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1. Glossary

| Abbreviation | Definition |
|--------------|---|
| AE | Adverse Event |
| ADE | Adverse Device Effect |
| CEC | Clinical Events Committee |
| CFR | Code of Federal Regulations |
| CGM | Continuous Glucose Monitoring |
| CSII | Continuous Subcutaneous Insulin Infusion |
| DKA | Diabetic Ketoacidosis |
| eCRF | Electronic Case Report Form |
| EOS | End of Study |
| ER | Emergency Room |
| EWIS | Extended Wear Infusion Set |
| FDA | United States Food and Drug Administration |
| GCP | Good Clinical Practice |
| GENMOD | Generalized Linear Model |
| HbA1c | Glycosylated hemoglobin |
| HIPAA | Health Insurance Portability and Accountability Act of 1996 |
| ICF | Informed Consent Form |
| IDE | Investigational Device Exemption |
| IEC | Independent Ethic Committee |
| IFU | Instructions for Use |

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| IRB | Institutional Review Board |
| ITT | Intention to Treat |
| MC2 | Medtronic Core Clinical Solutions |
| OC-RDC | Oracle Clinical Remote Data Capture |
| PC | Personal Computer |
| PP | Per Protocol |
| RF | Radio Frequency |
| SAE | Serious Adverse Event |
| SADE | Serious Adverse Device Events |
| SG | Sensor Glucose |
| SID | Subject ID |
| SMBG | Self-Monitoring of Blood Glucose |
| TLS | Transport Layer Security |
| TS | Technical Support |
| UADE | Unanticipated Adverse Device Effect |

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2. Synopsis

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| Title | Evaluation of Extended Wear Infusion Set (EWIS) in Patients with Type 1 Diabetes |
| Investigational Device Exemption (IDE) Number | G190174 |
| Devices | <p>Investigational devices:</p> <ul style="list-style-type: none"> • Medtronic Extended Wear infusion set (MMT-405) <p>Non-Investigational devices:</p> <ul style="list-style-type: none"> • MiniMed™ 670G Insulin Pump, version 3.0 (MMT-1780) – owned by subjects, not provided through study • Guardian™ Link (3) Transmitter (MMT-7811) • Guardian™ Sensor (3) Glucose Sensor (MMT-7020)- referred to as Guardian Sensor (3) throughout this protocol • One-Press Serter (MMT-7512) -referred to as the Serter throughout this protocol • Transmitter Charger (MMT-7715) • Tester (MMT-7736L) • Medtronic CareLink™ Personal Therapy Management Software for Diabetes (MMT-7333) For Clinical Research – referred to as CareLink™ Personal For Clinical Research throughout this protocol • CONTOUR® NEXT LINK 2.4 Blood Glucose Meter (MMT-1152 or MMT-1352) - referred to as the CONTOUR® NEXT LINK 2.4 study meter throughout this protocol • Abbott™* Precision Xtra™* meter to be used for blood ketone measurements only -referred to as the Precision Xtra™* ketone meter throughout this protocol. |
| Purpose | The purpose of this study is to collect confirmatory clinical data to support 6 or 7 days wear of EWIS. |
| Objective | The objective of this study is to evaluate the EWIS in patients with type 1 diabetes on insulin pump therapy. |

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| <p>Study Design</p> | <p>This study is a multi-center, non-randomized, prospective single arm study with type 1 patients with diabetes on insulin pump therapy with Continuous Glucose Monitoring (CGM).</p> <p>A total of up to 300 subjects will be enrolled at up to 20 investigational centers in the US in order to have 240 subjects meeting eligibility criteria. Each subject will wear their own MiniMed™ 670G insulin system. Each subject will be given 12 infusion sets to wear (each infusion set for at least 174 hours, or until infusion set failure if this occurs before 174 hours). The infusion set with the longest length (43 in) will be used for this study. Subjects will change insulin reservoirs at least every 174 hours. The infusion set(s) or reservoir(s) can be replaced independent of each other as referenced in the subject instructions. The time of infusion set insertion will be taken from Daily Log.</p> <p>Infusion set failure used to determine primary endpoint is defined as any one of the following:</p> <ul style="list-style-type: none"> • Unexplained Hyperglycemia is defined as the following (See Primary Effectiveness Endpoint Sections 4.2.2 and 13.5.2) : <ul style="list-style-type: none"> ○ The study meter glucose >250 mg/dL (>3 hours post-meal) which may include time during subject’s sleeping hours ○ Failure of a correction dose(s) to lower the study meter glucose by at least 50 mg/dL. ○ One additional correction dose may be given after first correction dose and recommended to use the bolus calculator. The infusion set may remain in the body if the glucose improves after second correction dose within 90 minutes. Please note: if the glucose improves after the correction doses, and the infusion set does not need to be changed then this would NOT be considered an adverse event (e.g. unexplained hyperglycemia) and NOT considered an infusion set failure. ○ SMBG should be checked every 60 minutes during this time • The presence of serum ketones ≥ 0.6 mmol/L with a study meter glucose >250 mg/dL in the absence of illness and blood glucose that does not respond to insulin correction dose(s) as described above. (See Primary Safety Endpoint Sections 4.2.1 and 13.5.1) • There are signs of infection at the infusion site (i.e. erythema (> 1 cm in diameter) with warmth, pain, and/ or induration) . (See Primary Safety Endpoint Section 4.2.1 and 13.5.1) |
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Other known causes of infusion set failures which may or may not associated with hyperglycemia will be collected and analyzed as part of the overall safety assessment:

- Accidental removals
- Leakage
- Loss of insertion (e.g. patient does not appear to be receiving insulin within 12 hours after infusion set is inserted)
- Kinked or bent cannula
- Removal due to discomfort at site
- Mechanical failure
- Adhesive issue

All severe hyperglycemic events as defined in Section 10.2 will be summarized: whether they are device related or not or whether they are associated with infusion set failure or not.

At home, the subject will be expected to inspect their infusion site on a daily basis and if they observe signs of infection (i.e. erythema > 1 cm in diameter with warmth, pain, and/ or induration) at the infusion site, they should call the investigational center. Also, subjects are requested to upload data from their insulin pump and CONTOUR® NEXT LINK 2.4 study meter into CareLink™ Personal For Clinical Research weekly. In addition to the study procedures, the subjects are to continue their standard routine care.

At each study visit, insulin pump and CONTOUR® NEXT LINK 2.4 study meter will be uploaded into CareLink™ Personal For Clinical Research.

Subjects will be instructed to test their blood glucose using the CONTOUR® NEXT LINK 2.4 study meter at least 4-6 times each day (before meals and bedtime). Subjects will be instructed to check blood ketones using a Precision Xtra™* ketone meter if the CONTOUR® NEXT LINK 2.4 study meter reading is greater than 250 mg/dL (ketones do not need to be checked if it is less than 3 hours post-prandial).

Subjects will be required to upload their pump and glucose meter at Visit 2 in order to obtain the previous month of CareLink™ data.

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| <p>Sample Size and Investigational Centers</p> | <p>A total of up to 300 subjects will be enrolled at up to 20 investigational centers in the US in order to have 240 subjects meeting eligibility criteria . Subjects will be replaced who have early withdrawal.</p> <ul style="list-style-type: none"> • Insulin Utilization <ul style="list-style-type: none"> ○ N = 100 Humalog™* ○ N = 100 Novolog™* |
| <p>Study Duration</p> | <p>The study is anticipated to last approximately 12 months from first subject enrollment to completion of all data entry. Subjects can expect to participate for approximately 12-16 weeks.</p> |
| <p>Inclusion Criteria</p> | <p>Subjects will be considered for enrollment in the study if they meet all of the following criteria:</p> <ol style="list-style-type: none"> 1. Subject is age 18 – 80 years at the time of screening 2. Subject has type 1 diabetes for more than one year <p>Study specific inclusion criteria</p> <ol style="list-style-type: none"> 3. Subject is on the MiniMed™ 670G insulin pump therapy within 1 year prior to screening and willing to utilize Auto Mode and CGM with Guardian™ Sensor (3) during the study. 4. Subject is willing and able to perform study procedures as per investigator discretion 5. Subject is willing to take one of the following insulins and can financially support the use of either of the 2 insulin preparations throughout the course of the study (i.e. co-payments for insulin with insurance or able to pay full amount): <ol style="list-style-type: none"> a. Humalog™* (insulin lispro injection) b. NovoLog™* (insulin aspart) |
| <p>Exclusion Criteria</p> | <p>Subjects who meet any of the following criteria are not eligible for study participation and these exclusion criteria are study specific:</p> <ol style="list-style-type: none"> 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 device in the last 2 weeks. 2. Subject is female and has a positive pregnancy screening test 3. Subject is female of child bearing age and who is sexually active should be excluded if she is not using a form of contraception deemed reliable by investigator 4. Subject is female and plans to become pregnant during the course of the study 5. Subject has Glycosylated hemoglobin (HbA1c) > 8.5 % at time of screening. |

Note: All HbA1c blood specimens will be sent to and tested by a NGSP certified Central Laboratory. HbA1c testing must follow National Glycohemoglobin Standardization Program (NGSP) standards.

6. Subject has had a history of 1 or more episodes of severe hypoglycemia, which resulted in any the following during the 6 months prior to screening
 - a. Medical assistance (i.e. Paramedics, Emergency Room [ER] or Hospitalization)
 - b. Coma
 - c. Seizures
7. Subject has taken any oral, injectable, or IV glucocorticoids within 8 weeks from time of screening visit, or plans to take any oral, injectable, or IV glucocorticoids during the course of the study.
8. Subject is unable to tolerate tape adhesive in the area of infusion set
9. Subject has any unresolved adverse skin condition in the area of infusion set placement (e.g., psoriasis, dermatitis herpetiformis, rash, Staphylococcus infection)
10. Subject has infection in the area of infusion set placement at time of screening
11. Subject has had Diabetic Ketoacidosis (DKA) in the 12 months prior to screening visit.
12. Subject is currently abusing illicit drugs
13. Subject is currently abusing alcohol
14. Subject is on dialysis (for renal failure)
15. Subject has history of adrenal disorder
16. Subject has a history of inpatient psychiatric treatment in the past 6 months prior to screening
17. Subject has any condition that the Investigator believes would interfere with study participation
18. Subject has a history of visual impairment which would not allow subject to participate in the study and perform all study procedures safely, as determined by the investigator
19. Subject has a sickle cell disease, hemoglobinopathy; or has received red blood cell transfusion or erythropoietin within 3 months prior to time of screening
20. Subject plans to receive red blood cell transfusion or erythropoietin over the course of study participation
21. Subject is using pramlintide (Symlin), SGLT2 inhibitors, GLP agonists, biguanides, DPP-4 inhibitors or sulfonylureas more than 2 weeks from time of screening
22. Subject has been diagnosed with chronic kidney disease requiring dialysis or resulting in chronic anemia
23. Subject has history of cardiovascular disease defined as any ischemic related event or clinically significant arrhythmia.
24. Subject has hypothyroidism and has out of reference range thyroid-stimulating hormone (TSH) on screening visit (prior labs in the last 3

