to be by myself when my sugar is likely to be low	0	1	2	3	4
3.	Keep blood sugars a little high to be on the safe side	0	1	2	3	4
4.	Keep blood sugar higher when I will be alone for awhile	0	1	2	3	4
5.	Eat something as soon as I feel the first sign of low blood sugar	0	1	2	3	4
6.	Take less insulin when I think my blood sugar might get too low	0	1	2	3	4
7.	Keep my blood sugar higher when I am going to be away from home	0	1	2	3	4
8.	Carry some kind of sugar, drink, or food with me	0	1	2	3	4
9.	Try not to do a lot of exercise when I think my sugar is low	0	1	2	3	4
10.	Check my blood sugar often when I go away from home	0	1	2	3	4

II. Below is a list of things that young people with diabetes sometimes worry about concerning low blood sugars. Circle the number that best describes YOU.

0=NEVER 1=RARELY 2=SOMETIMES 3=OFTEN 4=ALMOST ALWAYS

11.	Not recognizing that my blood sugar is low	0	1	2	3	4
12.	Not having food, fruit, or juice with me when my blood sugar gets low	0	1	2	3	4

Today's Date: _____ Study ID # _____

University of Virginia

Child/Teen Low Blood Sugar Survey

We want to find out more about what low blood sugar makes young people feel and do. Please answer the questions below as honestly as you can.

I. Below is a list of things young people with diabetes sometimes DO TO KEEP FROM HAVING LOW BLOOD SUGAR. Circle the number that best describes YOU.

	0=NEVER 1=RARELY 2=SOMETIMES 3=OFTEN 4=ALMOST ALWAYS					
1.	Eat large snacks at bedtime	0	1	2	3	4
2.	Try not to be by myself when my sugar is likely to be low	0	1	2	3	4
3.	Keep blood sugars a little high to be on the safe side	0	1	2	3	4
4.	Keep blood sugar higher when I will be alone for awhile	0	1	2	3	4
5.	Eat something as soon as I feel the first sign of low blood sugar	0	1	2	3	4
6.	Take less insulin when I think my blood sugar might get too low	0	1	2	3	4
7.	Keep my blood sugar higher when I am going to be away from home	0	1	2	3	4
8.	Carry some kind of sugar, drink, or food with me	0	1	2	3	4
9.	Try not to do a lot of exercise when I think my sugar is low	0	1	2	3	4
10.	Check my blood sugar often when I go away from home	0	1	2	3	4

II. Below is a list of things that young people with diabetes sometimes worry about concerning low blood sugars. Circle the number that best describes YOU.

	0=NEVER 1=RARELY 2=SOMETIMES 3=OFTEN 4=ALMOST ALWAYS					
11.	Not recognizing that my blood sugar is low	0	1	2	3	4
12.	Not having food, fruit, or juice with me when my blood sugar gets low	0	1	2	3	4

13.	Feeling dizzy or passing out in public because of low blood sugar	0	1	2	3	4
14.	Having a low blood sugar while asleep	0	1	2	3	4
15.	Embarrassing myself because of low blood sugar	0	1	2	3	4
16.	Having low blood sugar while I am by myself	0	1	2	3	4
17.	Looking "stupid" or clumsy in front of other people	0	1	2	3	4
18.	Losing control because of low blood sugar	0	1	2	3	4
19.	No one being around to help me during a low	0	1	2	3	4
20.	Making a mistake or having an accident at school	0	1	2	3	4
21.	Getting in trouble at school because of something that happens when my sugar is low	0	1	2	3	4
22.	Having seizures	0	1	2	3	4
23.	Getting long term complications from low blood sugar	0	1	2	3	4
24.	Feeling dizzy or woozy when my blood sugar is low	0	1	2	3	4
25.	Having a low blood sugar	0	1	2	3	4

18.1.7. **Pre Training / Device Placement Questionnaire**

Medtronic	PROTOCOL ID CEP 266	SUBJECT IDENTIFICATION STUDY # ☐☐☐ – SITE # ☐☐☐ – SUBJECT # ☐☐☐	

Subject Questionnaire at Screening

Experience and Training before Device Placement of the Minimed 530G System

Please provide information about your level of experience with insulin pumps and Continuous Glucose Monitoring (CGM)					
	None	Less than 1 year	1-3 years	4-5 years	Greater than 5 years
How much experience do you have with insulin pump use?					
How much experience do you have with CGM use?					