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| | <p>months are sufficient). Subject may repeat TSH draw to verify eligibility if not in range</p> |
| <p>Study Timeline</p> | <p>Each subject’s participation will be comprised of the following scheduled visits listed below and additional unscheduled visits (at investigational center or phone call) that could occur.</p> <p>Visit Schedule</p> <ul style="list-style-type: none"> • Visit 1 (Office): Screening and Consent. <ul style="list-style-type: none"> • Screening (including HbA1c) and consent • Visit 2 (Office) Study & Device Training and Study Initiation Visit: May occur up to 28 days after Visit 1 <ul style="list-style-type: none"> • Confirmation of eligibility criteria • Upload pump and glucose meter into CareLink • Study and device training • Study devices disbursement • Completion of study questionnaire by subject • Ask subject about any AEs • Visit 3 (Telephone Visit): Follow Up and Study Procedures Reminder- Approximately 14 (±3) Days after Visit 2 <ul style="list-style-type: none"> • Upload reminder • Daily Logs and acetaminophen log(s) reminder • Ask subject about any AEs • Visit 4 (Office): Approximately 30 (±5) days after Visit 2 <ul style="list-style-type: none"> • Collect used infusion sets • Upload pump and glucose meter into CareLink • Ask subject about any AEs • Daily Logs and acetaminophen log(s) reminder • Collect Daily Logs and acetaminophen log(s) • Visit 5 (Telephone Visit): Follow Up and Study Procedures Reminder- Approximately 45 (±5) Days after Visit 2 <ul style="list-style-type: none"> • Upload reminder • Daily Logs and acetaminophen log(s) reminder • Ask subject about any AEs • Visit 6 (Office): Approximately 60 (±7) Days after Visit 2 <ul style="list-style-type: none"> • Collect used infusion sets • Upload pump and glucose meter into CareLink |

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| | <ul style="list-style-type: none"> • Ask subject about any AEs • Daily Logs and acetaminophen log(s) reminder • Collect Daily Logs and acetaminophen log(s) • Visit 7 (Office) End of Study Visit: Approximately 100 (+10) days after Visit 2 or +7 Days after the last infusion set removal <ul style="list-style-type: none"> • Collect Daily Logs and acetaminophen log(s) • Collect used infusion sets • Upload pump and glucose meter into CareLink • Collect HbA1c • Ask subject about any AEs • Completion of study questionnaire by subject |
| <p>Safety Monitoring/Risk Analysis</p> | <p>Safety monitoring/risk analysis details are outlined in Section 8.6.</p> |
| <p>Device Deficiencies</p> | <p>Subject and investigational center reports of device deficiencies will be collected by subjects and/or investigational centers calling the 24-Hour Technical Support (TS) for device troubleshooting and device complaints. For additional information, see Section 12.</p> |
| <p>Study Success Criteria</p> | <p>Success Criteria for the study will be the achievement of the infusion set failure rate due to unexplained hyperglycemia at 6 or 7 days shall be $\leq 20\%$ (95% upper CI), as the mean failure rate is expected to be $\sim 16\%$.</p> |
| <p>Study Stopping Rules for Entire Study</p> | <p>The study will stop if there is:</p> <ol style="list-style-type: none"> 1. An Unanticipated Adverse Device Effects (UADE). 2. Site will notify the sponsor within approximately 24 hours of receiving knowledge of a SADE event. Sponsor will assess and determined if unanticipated. 3. Sponsor will notify FDA within 72 hours of notification of a SADE 4. Clinical Events Committee (CEC) is to review and adjudicate the event within 7 days from the time that the sponsor is notified. 5. CEC will provide recommendation to the sponsor on whether or not the entire study must be stopped, including study procedures for subjects who have already received study devices |
| <p>Subject Stopping Rules</p> | <ol style="list-style-type: none"> 1. Unanticipated Adverse Device Effects (UADEs); 2. Diabetic Ketoacidosis (DKA); 3. Severe hypoglycemia events that result in subject requiring paramedic assistance, an ER visit or subjects who experience seizure, coma or death. |

Statistical Analysis for Endpoints and Hypothesis

Primary Safety Endpoint

- Incidence of Serious Adverse Events (SAE)
- Incidence of Serious Adverse Device Effects (SADE)
- Incidence of Unanticipated Adverse Device Effects (UADE)
- Incidence of Severe Hypoglycemia
- Incidence of Severe Hyperglycemia
- Incidence of DKA
- Incidence of skin infections at infusion set insertion site

Primary Effectiveness Endpoint

The primary effectiveness endpoints will be independently evaluated in blocks of 2 in the study. Analysis will be done in the blocks of 2 as:

- Novolog™*
- Humalog™*

Rate of infusion set failure due to unexplained hyperglycemia (i.e. suspected occlusion) at the end of Day 6. The rate of infusion set failure is defined as the number of infusion set removals associated with unexplained hyperglycemia divided by total number of infusion sets inserted.

Secondary Effectiveness Endpoint

The secondary effectiveness endpoints will be independently evaluated in blocks of 2 in the study. Analysis will be done in the blocks of 2 as:

- Novolog™*
- Humalog™*

Rate of infusion set failure due to unexplained hyperglycemia (i.e. suspected occlusion) at the end of Day 7. The rate of infusion set failure is defined as the number of infusion set removals associated with unexplained hyperglycemia divided by total number of infusion sets inserted.

Descriptive Endpoints

- Descriptive summary of all infusion set failures and the day they failed. All causes of infusion set failures, such as removal due to discomfort of site, accidental removals, kinked or bent cannula, leakage, loss of insertion (e.g. patient does not appear to be receiving insulin within 12 hours after infusion set is inserted), mechanical failure, and adhesive issue will be collected and analyzed.

- HbA1c changes from baseline to the end of study.
- All severe hyperglycemic events as defined in Section 10.2 will be summarized whether they are device related or not or whether they are associated with infusion set failure or not.
- Descriptive summary of infusion set change at baseline

Device Deficiencies

Descriptive summary will be used to characterize device deficiencies.

Subject Feedback

Descriptive summary will be used to characterize study questionnaire results.

Sample Size Justification

The infusion set failure rate due to unexplained hyperglycemia (i.e. suspected occlusion) of 16% (FDA response Q180616/S001), around 20% upper limit, was used when generating simulation dataset for Day 6 and Day 7 evaluations, as supported by discussions with the Agency. Sample size estimation was performed based on data from Dr. Buckingham EWIS data in 2018 (20 subjects each wore 2 EWIS infusion sets with no missing data). The suspected occlusion occurrence rate was 12.5%. Subjects were sampled to enter the simulation dataset with a vector of 12 measurements (12 EWIS wears). The resulting simulation datasets have correlated occurrence rates. Therefore, a repeated-measure Generalized Linear Model (GENMOD) was used to determine the upper boundary of the occurrence rate. Using all available data for each subject, the intercept of a null GLM model, with a repeated factor for infusion set wear day, was used to estimate the overall occurrence rates. A simulation was performed 1000 times and the upper boundary of the intercept of the GENMOD was tested against the critical value of 20%. The results of the simulation indicated that a sample size of 100 per insulin group will yield power of over 80% to demonstrate that the infusion set failure rate due to unexplained hyperglycemia is not inferior to 20%, with two sided 0.05 significance level, which will ensure that $\leq 16\%$ rate is achieved.

3. Introduction

3.1. Background

Continuous subcutaneous insulin infusion (CSII) is an effective method for diabetic treatment. However, using current infusion sets, the insulin absorption decreases requiring patients to change infusion set every 2-3 days. Currently, the MiniMed Quick-set™ infusion sets are limited to 48-72 hours use (or per instruction by healthcare professionals). Medtronic Extended Wear Infusion Set (EWIS, MMT-405) should enhance patient wear time up to 7 days. This is done while maintaining insulin formulation stability (including physical, chemical, and microbiological stability) during infusion through the pump/infusion set system over extended time (up to 7 days).

This EWIS investigational device, as well as the early EWIS versions, has been used in previous animal/human feasibility trials, where the investigational device successfully extended the effective subcutaneous insulin infusion duration up to 7 days.

3.2. Purpose

The purpose of this study is to collect confirmatory clinical data to support 6 or 7 days wear of EWIS.

4. Objectives and Endpoints

4.1. Objectives

4.1.1. Primary Objective(s)

The objective of this study is to evaluate the EWIS in patients with type 1 diabetes on insulin pump therapy.

4.2. Endpoints

4.2.1. Primary Safety Endpoint

- Incidence of Serious Adverse Events (SAE)
- Incidence of Serious Adverse Device Effects (SADE)
- Incidence of Unanticipated Adverse Device Effects (UADE)
- Incidence of Severe Hypoglycemia
- Incidence of Severe Hyperglycemia
- Incidence of DKA
- Incidence of skin infections at infusion set insertion site

4.2.2. Primary Effectiveness Endpoint

The primary effectiveness endpoints will be independently evaluated in blocks of 2 in the study. Analysis will be done in the blocks of 2 as:

- Novolog™*
- Humalog™*

Rate of infusion set failure due to unexplained hyperglycemia (i.e. suspected occlusion) at the end of Day 6. The rate of infusion set failure is defined as the number of infusion set removals associated with unexplained hyperglycemia divided by total number of infusion sets inserted.

4.2.3. Secondary Effectiveness Endpoint

The secondary effectiveness endpoints will be independently evaluated in blocks of 2 in the study. Analysis will be done in the blocks of 2 as:

- Novolog™*
- Humalog™*

Rate of infusion set failure due to unexplained hyperglycemia (i.e. suspected occlusion) at the end of Day 7. The rate of infusion set failure is defined as the number of infusion set removals associated with unexplained hyperglycemia divided by total number of infusion sets inserted.

4.2.4. Descriptive Endpoints

- Descriptive summary of all infusion set failures and the day they failed. All causes of infusion set failures, such as removal due to discomfort of site, accidental removals, kinked or bent cannula, leakage, loss of insertion (e.g. patient does not appear to be receiving insulin within 12 hours after infusion set is inserted), mechanical failure, and adhesive issue will be collected and analyzed.
- HbA1c changes from baseline to the end of study.
- All severe hyperglycemic events as defined in Section 10.2 will be summarized whether they are device related or not or whether they are associated with infusion set failure or not.
- Descriptive summary of infusion set change at baseline

4.2.5. Device Deficiencies

Descriptive summary will be used to characterize device deficiencies.

4.2.6. Subject Feedback

Descriptive summary will be used to characterize study questionnaire results.

5. Study Design

This study is a multi-center, non-randomized, prospective single arm study with type 1 patients with diabetes on insulin pump therapy with Continuous Glucose Monitoring (CGM).

A total of up to 300 subjects will be enrolled at up to 20 investigational centers in the US in order to have 240 subjects meeting eligibility criteria. Each subject will wear their own MiniMed™ 670G insulin system. Each subject will be given 12 infusion sets to wear (each infusion set for at least 174 hours, or until infusion set failure if this occurs before 174 hours). The infusion set with the longest length (43 in) will be used for this study. Subjects will change insulin reservoirs at least every 174 hours. The infusion set(s) or reservoir(s) can be replaced independent of each other as referenced in the subject instructions. The time of infusion set insertion will be taken from Daily Log.

Infusion set failure used to determine primary endpoint is defined as any one of the following:

- Unexplained Hyperglycemia is defined as the following (See Primary Effectiveness Endpoint Sections 4.2.2 and 13.5.2) :
 - The study meter glucose >250 mg/dL (>3 hours post-meal) which may include time during subject's sleeping hours
 - Failure of a correction dose(s) to lower the study meter glucose by at least 50 mg/dL.
 - One additional correction dose may be given after first correction dose and recommended to use the bolus calculator. The infusion set may remain in the body if the glucose improves after second correction dose within 90 minutes. Please note: if the glucose improves after the correction doses, and the infusion set does not need to be changed then this would NOT be considered an adverse event (e.g. unexplained hyperglycemia) and NOT considered an infusion set failure.
 - SMBG should be checked every 60 minutes during this time
- The presence of serum ketones ≥ 0.6 mmol/L with a study meter glucose >250 mg/dL in the absence of illness and blood glucose that does not respond to insulin correction dose(s) as described above. (See Primary Safety Endpoint Sections 4.2.1 and 13.5.1)
- There are signs of infection at the infusion site (i.e. erythema (> 1 cm in diameter) with warmth, pain, and/ or induration) . (See Primary Safety Endpoint Section 4.2.1 and 13.5.1)

Other known causes of infusion set failures which may or may not associated with hyperglycemia will be collected and analyzed as part of the overall safety assessment:

- Accidental removals
- Leakage
- Loss of insertion (e.g. patient does not appear to be receiving insulin within 12 hours after infusion set is inserted)
- Kinked or bent cannula
- Removal due to discomfort at site
- Mechanical failure
- Adhesive issue

All severe hyperglycemic events as defined in Section 10.2 will be summarized: whether they are device related or not or whether they are associated with infusion set failure or not.

At home, the subject will be expected to inspect their infusion site on a daily basis and if they observe signs of infection (i.e. erythema > 1 cm in diameter with warmth, pain, and/ or induration) at the infusion site, they should call the investigational center. Also, subjects are requested to upload data from their insulin pump and CONTOUR® NEXT LINK 2.4 study meter into CareLink™ Personal For Clinical Research weekly. In addition to the study procedures, the subjects are to continue their standard routine care.

At each study visit, insulin pump and CONTOUR® NEXT LINK 2.4 study meter will be uploaded into CareLink™ Personal For Clinical Research.

Subjects will be instructed to test their blood glucose using the CONTOUR® NEXT LINK 2.4 study meter at least 4-6 times each day (before meals and bedtime). Subjects will be instructed to check blood ketones using a Precision Xtra™* ketone meter if the CONTOUR® NEXT LINK 2.4 study meter reading is greater than 250 mg/dL (ketones do not need to be checked if it is less than 3 hours post-prandial).

Subjects will be required to upload their pump and glucose meter at Visit 2 in order to obtain the previous month of CareLink™ data.

5.1. Duration

The study is anticipated to last approximately 12 months from first subject enrollment to completion of all data entry. Subjects can expect to participate for approximately 12-16 weeks.

5.2. Rationale

The rationale for conducting this study is to obtain infusion set characterization (e.g., survival of infusion set and overall safety) in order to receive market approval.

6. Product Description

6.1. Intended Population

A population of type 1 diabetes patients on insulin pump therapy will be studied. The study population will have a large range for glycemic control, as measured by HbA1c.

They will be enrolled in the study if currently using the MiniMed™ 670G insulin system.

6.2. Investigational Device

Medtronic Extended Wear Infusion Set (EWIS)

Infusion sets are single-used by patients with diabetes mellitus requiring subcutaneous administered insulin to maintain acceptable blood glucose levels. The EWIS is an infusion set with a pre-loaded inserter, inserted into the subcutaneous tissue of a user, and is connected to a Medtronic MiniMed medication reservoir (for use with a Medtronic MiniMed insulin pump). There are three basic components of the infusion set:

1. Catheter hub with cannula and adhesive patch
2. Tubing
3. Tubing connector

The cannula, connected to the catheter hub, is introduced into subcutaneous tissue (i.e. infusion site). The tubing connects the catheter hub and the tubing connector to provide the fluid from the medication reservoir housed within the insulin pump.

The catheter hub with cannula in the investigational device remains unchanged from the current MiniMed Mio™ Advance Infusion Set (MMT-242/MMT-244, the base infusion set) for the 6 mm/9 mm cannula length. The investigational device utilizes a new high-performance tubing connector (H-Cap) to replace the current proprietary Paradigm connector (P-Cap), an extended wear tubing to replace the current tubing, and an extended wear adhesive patch to replace current adhesive patch on the predicate MiniMed Mio™ Advance Infusion Set. **Figure 1** and **Figure 2** illustrate the investigational device and the tubing connectors.

The existing MiniMed Mio™ Advance Infusion Set is indicated to be worn for up to 3 days. The EWIS enhances patient wear time to 7 days. This is done by maintaining insulin formulation stability (including physical, chemical, and microbiological stability) during infusion through the pump/infusion set system over extended time (up to 7 days).

Figure 1. EWIS

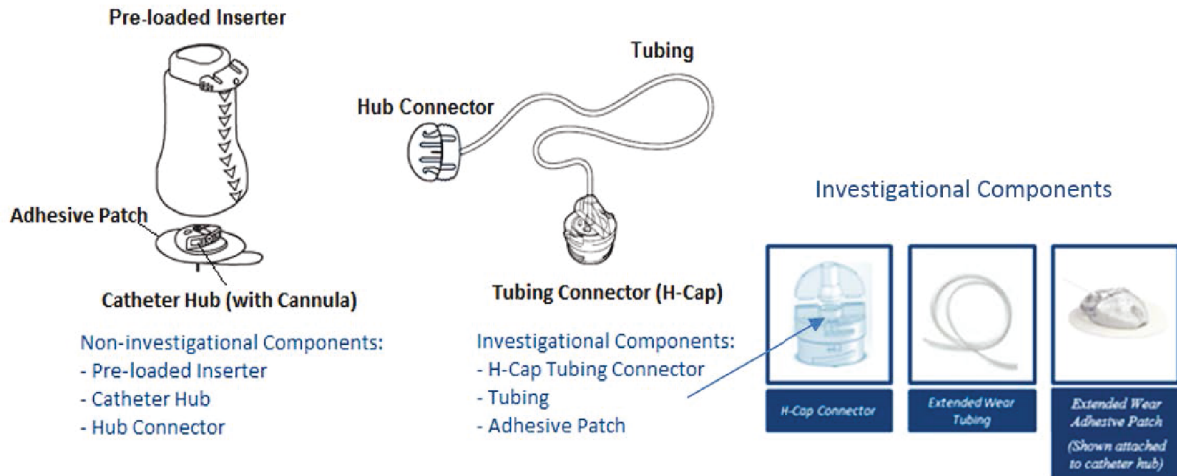


Figure 2. Connector, P-Cap (Left); High-Performance Connector, H-Cap (Right)



6.3. Non-Investigational Devices

The following non-investigational devices designated for use in the study are described in this section.

6.3.1. MiniMed™ 670G Insulin Pump, version 3.0 – not provided through study

The MiniMed™ 670G Insulin Pump, version 3.0 is capable of continuous insulin delivery, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin. When used with the CGM components (Guardian™ Sensor (3), Guardian™ Link (3) Transmitter), the pump system is capable of continuous or periodic monitoring of glucose levels in the interstitial fluid under the skin and detection of possible low or high blood glucose episodes. The pump also displays SG values, storing this data so that it can be retrospectively analyzed to Cohort patterns and improve diabetes management. These features are similar to the commercially available Medtronic sensor-enabled system (e.g. MiniMed™ 530G System (P120010) in the US, MiniMed™ 640G and Veo System OUS, which has the threshold suspend feature).

The MiniMed™ 670G Insulin Pump also includes the hybrid closed loop (HCL) algorithm as part of the SmartGuard® collection of features that may be enabled by the user. SmartGuard is comprised of Manual Mode Low Management, which includes the suspend on low feature (suspends insulin delivery when a pre-set low SG threshold is reached), the suspend before low feature (enables insulin to suspend 30 minutes before a pre-set low SG threshold is reached) and Auto Mode (hybrid closed loop) feature. The Auto Mode and Manual Mode -Low Management features cannot be active at the same time.

The pump may also be used as a simple pump without CGM or as a sensor augmented pump without the SmartGuard features.

When Auto Mode is enabled on the MiniMed™ 670G insulin pump, the SG values received from the Guardian™ Link (3) Transmitter by the insulin pump will be used to automatically calculate the insulin dose. It will then deliver insulin to the patient, at five-minute intervals, to achieve glycemic control.

With the HCL system, subjects must still deliver bolus insulin for meals and corrections to the target SG level, as calculated by the insulin to carbohydrate ratio. This ratio is determined by the HCP/patient. In addition, the setting for active insulin must be programmed. Basal rates are set for period of open loop therapy.

When Auto Mode is not enabled, the user may enable the Low Management feature. Here, basal rate delivery will be suspended either when the SG reached a programmed low threshold (Suspend on Low) or before the SG value has reached the programmed low threshold (Suspend before Low).

Figure 3. MiniMed™ 670G Insulin Pump, version 3.0



6.3.2. Guardian™ Sensor (3)

The Guardian™ Sensor (3) glucose sensor, referred to as Guardian™ Sensor (3) in this protocol, is a sensor that contains one microelectrodes with a thin coating of glucose oxidase beneath several layers of biocompatible membrane. The sensor represents the next generation in the Enlite™ sensor family with design changes in the engineering reports for improved accuracy. It is intended to penetrate the skin at a 90-degree angle, similar to the Enlite™ sensor. The sensor is tubeless and as a result has a smaller volume than previous Medtronic MiniMed sensors. An introducer needle penetrates the skin surface and provides support for the sensor microelectrode during insertion. The sensor continuously converts small amounts of glucose from the subject's interstitial fluid into an electronic signal that is received by a transmitter or recorder, the strength of which is proportional to the amount of glucose present in the blood. The electrode is composed of embedding, signal-conducting and insulating layers.

6.3.3. Guardian™ Link (3) Transmitter

The Guardian™ Link (3) transmitter is a device that has the same housing and sensor interface as the MiniLink™ transmitter. However, the internal electronics and firmware of the Guardian™ Link (3) transmitter are new. Like the MiniLink™ transmitter, the Guardian™ Link (3) transmitter reads the electronic signal generated by the sensor. In addition, the transmitter contains a custom Application Specific Integrated Circuit (ASIC), which enables EIS. The EIS measurements are used as diagnostics for the sensor, which are incorporated into the sensor calibration logic.

In addition, the transmitter also contains the sensor calibration algorithm which converts the sensor signal to a SG value using calibration BG values from a meter relayed to the transmitter through the pump. The transmitter transmits the calculated glucose data to the pump via 2.4GHz RF technology (Tel-D communication protocol). Some elements of the new calibration logic include prompting the user to calibrate when needed, referred to as "Smart Cal," instead of strictly scheduled time-based calibration requirements. The new algorithm is designed to improve and optimize performance when paired with the sensors.

In this study the Guardian™ Link (3) transmitter will be connected to a Guardian™ Sensor 3.

Figure 4. Guardian Link (3) Transmitter



6.3.4. One-Press Serter

The One-Press Serter, referred to as the Serter (Figure 3) in this protocol, is an insertion device that is used to ensure correct placement of the Guardian™ Sensor (3) into the user's subcutaneous tissue. Insertion is triggered when the two spring loaded buttons on the sides of the Serter are pressed simultaneously. The Serter is intended as a single patient, non-sterile, multi-use device.