Please provide information about the training you have received for the insulin pump you currently use as well as for Continuous Glucose Monitoring (provided you have or are currently using CGM)			
	Yes	No	Not applicable
Have you received pump training for the pump you have now?			
Based on the training you have received, do you have a good understanding regarding pump use?			
Have you received CGM training?			
Based on the training you have received, do you have a good understanding regarding CGM use?			

Comments:

Please initial and date: _____ ____ / ___ ___ ___ / ___ ___ ___ ___
Initials DD Mon YYYY

Version	Version Date

18.1.8. **Post Training / Device Placement Questionnaire**

Medtronic	PROTOCOL ID CEP 266	SUBJECT IDENTIFICATION STUDY # ☐☐☐ – SITE # ☐☐☐ – SUBJECT # ☐☐☐	

Subject Questionnaire after Training Session and Device Placement

Please answer the questions below about the device training you have received for the Minimed 530G System

Training Session	Strongly Disagree	Disagree	Somewhat Disagree	Neutral	Somewhat Agree	Agree	Strongly Agree
The pace of the training session was acceptable	1	2	3	4	5	6	7
The amount of information was appropriate	1	2	3	4	5	6	7
Instructional Materials	**Strongly Disagree**	**Disagree**	**Somewhat Disagree**	**Neutral**	**Somewhat Agree**	**Agree**	**Strongly Agree**
Overall, the Minimed 530G instructional materials can be understood	1	2	3	4	5	6	7
The instructional materials are complete and contain the information I need.	1	2	3	4	5	6	7
I would rather call the 24-hour Help Line than read the User Guide, if I need assistance.	1	2	3	4	5	6	7

Comments

Please initial and date: _____ _____ / ___ ___ ___ / ___ ___ ___ ___
Initials DD Mon YYYY

Version	Version Date

18.2. Sensor Dislodgement / Suspected Occlusion Diary

Medtronic	PROTOCOL ID CEP 266	STUDY / SITE / SUBJECT 2 6 6 – ☐☐☐ – ☐☐☐	

Sensor Dislodgement / Suspected Occlusion (w/o Occlusion Alarm)

Subject Log

Please record date when your sensor becomes dislodged or when you suspect that an occlusion of your infusion set has occurred. Select a reason for it from the "How did it happen?" drop-down list. If the reason is not listed there, please explain in the adjacent "Comment" field.

Date	What happened?	How did it happen?	Comment (if reason is "Other")
Click here to enter a date.	Choose an item.	Choose an item.	
Click here to enter a date.	Choose an item.	Choose an item.	
Click here to enter a date.	Choose an item.	Choose an item.	
Click here to enter a date.	Choose an item.	Choose an item.	
Click here to enter a date.	Choose an item.	Choose an item.	
Click here to enter a date.	Choose an item.		
Click here to enter a date.	Choose an item.		
Click here to enter a date.	Choose an item.		
Click here to enter a date.	Choose an item.		
Click here to enter a date.	Choose an item.	Choose an item.	
Click here to enter a date.	Choose an item.	Choose an item.	
Click here to enter a date.	Choose an item.	Choose an item.	
Click here to enter a date.	Choose an item.	Choose an item.	

Choices:
1. Bumped sensor against object.
2. Came off during clothing change
3. Came off during exercise
4. Came off during sleep
5. Cannot tell how it happened
6. When infusion set was inserted
7. Other

Choices:
1. Complete Sensor Dislodgement
2. Partial sensor dislodgement with sensor remaining in skin
3. Suspected Occlusion without occlusion alarm

Version	Version Date
Draft	29 Jul 2013