Figure 5. One-Press Serter



6.3.5. Charger

The Charger is used to recharge the Guardian™ Link (3) Transmitter as needed. A fully charged battery provides up to 7 days of Guardian™ Link (3) Transmitter use. The system includes a battery charger that will recharge the device according to the user guide.

6.3.6. Tester

The 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.

6.3.7. CareLink™ Personal For Clinical Research

Medtronic CareLink™ Personal Management Software for Diabetes For Clinical Research is an internet-based software system which allows the device data to be viewed and easily evaluated by the subject and his/her physician. A personal computer (PC) is used to access the Medtronic CareLink™ Personal For Clinical Research system via the Internet, which then allows subjects and investigational center staff to upload data from Medtronic MiniMed insulin pumps and a range of system-supported, third-party BG meters. For the purposes of this study, all references to CareLink™ Personal For Clinical Research software in this document relate to the clinical support version of Medtronic CareLink™ Personal Management Software for Diabetes and throughout the protocol will be referred to as CareLink™ Personal For Clinical Research software. The data contained in CareLink™ Personal For Clinical Research is accessible to users using a standard browser, i.e., Microsoft® Internet Explorer, on an Internet enabled PC.

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

- The internet to the web server;
- Web server to the application server;
- Application server to the database server.

6.3.8. CONTOUR® NEXT LINK 2.4 Study Meter

A CONTOUR® NEXT LINK 2.4 BG meter, referred to as the CONTOUR® NEXT LINK 2.4 study meter in this protocol, will be provided to all subjects. The radio frequency (RF)enabled study meter measures a subject's capillary blood glucose level using the CONTOUR® NEXT Strips, which is then used to calibrate the glucose sensor. The result of the finger stick (capillary self-monitoring of blood glucose [SMBG]) reading is entered into the MiniMed™ 670G insulin pump and can be stored in its memory as a glucose data point. The MiniMed™ 670G insulin pump asks if the user wants to use the linked meter BG for calibration. If yes is selected, the glucose value will be stored in memory as a calibration data point.

6.3.9. Abbott™* Precision Xtra™* Blood Glucose & Ketone Monitoring System

The Abbott™* Precision Xtra™* Blood Glucose& Ketone Monitoring System, referred to as Precision Xtra™* ketone meter throughout this protocol, can measure both blood glucose (sugar) and blood β -Ketone. In this study, however, the meter will only be used to measure β -Ketone levels, which will be collected for reporting and review (see Investigator/Coordinator binder for details) and as described in the body of this study protocol. This particular meter will be used because it is the only commercially available meter which allows quantification of blood β -Ketone levels and is the preferred patient method of testing over urine testing.

Note: In the event the blood ketone meter is not used to collect ketone values, urine ketones must be measured and entered into CareLink™ Personal For Clinical Research software instead.

6.4. Consumable devices

Glucose meter accessories and other consumable materials will be provided to subjects for use in the study.

6.5. MiniMed™ 670G Insulin Pump and Insulin

Subjects will use their own MiniMed™ 670G insulin pump and willing to use rapid-acting analogue insulin (Novolog™* or Humalog™*) during this study.

6.6. Anticipated Devices Change

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

6.7. Device Accountability

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

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

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

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

Table 1 Device Accountability Requirements

| Device | Record on Site Received eCRF | Record Disbursement, Returned or Not Returned on Subject Device Disposition eCRF | Subject Return Device to Investigational Center | Record Returned or Not Returned on Site Returned eCRF | Site Return Device to Sponsor at Conclusion of Study |
|--|------------------------------|--|---|---|---|
| EWIS (MMT-405) | Yes | Yes | Yes (Used and unused) | Yes | Yes (Used and unused) |
| Guardian™ Sensor (3) (MMT-7020) | No | No | No | No | Used and unused do not need to be returned to sponsor |
| Guardian™ Link (3) Transmitter (MMT-7811)* | No | No | No | No | Yes (Used and unused) |
| One-Press Serter (MMT-7512)* | No | No | No | No | Yes (Unused only) |

| Device | Record on Site Received eCRF | Record Disbursement, Returned or Not Returned on Subject Device Disposition eCRF | Subject Return Device to Investigational Center | Record Returned or Not Returned on Site Returned eCRF | Site Return Device to Sponsor at Conclusion of Study |
|--|------------------------------|--|---|---|---|
| Charger (MMT-7715)* | No | No | No | No | Yes (Unused only) |
| Tester (MMT-7736L)* | No | No | No | No | Yes (Unused only) |
| CONTOUR® NEXT LINK 2.4 study meter (MMT-1152/1352) | Yes | Yes | No | Yes | Used and unused do not need to be returned to sponsor |
| Precision Xtra™* ketone meter | No | No | No | No | Return unused to sponsor |

*Devices may be combined and distributed in kits.

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

6.7.1. Receipt and Inventory of Investigational Devices by Investigational Center

- Upon receipt of the study devices, investigational center staff take inventory of the shipment, making sure that information on the packing slips/invoices matches exactly the contents of the containers, as applicable, including:
 - Ship to Address
 - Reference Number
 - Device Type
 - Quantity
 - Quantity per package
 - Lot number (where applicable)
 - Serial number (where applicable)
- Ensure that devices and supplies received have not reached or exceeded their expiration date

- Sign and date the packing slips/invoices, noting any discrepancies, and file in appropriate study binder
- Notify the study monitor of any discrepancies
- Enter the study device information on the appropriate electronic case report form (eCRF) in the study database.

6.7.2. Storage of Study Devices at Investigational Center

Study devices are to be stored in a secure environment with access limited to authorized research personnel. Study devices are stored in the proper environmental conditions as identified in the Instructions for Use (IFU)/labeling.

The infusion set has been tested successful for the following storage conditions:

- A temperature range of -20 °C to 50 °C
- A relative humidity range of 5% to 95%, non-condensing
- An atmospheric pressure range of 496.4 hPa (5500 m altitude) to 1061.8 hPa (-400 m depth)

6.7.3. Disbursement of Study Devices

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

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

6.7.4. Return or Disposal of Study Devices

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

Requirements for return of devices by subjects to the investigational center and return of device by the investigational center to the sponsor are listed in in Table 1. The devices that are being returned to the investigational center may be returned to the sponsor as subjects complete the study, at the EOS visit or upon sponsor request.

Other unused consumable devices (i.e., alcohol wipes, study meter supplies, tape, etc.), supplies or materials may be returned to the sponsor, they may be retained by investigational centers for educational purposes only, or they may be disposed of properly by investigational center staff.

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

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

7. Selection of Subjects

7.1. Study Population

A total of up to 300 subjects will be enrolled at up to 20 investigational centers in the US in order to have 240 subjects meeting eligibility criteria . Subjects will be replaced who have early withdrawal.

- Insulin Utilization
 - N = 100 Humalog™*
 - N = 100 NovoLog™*

7.2. Subject Enrollment

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

A subject will be assigned a unique study subject ID (SID) via the eCRF, which is a 9-digit code (298XXXXXX). The first three numbers refer to the CIP number (298), the next three numbers refer to the investigational center number, and the last 3 numbers refer to the subject number assigned during Visit 1 (e.g., 298002001 is subject 001 from site 002).

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

7.3. Inclusion Criteria

Subjects will be considered for enrollment in the study if they meet all of the following criteria:

1. Subject is age 18 – 80 years at the time of screening
2. Subject has type 1 diabetes for more than one year

Study specific inclusion criteria

3. Subject is on the MiniMed™ 670G insulin pump therapy within 1 year prior to screening and willing to utilize Auto Mode and CGM with Guardian™ Sensor (3) during the study.
4. Subject is willing and able to perform study procedures as per investigator discretion
5. Subject is willing to take one of the following insulins and can financially support the use of either of the 2 insulin preparations throughout the course of the study (i.e. co-payments for insulin with insurance or able to pay full amount):
 - a. Humalog™* (insulin lispro injection)
 - b. NovoLog™* (insulin aspart)

7.4. Exclusion Criteria

Subjects who meet any of the following criteria are not eligible for study participation and **these exclusion criteria are study specific:**

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 device in the last 2 weeks.
2. Subject is female and has a positive pregnancy screening test
3. Subject is female of child bearing age and who is sexually active should be excluded if she is not using a form of contraception deemed reliable by investigator
4. Subject is female and plans to become pregnant during the course of the study
5. Subject has Glycosylated hemoglobin (HbA1c) > 8.5 % at time of screening.

Note: All HbA1c blood specimens will be sent to and tested by a NGSP certified Central Laboratory. HbA1c testing must follow National Glycohemoglobin Standardization Program (NGSP) standards.

6. Subject has had a history of 1 or more episodes of severe hypoglycemia, which resulted in any the following during the 6 months prior to screening
 - a. Medical assistance (i.e. Paramedics, Emergency Room [ER] or Hospitalization)
 - b. Coma
 - c. Seizures
7. Subject has taken any oral, injectable, or IV glucocorticoids within 8 weeks from time of screening visit, or plans to take any oral, injectable, or IV glucocorticoids during the course of the study.
8. Subject is unable to tolerate tape adhesive in the area of infusion set
9. Subject has any unresolved adverse skin condition in the area of infusion set placement (e.g., psoriasis, dermatitis herpetiformis, rash, Staphylococcus infection)
10. Subject has infection in the area of infusion set placement at time of screening
11. Subject has had Diabetic Ketoacidosis (DKA) in the 12 months prior to screening visit.
12. Subject is currently abusing illicit drugs
13. Subject is currently abusing alcohol
14. Subject is on dialysis (for renal failure)
15. Subject has history of adrenal disorder
16. Subject has a history of inpatient psychiatric treatment in the past 6 months prior to screening
17. Subject has any condition that the Investigator believes would interfere with study participation
18. Subject has a history of visual impairment which would not allow subject to participate in the study and perform all study procedures safely, as determined by the investigator
19. Subject has a sickle cell disease, hemoglobinopathy; or has received red blood cell transfusion or erythropoietin within 3 months prior to time of screening
20. Subject plans to receive red blood cell transfusion or erythropoietin over the course of study participation
21. Subject is using pramlintide (Symlin), SGLT2 inhibitors, GLP agonists, biguanides, DPP-4 inhibitors or sulfonylureas more than 2 weeks from time of screening
22. Subject has been diagnosed with chronic kidney disease requiring dialysis or resulting in chronic anemia
23. Subject has history of cardiovascular disease defined as any ischemic related event or clinically significant arrhythmia.

24. Subject has hypothyroidism and has out of reference range thyroid-stimulating hormone (TSH) on screening visit (prior labs in the last 3 months are sufficient). Subject may repeat TSH draw to verify eligibility if not in range

8. Study Procedures

8.1. Study Timeline

Each subject's participation will be comprised of the following scheduled visits listed below and additional unscheduled visits (at investigational center or phone call) that could occur.

Visit Schedule

- **Visit 1 (Office): Screening and Consent.**
 - Screening (including HbA1c) and consent

- **Visit 2 (Office) Study & Device Training and Study Initiation Visit: May occur up to 28 days after Visit 1**
 - Confirmation of eligibility criteria
 - Upload pump and glucose meter into CareLink
 - Study and device training
 - Study devices disbursement
 - Completion of study questionnaire by subject
 - Ask subject about any AEs

- **Visit 3 (Telephone Visit): Follow Up and Study Procedures Reminder- Approximately 14 (± 3) Days after Visit 2**
 - Upload reminder
 - Daily Logs and acetaminophen log(s) reminder
 - Ask subject about any AEs

- **Visit 4 (Office): Approximately 30 (± 5) days after Visit 2**
 - Collect used infusion sets
 - Upload pump and glucose meter into CareLink
 - Ask subject about any AEs
 - Daily Logs and acetaminophen log(s) reminder
 - Collect Daily Logs and acetaminophen log(s)

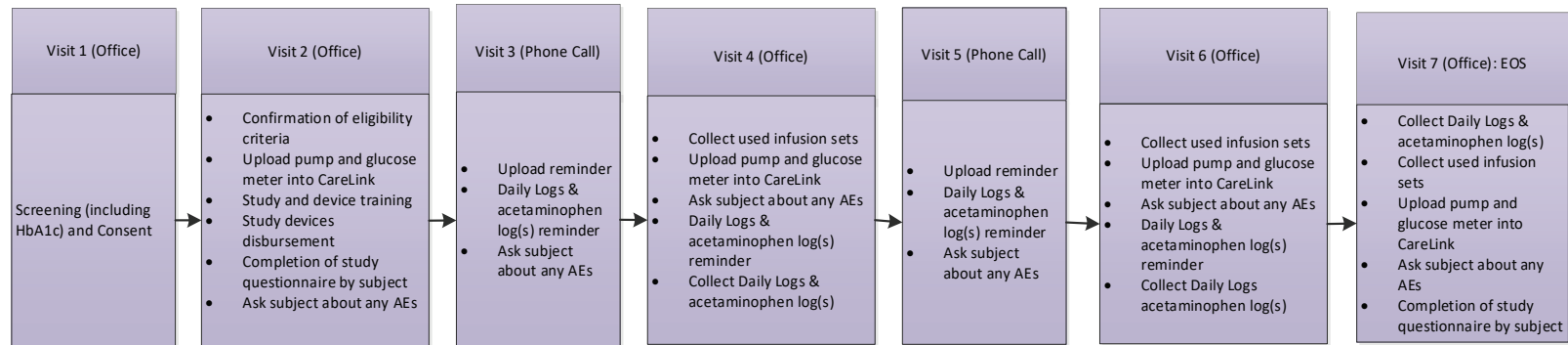
- **Visit 5 (Telephone Visit): Follow Up and Study Procedures Reminder- Approximately 45 (± 5) Days after Visit 2**
 - Upload reminder
 - Daily Logs and acetaminophen log(s) reminder
 - Ask subject about any AEs

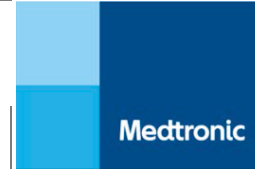
- **Visit 6 (Office): Approximately 60 (± 7) Days after Visit 2**
 - Collect used infusion sets
 - Upload pump and glucose meter into CareLink
 - Ask subject about any AEs
 - Daily Logs and acetaminophen log(s) reminder
 - Collect Daily Logs and acetaminophen log(s)

- **Visit 7 (Office) End of Study Visit: Approximately 100 (+10) days after Visit 2 or +7 Days after the last infusion set removal**
 - Collect Daily Logs and acetaminophen log(s)
 - Collect used infusion sets
 - Upload pump and glucose meter into CareLink
 - Collect HbA1c
 - Ask subject about any AEs
 - Completion of study questionnaire by subject



Figure 6. Visit Schedule





8.2. Schedule of Events

Refer to Table 2 for the Visit Details.

Table 2. Visit Details

| | Visit 1 | Visit 2 | Visit 3 Phone | Visit 4 | Visit 5 Phone | Visit 6 | Visit 7 Exit |
|---|----------------|----------------|----------------------|----------------|----------------------|----------------|---------------------|
| Things to do: | | | | | | | |
| Administer Informed Consent | x | | | | | | |
| Assess Subject Eligibility | x | | | | | | |
| Obtain demographic and baseline characteristics according to CRF questions: <ul style="list-style-type: none"> • Age • Gender • Race • Ethnicity • Height and Weight Note: BMI will be calculated automatically in the study database, based on height and weight measurements entered. <ul style="list-style-type: none"> • Date of diabetes diagnosis | x | | | | | | |
| Collect concomitant medication data | x | | | | | | |
| Obtain Urine Pregnancy for females of child bearing age (Point of Care or local lab) | x | | | | | | |
| Obtain TSH (Prior labs in the last 3 months are sufficient) § TSH may be repeated once within 14 days of screening for values that are out of reference range | x | | | | | | |

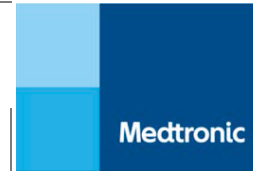
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| | Visit 1 | Visit 2 | Visit 3 Phone | Visit 4 | Visit 5 Phone | Visit 6 | Visit 7 Exit |
|---|---------|---------|---------------|---------|---------------|---------|--------------|
| Confirm subject eligibility, including lab results, prior to moving forward with any study procedures | | x | | | | | |
| Collect HbA1c Lab Test 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. | x | | | | | | x |
| Enroll subjects in CareLink Personal For Clinical Research - Refer to CareLink Personal For Clinical Research Site Enrollment Instructions | | x | | | | | |
| Provide subjects with study reference materials | | x | | | | | |
| Disburse the CONTOUR® NEXT LINK 2.4 study meter | | x | | | | | |
| Disburse the Precision Xtra™* ketone meter | | x | | | | | |
| Ask subjects about the use of non-study glucose meter(s), any pump other than the MiniMed™ 670G and if subjects replaced any part of the EWIS investigational set before using all 12 EWIS sets (reservoir, tubing or any aspect of insulin set) with their own infusion set (reservoir, tubing or any aspect of infusion set) during the study. (See 8.9 for Deviation Handling) | | x | | x | | x | x |
| Disburse the EWIS <ul style="list-style-type: none"> • Provide subjects specimen containers for each used infusion set (dry with biohazard labeling) • Instruct subjects to return all used (in the specimen container) and unused EWIS to the investigational center. | | x | | x | | x | |
| Disburse other study supplies (includes tape measure for infusion site) as needed | | x | | x | | x | |
| Disburse Daily Logs and acetaminophen logs | | x | | x | | x | |
| Collect and Review Daily Logs for any unreported adverse event(s) | | | | x | | x | X |

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| | Visit 1 | Visit 2 | Visit 3 Phone | Visit 4 | Visit 5 Phone | Visit 6 | Visit 7 Exit |
|---|---------|---------|---------------|---------|---------------|---------|--------------|
| Collect and Review acetaminophen log(s) | | | | x | | x | x |
| Collect/Assist with Questionnaires - Refer to the following Study Questionnaires Material: <ul style="list-style-type: none"> Extended Wear Infusion Set Questionnaire – Intake Extended Wear Infusion Set Questionnaire – Exit | | x | | | | | x |
| At study end, the site will complete the following questionnaire assessing, at a minimum: “The user guide and instructional materials provided the instructions I needed.” (strong agreement or disagreement ranked using 5 point Likert scale) | | | | | | | x |
| Schedule the next visit date and time | x | x | x | x | x | x | |
| Collect used infusion set(s) | | | | x | | x | x |
| Collect unused infusion set(s) | | | | | | | x |
| Upload the MiniMed™ 670G pump and CONTOUR® NEXT LINK 2.4 study meter during office visit | | x | | x | | x | x |
| Enter eCRFs into the study database as appropriate | x | x | x | x | x | x | x |
| Collect study devices from subjects upon exit from study | | | | | | | x |
| Things to ask about | | | | | | | |
| Provide subjects with the opportunity to bring up study-related questions and concerns. | x | x | x | x | x | x | x |

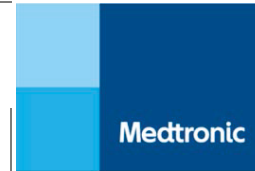
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| | Visit 1 | Visit 2 | Visit 3 Phone | Visit 4 | Visit 5 Phone | Visit 6 | Visit 7 Exit |
|---|---------|---------|---------------|---------|---------------|---------|--------------|
| <p>Ask subjects about the occurrence of adverse events</p> <ul style="list-style-type: none"> 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, such as sickness or glycemic problems. Instruct subject to call the investigational center to report any changes to their health status (see adverse event definition). | | X | X | X | X | X | X |
| <p>Ask subjects about device performance issues and if they called the 24 -Hour Technical Support (TS) to report them</p> <p>Instruct/Remind subjects to contact the Medtronic 24-Hour TS in the event they experience problems with their study devices.</p> | | X | X | X | X | X | X |
| General Instructions/Training/Review | | | | | | | |
| Review EZ reference guide and Daily Logs with subjects | | X | | | | | |
| Train subjects on CareLink Personal For Clinical Research - Refer to Subject CareLink Uploading Instructions | | X | | | | | |
| Print and review CareLink Reports | | | | X | | X | X |
| Review Site Instruction for CareLink Personal For Clinical Research Enrollment and Uploading | | X | | | | | |
| Review surveillance report provided through Sponsor | | | | X | | X | X |
| Instruct subjects to change insulin reservoirs at least every 174 hours. The infusion set(s) or reservoir(s) can be replaced independent of each other as referenced in the subject instructions. | | X | X | X | X | X | |

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| Instruct subjects that they will be required to source their own insulin. As indicated in inclusion criterion, all subjects is willing to take one of the following insulins and can financially support the use of either of the 2 insulin preparations throughout the course of the study (i.e. co-payments for insulin with insurance or able to pay full amount) <ul style="list-style-type: none"> a. Humalog™* (insulin lispro injection) b. NovoLog™* (insulin aspart) | | X | | | | | |
| Instruct subjects to check their blood glucose at least 4-6 times each day (before meals and bedtime) for diabetes self-management (SMBG), using the supplied CONTOUR® NEXT LINK 2.4 study meter <ul style="list-style-type: none"> o Subject compliance with SMBG (according to the user guide) will be encouraged. | | X | X | X | X | X | |
| Instruct subjects to always base their diabetes therapy decisions on a confirmatory finger stick (per user guide). Note: In this study, finger stick measurements will be used exclusively; no alternate site testing will be allowed | | X | X | X | X | X | |
| Instruct subjects that blood ketone testing is required every time BG is greater than 250mg/dL, as measured by the CONTOUR® NEXT LINK 2.4 study meter (ketones do not need to be checked if it is less than 3 hours post-prandial) Blood ketone testing: <ul style="list-style-type: none"> o If ketone testing occurred, the results should be entered into the CareLink Personal For Clinical Research Logbook at least weekly prior to Monday morning. | | X | X | X | X | X | |
| Instruct subjects that they must upload weekly the MiniMed 670G pump and CONTOUR® NEXT LINK 2.4 study meter to CareLink Personal For Clinical Research. If the CONTOUR® NEXT LINK 2.4 study meter does not link to the subjects' insulin pump, instruct subjects to manually enter the study meter reading into the insulin pump. | | X | X | X | X | X | |

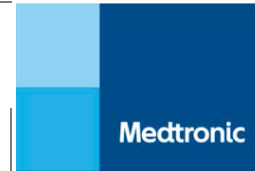
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| Remind subject to bring in both CONTOUR® NEXT LINK 2.4 study meter and ketone meter | | X | X | X | X | X | |
| Instruct subjects to verify appropriate meter operation for both the CONTOUR® NEXT LINK 2.4 study meter and the Ketone Meter during home use. The respective user guides should be consulted to determine frequency of control solution testing. | | X | | | | | |
| Inform subjects that observation by Sponsor may occur at any time during the study | | X | | | | | |
| Instruct/remind subjects to complete Daily Logs | | X | X | X | X | X | |
| Instruct subjects to refer regular healthcare providers who manage subjects' non-emergency diabetes treatment to the investigational center staff if they have any questions about study devices and their functions | | X | X | X | X | X | |
| Instruct subjects to consider avoiding the use of products containing Acetaminophen If medications containing acetaminophen are taken: <ul style="list-style-type: none"> Instruct subjects to record the use of acetaminophen on a log Instruct subjects to use additional BG meter readings (they are not to calibrate with those readings) to verify their glucose levels Instruct subjects to consider exiting Auto Mode | | X | X | X | X | X | |
| Infusion Set Training - General | | | | | | | |
| Instruct subjects on the use of the infusion sets (this includes infusion sets removal and replacing reservoirs without changing infusion sets); provide user guide, etc. | | X | | | | | |
| Instruct subjects to self-insert each infusion set per user guide | | X | | | | | |
| Subjects will be given 12 infusion sets to wear throughout the study. | | X | X | X | X | X | |

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| <p>Instruct subjects to wear at least 174 hours for each infusion set or until infusion set failure if this occurs before 174 hours, whichever occurs first:</p> <p>Infusion set failure used to determine primary endpoint is defined as any one of the following:</p> <ul style="list-style-type: none"> Unexplained Hyperglycemia is defined as the following (See Primary Effectiveness Endpoint Sections 4.2.2 and 13.5.2) : <ul style="list-style-type: none"> The study meter glucose >250 mg/dL (>3 hours post-meal) which may include time during subject’s sleeping hours Failure of a correction dose(s) to lower the study meter glucose by at least 50 mg/dL. One additional correction dose may be given after first correction dose and recommended to use the bolus calculator. The infusion set may remain in the body if the glucose improves after second correction dose within 90 minutes. Please note: if the glucose improves after the correction doses, and the infusion set does not need to be changed then this would NOT be considered an adverse event (e.g. unexplained hyperglycemia) and NOT considered an infusion set failure. SMBG should be checked every 60 minutes during this time The presence of serum ketones ≥ 0.6 mmol/L with a study meter glucose >250 mg/dL in the absence of illness and blood glucose that does not respond to insulin correction dose(s) as described above. (See Primary Safety Endpoint Sections 4.2.1 and 13.5.1) There are signs of infection at the infusion site (i.e. erythema (> 1 cm in diameter) with warmth, pain, and/ or induration) . (See Primary Safety Endpoint Section 4.2.1 and 13.5.1) | | x | x | x | x | x | |

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| Other known causes of infusion set failures which may or may not associated with hyperglycemia will be collected and analyzed as part of the overall safety assessment: <ul style="list-style-type: none"> • Accidental removals • Leakage • Loss of insertion (e.g. patient does not appear to be receiving insulin within 12 hours after infusion set is inserted) • Kinked or bent cannula • Removal due to discomfort at site • Mechanical failure • Adhesive issue | | | | | | | |
| Instruct subjects to inspect their infusion site on a daily basis and to call the investigational center staff if they observe signs of infection (i.e. erythema > 1 cm in diameter with warmth, pain, and/ or induration). | | X | X | X | X | X | |
| Instruct/remind subjects if an infusion set failure occurs at home, the subjects will remove the study EWIS | | X | X | X | X | X | |
| Instruct subjects to return all used (in the specimen container) EWIS to the investigational center . | | X | X | X | X | X | |

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8.3. Subject Consent

Informed Consent 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 Bill of Rights (if applicable), the IRB and Medtronic approved ICF and an Authorization Form required by the Health Insurance Portability and Accountability Act (HIPAA) will be presented to each subject to review and sign as applicable. The subject or parent/guardian will be offered the opportunity to review these documents away from the investigational center.

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

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

Subjects will complete California Experimental Subject's Bill of Rights (if applicable), the HIPAA Form, and the ICF. The consenting process must be documented in the subject's source files. The subject will receive copies of the fully executed documents. A subject's participation in study procedures cannot begin before the consent process has been properly executed.

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

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

If the ICF is amended during the course of the study, the IRB will determine:

- Whether or not active subjects should be re-consented at their next visit and
- Whether or not subjects who have completed the study at the time of the amendment should repeat the informed consent process.

Subjects will be informed that qualified personnel from the investigational center, the sponsor (Medtronic), agencies such as the United States Food and Drug Administration (FDA) and/or the IRB, may have access to the clinic records that reveal their identity and health care information.

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

- Failure to obtain informed consent from subject.
- Failure to obtain informed consent prior to performing one or more study procedures.
- Failure to maintain ICFs on file for all subjects who have provided informed consent.

- Use of an ICF that has not received approval from the IRB.
- Use of an incorrect version of the ICF.

8.4. Assessment of Safety

AE information is collected in this study. See Section 10 for further information regarding the collection of AEs and safety information.

8.5. Medical Oversight

In order to conduct the study, investigational center staff that have the appropriate medical training is required.

8.5.1. Medical Staff

A physician (or designee) who has managed patients on both CGM and insulin pump therapy will be included in the study as the principal investigator.

8.5.2. Qualification

The investigator (or designee) will need to have one of the following qualifications: Endocrinology fellowship or management in patients with diabetes in a clinical practice. The provider must be qualified to treat diabetic emergencies.

8.6. Safety Monitoring/Risk Analysis

8.6.1. Glucose Monitoring Risk

- Subjects will be instructed to make sure they have clean fingers when performing finger stick glucose testing.
- Subjects will be instructed to test blood glucose at least 4-6 times a day (before each meal and before bedtime).
- Subjects will have training on diabetes self-management principles.

8.6.2. Hypoglycemic/Hyperglycemic Risk

Intervention and treatment for hypoglycemia and hyperglycemia is addressed in Section 9.

8.6.3. Reuse Risk

The investigational study device, EWIS, will be single patient use.

8.6.4. Sterilization Risk

The EWIS devices will be supplied sterilized.

8.6.5. Misuse Risk

Comprehensive training will take place at the initiation visit for investigational center staff regarding the use of EWIS, to include all of its functional components and all other study devices to be used during the study at the investigational center.

8.6.6. Risk of Blood Sample Collection, Contamination from Sampling Techniques

Detailed mitigations to blood sampling risk are provided in Section 9.

8.6.7. HbA1c Risk

A Central laboratory will be used for HbA1c testing.

8.7. Glucose and Glycemia Measurements

During the course of the study, the subjects' BG levels, sensor glucose (SG) levels, HbA1c, and blood ketones will be assessed using the methods outlined in this section.

8.7.1. Daily Blood Glucose

Values will be assessed during the study by all subjects using the CONTOUR® NEXT LINK 2.4 study meter. The control solution test will be performed following the manufacturer's user guide during home use. Subjects will be trained on the use of the CONTOUR® NEXT LINK 2.4 study meter per the manufacturer's instructions.

8.7.2. Blood Ketone Values

Blood ketones will be measured by all subjects using the Precision Xtra™* ketone meter during home use when certain conditions are met. The control solution test will be performed following the manufacturer's user guide during home use. The investigational center staff will be trained on the use of the Precision Xtra™* ketone meter per the manufacturer's instructions. All ketone measurements will be entered by study subjects into the Log Book section of the CareLink™ Personal For Clinical Research software.

Note: In the event the blood ketone meter is not used by subjects to collect ketone values, urine ketones should be measured and entered appropriately into the CareLink™ Personal For Clinical Research software as urine ketones.

8.7.3. Sensor Glucose Values

SG data will be collected by subject's MiniMed™ 670G insulin pump and calibrated by each subject's CONTOUR® NEXT LINK 2.4 study meter.

8.7.4. HbA1c

Collected at screening, the HbA1c value will be used as exclusion criteria information only. HbA1c is also collected at the end of subjects' participation.

8.8. Recording Data

Data will be captured on eCRFs using Oracle Clinical Remote Data Capture (OC-RDC) module. Original eCRFs will not be considered as source data and supporting documentation will be required.

Electronic device data will be collected from the MiniMed™ 670G Pump System using CareLink™ Personal For Clinical Research software. The system uses TLS technology, which encrypts all data it stores (21 CFR Part 11 compliant). Certain data points stored in the downloaded information may also be captured on the appropriate eCRF.

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

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

8.9. Deviation Handling

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

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

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

The following clarifications apply to deviations related to study procedures:

- If subjects use a non-study glucose meter, any pump other than the MiniMed™ 670G and if subjects replaced any part of the EWIS investigational set before using all 12 EWIS sets (reservoir, tubing or any aspect of insulin set) with their own infusion set (reservoir, tubing or any aspect of infusion set) during the study, a study deviation will be given.
- If subjects do not follow the fingerstick recommendations perfectly, no study deviation will be given unless site did not train subject on SMBG study procedures.

8.9.1. Documenting Requirements for Study Deviations

8.9.1.1. Unplanned CIP Deviations

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

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

CIP deviations should be reported as follows:

- a) To the IRB for notification/acknowledgement;
- b) To the sponsor and, if required;
- c) To the regulatory agency

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

8.9.1.2. Minor or Administrative CIP deviations

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

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

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

8.9.2. Reporting Requirements for Study Deviations

All study deviations must be reported on the eCRF regardless of whether medically justifiable, an inadvertent occurrence, or taken to protect the subject in an emergency. The date and reason for each deviation will be documented (21 CFR 812.140 Records). In the occurrence of a corrupted device interrogation file, Sponsor may request a deviation to document that a readable interrogation file is unavailable.

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

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

- Failure to obtain informed consent, i.e., there is no documentation of informed consent
- Informed consent obtained after initiation of study procedures
- Enrollment of a subject who did not meet all inclusion/exclusion criteria
- Performing study procedure not approved by the IRB
- Failure to inform IRB and sponsor of reportable AEs (see Section 10)
- Investigational study device dispensed without obtaining informed consent

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

8.9.3. Analyzing Deviations

Medtronic is responsible for reviewing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, conduct additional training, terminate the investigation). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and investigational center, and in some cases, necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study.

8.10. Subject Withdrawal or Discontinuation

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

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

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

- In the opinion of the investigator, the subject's health or safety would be compromised by continuing in the study
- In the opinion of the investigator, it is in the subject's best interest to discontinue participation in the study
- 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 alcohol.
- During the study, (female) subject becomes pregnant.
- During the study, the subject experiences one severe hypoglycemic episode
- During the study, the subject experiences one episode of DKA
- During the course of the study subject begins using pramlintide (Symlin), DPP-4 inhibitors, liraglutide (Victoza or other GLP-1 agonists), metformin, canagliflozin (Invokana or other SGLT2 inhibitors).
- During the course of the study, subject receives red blood cell transfusion or erythropoietin.
- During the course of the study, subject is taking oral, injectable, or IV glucocorticoids for 3 or more weeks (e.g. oral prednisone daily or weekly glucocorticoid administration)

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

8.11. Stopping Rules

8.11.1. Subject Stopping Rules

4. Unanticipated Adverse Device Effects (UADEs);
5. Diabetic Ketoacidosis (DKA);
6. Severe hypoglycemia events that result in subject requiring paramedic assistance, an ER visit or subjects who experience seizure, coma or death.

8.11.2. Stopping Rules for Entire Study

The study will stop if there is:

1. An Unanticipated Adverse Device Effects (UADE).
2. Site will notify the sponsor within approximately 24 hours of receiving knowledge of a SADE event. Sponsor will assess and determined if unanticipated.
3. Sponsor will notify FDA within 72 hours of notification of a SADE
4. Clinical Events Committee (CEC) is to review and adjudicate the event within 7 days from the time that the sponsor is notified.

5. CEC will provide recommendation to the sponsor on whether or not the entire study must be stopped, including study procedures for subjects who have already received study devices

8.12. Study Success Criteria

Success Criteria for the study will be the achievement of the infusion set failure rate due to unexplained hyperglycemia at 6 or 7 days shall be $\leq 20\%$ (95% upper CI), as the mean failure rate is expected to be $\sim 16\%$.

9. Risks and Benefits

9.1. Potential Risks

| Risks with Infusion Sets | Prevention and Mitigation |
|--|---|
| <p>Risks with infusion sets may include:</p> <ul style="list-style-type: none"> • Localized infection • Skin irritation/redness • Bruising • Discomfort/pain • Bleeding • Irritation • Rash • Hyperglycemia secondary to infusion set occlusion or infusion site failure including DKA • Hyperglycemia secondary to site falling off including DKA • Anxiety associated with insertion | <p>Prevention and mitigation include:</p> <ul style="list-style-type: none"> • 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. • In case of hyperglycemia secondary to infusion set occlusion, remove current infusion set and replace with new infusion set and give correction insulin if needed with syringe. • Follow the provided user guides for insulin pump management. • Training prior to study on device use and diabetes management principles and told to call with problems. |
| Risks with Insulin Administration and Pumps | Prevention and Mitigation |
| <p>Risks with the use of an insulin infusion pump may include the risk of malfunction of the components of the system (pump, software,</p> | <p>Prevention and mitigation include:</p> |

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|---|---|
| <p>infusion set and reservoir) as well as the risk of use error during use of the system. Device deficiencies or use errors can result in administration of too much or too little insulin which can lead to the following clinical consequences:</p> <ul style="list-style-type: none"> • Hypoglycemia • Hyperglycemia • Diabetic ketoacidosis • Severe hypoglycemia with or without associated seizure, coma or death • Kinked cannula leading to hyperglycemia • Infusion set disconnection from pump leading to hyperglycemia • Subject removes the reservoir from the pump but forgets to disconnect the infusion set from the body which results in hypoglycemia or severe hypoglycemia. • Dislodged cannula leading to hyperglycemia • A pump error may lead to under delivery or over-delivery of insulin • Battery failure – no insulin delivered • Insulin deterioration leading to hyperglycemia • Incomplete priming; fails to prime tubing and/or cannula, leading to hyperglycemia • Remove a reservoir, without suspending and reconnecting after a while resulting in a Hypoglycemia • Patient not filling pump reservoir when needed leading to hyperglycemia • Magnetic Resonance Imaging resulting in pump/transmitter malfunction • Inaccurate insulin delivery due to sudden altitude changes. • Hypoglycemia or hyperglycemia from manual bolus • Hypoglycemia or hyperglycemia from computer hacking | <ul style="list-style-type: none"> • Follow the provided user guides & instructions for insulin pump management which includes information on infusion set change. • Training prior to study on device use and diabetes management principles and told to call with problems. • Check SMBG 4-6 times a day and also before driving (as applicable). • Instructed to have glucose on hand for hypoglycemia • Change infusion set if suspected catheter occlusion or administer insulin with syringe for persistent hyperglycemia especially if ketones develop. |
| <p>Risks with hyperglycemia may include</p> <ul style="list-style-type: none"> • Diabetic ketoacidosis • Symptomatic ketosis • Cardiovascular event • Dehydration • Potassium and sodium imbalance • Shock • Altered mental status • Coma • Acidosis | <p>Prevention and mitigation include:</p> <ul style="list-style-type: none"> • Follow the provided user guides for insulin pump management. • Training prior to study on device use and diabetes management principles. • Check SMBG 4-6 times a day. • Alternative method of managing glucose levels should be available (insulin and syringe for example) |

| | |
|---|--|
| <p>Risks with hypoglycemia may include:</p> <ul style="list-style-type: none"> • Seizure • Coma • Altered mental status • Loss of consciousness • Cardiovascular event • Death • Risk of rebound hyperglycemia with ketosis | <p>Prevention and mitigation include:</p> <ul style="list-style-type: none"> • Follow the provided user guides for insulin pump management. • Training prior to study on device use and diabetes management principles. • Check SMBG 4-6 times a day. • Instructed to have glucose on hand for hypoglycemia |
| <p>Risk with Sensors</p> | <p>Prevention and Mitigation</p> |
| <p>Risks with Sensors may include:</p> <ul style="list-style-type: none"> • Skin irritation or reaction to adhesives • Bruising • Discomfort • Redness • Bleeding • Excessive bleeding due to anticoagulants • Pain • Rash • Infection • Irritation from tapes used with glucose-sensing products • Raised bump • Appearance of a small "freckle-like" dot where needle was inserted • Allergic reaction • Syncopal episode secondary to needle insertion • Soreness or tenderness • Swelling at insertion site • Sensor fracture, breakage or damage • Minimal blood splatter associated with sensor needle removal • Residual redness associated with adhesive and/ or tapes • Scarring • Scab • Blister • Itchiness • Inflammation • Anxiety • Incorrect sensor glucose reading results in incorrect diabetes management • Subject over-treating secondary to alarms which can result in hyperglycemia or hypoglycemia • Anxiety associated with insertion | <p>Prevention and mitigation include:</p> <ul style="list-style-type: none"> • Follow the provided user guides for insertions and care of sensors. • If a sensor site becomes infected or inflamed, the sensor should be removed and another placed in a new location • Base diabetes management on fingerstick readings and not sensor glucose values. |

| Risks with Transmitter | Prevention and Mitigation |
|--|--|
| <p>Risks with Transmitter may include:</p> <ul style="list-style-type: none"> • Skin irritation or reaction to adhesives • Bruising • Discomfort • Redness • Pain • Rash • Infection • Irritation from tapes used with glucose-sensing products • Raised bump • Allergic reaction • Soreness or tenderness • Residual redness associated with adhesive and/ or tapes • Scarring • Scab • Blister • Itchiness • Inflammation | <p>Prevention and mitigation include:</p> <ul style="list-style-type: none"> • Follow the provided user guides for transmitters. • Training on proper use of the transmitters |
| Risks with Serter | Prevention and Mitigation |
| <p>Risks with Serters may include:</p> <ul style="list-style-type: none"> • Improper insertion may lead to device performance issue or hyperglycemia | <p>Prevention and mitigation include:</p> <ul style="list-style-type: none"> • Follow the provided user guides for insertions and care of Serters. • Training on proper use of the Serter and skin preparation prior to insertion. |
| Risks with Finger Sticks | Prevention and Mitigation |
| <p>Risks with frequent finger stick testing may include:</p> <ul style="list-style-type: none"> • Potential risks associated with frequent meter testing of blood glucose and blood ketones include discomfort and ecchymosis at tips of fingers • Potential risks associated with finger stick testing include discomfort and bruising | <p>Prevention and mitigation include:</p> <ul style="list-style-type: none"> • Follow the provided user guides for use of the study meter with fingerstick testing. • Training on proper use of the meter and fingerstick testing. |

| Risk with Closed Loop Therapy | Prevention and Mitigation |
|---|--|
| <p>Risks with Closed Loop may include:</p> <ul style="list-style-type: none"> • Hypoglycemia • Severe hypoglycemia • Hyperglycemia • Diabetic ketoacidosis User Entry Error <ul style="list-style-type: none"> ○ Patient administering boluses by entering false carb doses leading to hypoglycemia or hyperglycemia ○ Patient entering false glucose values for any reason leading to hypoglycemia and hyperglycemia ○ Patient entering false BG values for calibration leading to hypoglycemia or hyperglycemia • Sensor failure resulting from patient failure to calibrate leading to hypoglycemia or hyperglycemia • Sensor over-reading resulting in hypoglycemia • Sensor under-reading resulting in hyperglycemia • Sensor missed transmission, or any other fault resulting in no SG value, leading to hyperglycemia or hypoglycemia • Voluntary insulin delivery (with the pump or with a syringe) immediately prior to entering Auto Mode may result in severe hypoglycemia despite shutting down insulin delivery by the algorithm • Patient takes insulin via injection while in Closed Loop (Auto Mode) • Hypoglycemia or hyperglycemia related to entering or exiting Closed Loop (Auto Mode) • Insulin over-delivery due to potential interference from acetaminophen | <p>Prevention and mitigation include:</p> <ul style="list-style-type: none"> • Follow the provided user guides for insulin pump management. • Training prior to study on device use and diabetes management principles and told to call with problems. • Check SMBG 4-6 times a day. • Instructed to have glucose on hand for hypoglycemia • Subjects will be instructed to consider avoiding the use of products containing acetaminophen • If acetaminophen is taken, subjects will be instructed to use additional BG meter readings (they are not to calibrate with those readings) to verify their glucose levels. • If acetaminophen is taken, subjects should consider exiting Auto Mode |
| <p>Risks with hyperglycemia may include</p> <ul style="list-style-type: none"> • Diabetic ketoacidosis Symptomatic ketosis • Cardiovascular event • Dehydration • Potassium and sodium imbalance • Shock • Altered mental status • Coma Acidosis | <p>Prevention and mitigation include:</p> <ul style="list-style-type: none"> • Follow the provided user guides for insulin pump management. • Training prior to study on device use and diabetes management principles and told to call with problems. • Check SMBG 4-6 times a day. |
| <p>Risks with hypoglycemia may include:</p> <ul style="list-style-type: none"> • Seizure • Coma • Altered mental status • Loss of consciousness | <p>Prevention and mitigation include:</p> <ul style="list-style-type: none"> • Follow the provided user guides for insulin pump management. |

| <ul style="list-style-type: none"> • Cardiovascular event • Death • Risk of rebound hyperglycemia with ketosis | <ul style="list-style-type: none"> • Training prior to study device use and diabetes management principles. • Check SMBG 4-6 times a day. • Instructed to have glucose on hand for hypoglycemia |
|--|--|
| Risk with Acetaminophen Use | Prevention and Mitigation |
| <p>Potential risks with acetaminophen may include:</p> <ul style="list-style-type: none"> • False elevation of sensor glucose readings. The level of inaccuracy depends on the amount of acetaminophen active in subject's body and may be different for each subject | <p>Prevention and mitigation include:</p> <ul style="list-style-type: none"> • Follow the user guide • Subjects should be instructed to consider avoiding the use of products containing acetaminophen • If acetaminophen is taken, subjects should use additional BG meter readings (they are not to calibrate with those readings) to verify their glucose levels • Subjects should consider exiting Auto Mode |

9.2. Potential Benefits

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

9.3. Risk-Benefit Rationale

The ability to wear an infusion set for extended periods may help decrease local skin reactions from the frequent insertion and removal of infusion sets which results in removal of portions of the top layer of the epidermis which may lead to a higher risk of infections if a new infusion set or sensor is inserted into this area before the epidermis is completely healed.

If there is less unexplained hyperglycemia and fewer episodes of ketosis with prolonged infusion set wear as a result of the Extended wear infusion set, this would be a significant benefit to all people using insulin infusion pumps.

If the EWIS could extend the use of a subcutaneous infusion sets to 7 days, this would allow of the

future development of a combination infusion set and continuous glucose sensor. Such a platform would play an integral role in the development of a simplified closed-loop artificial pancreas system.

9.4. Risk Determination

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

- The devices could present a potential for serious risk to subject health, safety or welfare.
- The devices are for a use of substantial importance in treating disease, and presents potential for serious risk to subject health, safety or welfare.

Therefore, submission of an Investigational Device Exemption (IDE) application to the United States Food and Drug Administration is required.

9.5. Subject Compensation and Indemnification

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

10. Adverse Events Assessments

10.1. Adverse Events

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

10.2. Definitions and Classification of Adverse Events

Medtronic uses the definitions provided in ISO 14155:2011 and 21 CFR 812 for AE definitions. Where the definition indicates "device", it refers to any device used in the study. This might be the device under investigation, or any market released component of the system. Medtronic follows MEDDEV 2.7/3 revision 3 guidelines for classifying causality levels; but will apply these causality definitions across all events, not only serious adverse events and definitions have been adapted accordingly.

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

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

Severe Hyperglycemia is defined as Hyperglycemia (blood glucose greater than (>)250 mg/dL (13.9 mmol/L) with blood glucose ketones greater than or equal (\geq) 0.6 mmol/L, urine ketones moderate or large, or accompanied by symptoms of nausea, vomiting or abdominal pain.

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

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

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

Unexplained Hyperglycemia:

- The study meter glucose >250 mg/dL (>3 hours post-meal) which may include time during subject's sleeping hours
- Failure of a correction dose(s) to lower the study meter glucose by at least 50 mg/dL.
- One additional correction dose may be given after first correction dose and recommended to use the bolus calculator. The infusion set may remain in the body if the glucose improves after second correction dose within 90 minutes. Please note: if the glucose improves after the correction doses, and the infusion set does not need to be changed then this would NOT be considered an adverse event (e.g. unexplained hyperglycemia) and NOT considered an infusion set failure.

Adverse Event (AE) (ISO 14155-2011)

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

- Note 1:** This definition includes events related to the investigational medical device or the comparator.
- Note 2:** This definition includes events related to the procedures involved.
- Note 3:** For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse Device Effect (ADE) (ISO 14155-2011)

Adverse event related to the use of an investigational medical device.

- Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
- Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Serious Adverse Event (SAE) (ISO 14155-2011)

An adverse event that

- a) Led to a death,
- b) Led to a serious deterioration in the health of the subject, that either resulted in
 1. a life-threatening illness or injury, or
 2. a permanent impairment of a body structure or a body function, or
 3. in-patient* or prolonged hospitalization, or
 4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- c) Led to foetal distress, foetal death or a congenital abnormality or birth defect

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

**For the purpose of this study, Inpatient Hospitalization is defined as: admission to the hospital for a period of 24 hours or more based on urgent medical need rather than elective admission.*

For the purpose of this study, the term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. (ICH Topic E 2 A Clinical Safety Data Management: Definitions & Standards for Expedited Reporting. EMEA 2006)

Serious Adverse Device Effect (SADE) (ISO 14155-2011)

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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.

10.3. Reporting of Adverse Events

The investigator or designee will record ALL AEs while the subject is enrolled in the clinical study.

Each AE needs to be assessed for its device or procedure relatedness. A device related AE is associated with the use of the study device (e.g. infection of sensor site or infusion set occlusion resulting in DKA). A procedure related AE is associated with testing related to the study procedures specified in the CIP (e.g. needle (blood draw) insertion pain).

Examples of device or procedure related AEs include:

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

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

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

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

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

Adverse events that have not resolved at the time of the subject's discontinuation or completion of the study should have an "outcome" of Not Recovered/Not Resolved at study end in subject source and on an eCRF. The investigator should ensure that subject is aware of any follow-up or additional treatment

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that is required for any ongoing AE at end of study participation; however, there will be no eCRF entry for the ongoing follow-up.

10.4. Notification of Adverse Events

Sponsor Notification:

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

10.5. Expedited Safety Reporting Requirements

For device studies, investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (812.150(a)(1)).

The sponsor will notify the investigator and IRB of any event that results in a safety report per regulations to the FDA. Documentation of IRB notification of any safety event must be kept at the investigational center and a copy sent to the sponsor.

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

10.6. Causality Assessment

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

Causality assessment is the determination of the relationship between an AE and the device being studied. It is expected that the investigational center will review all elements surrounding the AE to properly assess the causality of the event to the study device or to a study procedure.

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

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

- a) **Not related:** relationship to the device or procedures can be excluded when:
- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures
 - the event has no temporal relationship with the use of the investigational device or the procedures;
 - the event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
 - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
 - the event involves a body-site or an organ not expected to be affected by the device or procedure;
 - the event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
 - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
 - harms to the subject are not clearly due to use error;
 - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
- b) **Unlikely:** the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but a relationship to the device cannot be completely ruled out.
- c) **Possible:** the relationship with the use of the investigational device is weak. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed should also be classified as possible.
- d) **Probable:** the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause.
- e) **Causal relationship:** the event is associated with the investigational device or with procedures beyond reasonable doubt when:
- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
 - the event has a temporal relationship with investigational device use/application or procedures;
 - the event involves a body-site or organ that
 - the investigational device or procedures are applied to;
 - the investigational device or procedures have an effect on;
 - the event follows a known response pattern to the medical device (if the response pattern is previously known);
 - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible);
 - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and

- an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Example: A severe hyperglycemia AE with the following event description would have the following causality assessment for device relatedness:

| | |
|--|----------------------------|
| Improved glucose without an infusion set/site change | Not related |
| Changed infusion set was associated with glucose improvement but the cause of hyperglycemia could have been related to an issue reported on CRF or CareLink such as missed meal bolus, non-compliance, or patient was ill. | Unlikely |
| Changed infusion set was associated with glucose improvement and no other identified issue as cause for improvement. | Possible |
| Infusion set fell out, bent cannula, occlusion alarm | Causal relationship |

10.7. Anticipated or Unanticipated

If an AE is determined to be related to the study device, the sponsor will then assess the event to determine if it is anticipated or unanticipated.

- **Anticipated:** the event is identified in the CIP; labeling; report of priors/IB or user guide.
- **Unanticipated:** the event has not been previously identified in the CIP; labeling; report of priors/IB or user guide.

11. Data Review Committees

11.1. Clinical Events Committee

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

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

The sponsor will notify the investigator of any disagreement in assessment of an event by the CEC.

CEC will also determine if infusion set failure used for primary endpoint as defined as below was met:

- Unexplained Hyperglycemia is defined as the following (See Primary Effectiveness Endpoint Sections 4.2.2 and 13.5.2) :
 - The study meter glucose >250 mg/dL (>3 hours post-meal) which may include time during subject's sleeping hours
 - Failure of a correction dose(s) to lower the study meter glucose by at least 50 mg/dL.
 - One additional correction dose may be given after first correction dose and recommended to use the bolus calculator. The infusion set may remain in the body if the glucose improves after second correction dose within 90 minutes. Please note: if the glucose improves after the correction doses, and the infusion set does not need to be changed then this would NOT be considered an adverse event (e.g. unexplained hyperglycemia) and NOT considered an infusion set failure.
 - SMBG should be checked every 60 minutes during this time
- The presence of serum ketones \geq 0.6 mmol/L with a study meter glucose >250 mg/dL in the absence of illness and blood glucose that does not respond to insulin correction dose(s) as described above. (See Primary Safety Endpoint Sections 4.2.1 and 13.5.1)
- There are signs of infection at the infusion site (i.e. erythema (> 1 cm in diameter) with warmth, pain, and/ or induration

CEC will also determine if the infusion set failure was associated with these known causes if sponsor disagrees with investigator assessment:

- Accidental removals
- Leakage
- Loss of insertion (e.g. patient does not appear to be receiving insulin within 12 hours after infusion set is inserted)
- Kinked or bent cannula
- Removal due to discomfort at site
- Mechanical failure
- Adhesive issue

12. Device Deficiencies and Troubleshooting

The Medtronic 24-Hour TS will be consulted for device troubleshooting (e.g. assistance is needed by subject to operate their device(s)). When subjects call the TS, they are instructed to notify the TS operator that they are currently participating in a clinical research study. All device deficiencies that are reported to the TS will be documented by the TS staff.

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

All device deficiencies reported directly to the investigational center staff by a subject should either be reported to the TS by the subject or investigational center staff. Any device deficiency the investigational center may have should be reported to the TS. A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. NOTE: Device deficiencies include malfunctions, use errors, and inadequate labeling. **(Adapted from ISO14155:2011)**

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

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

13. Statistical Design and Methods

13.1. General Considerations

All data collected from the time of screening until the end of the study will be collected either on eCRFs or electronically by uploading the various devices.

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

13.2. Subject Disposition

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

13.3. Subject Demographics and Baseline Characteristics

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

13.4. Study Population

Intention to Treat (ITT) Population

The primary study population is the Intention to Treat (ITT) population, which consists of all enrolled subjects. All analysis will be evaluated for ITT population.

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Per Protocol (PP) Population

The Per Protocol (PP) population will include all subjects who completed 12 sets of infusion set wears. Primary and secondary effectiveness endpoints will be evaluated for PP population.

Safety Population

The safety population will include all enrolled subjects.

13.5. Endpoints and Hypotheses

13.5.1. Primary Safety Endpoint

- Incidence of Serious Adverse Events (SAE)
- Incidence of Serious Adverse Device Effects (SADE)
- Incidence of Unanticipated Adverse Device Effects (UADE)
- Incidence of Severe Hypoglycemia
- Incidence of Severe Hyperglycemia
- Incidence of DKA
- Incidence of skin infections at infusion set insertion site

13.5.2. Primary Effectiveness Endpoint:

The primary effectiveness endpoints will be independently evaluated in blocks of 2 in the study. Analysis will be done in the blocks of 2 as:

- Novolog™*
- Humalog™*

Rate of infusion set failure due to unexplained hyperglycemia (i.e. suspected occlusion) at the end of Day 6. The rate of infusion set failure is defined as the number of infusion set removals associated with unexplained hyperglycemia divided by total number of infusion sets inserted.

The hypothesis is that the overall rate of infusion set failure due to unexplained hyperglycemia (i.e. suspected occlusion) at the end of day 6 is not inferior to 20%, with two sided 0.05 significance level, which will ensure the mean rate of infusion set failure due to unexplained hyperglycemia is $\leq 16\%$. The hypothesis is mathematically expressed as:

$$H_0: \mu \geq 0.20$$

$$H_a: \mu < 0.20$$

Where μ is the mean rate of infusion set failure due to unexplained hyperglycemia at the end of day 6.

A generalized estimating equation method model will be used. The one sided 97.5% upper confidence limit of the failure rate will be tested against the threshold of 20%.

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

13.5.3. Secondary Effectiveness Endpoint:

The secondary effectiveness endpoints will be independently evaluated in blocks of 2 in the study. Analysis will be done in the blocks of 2 as:

- Novolog™*
- Humalog™*

Rate of infusion set failure due to unexplained hyperglycemia (i.e. suspected occlusion) at the end of Day 7. The rate of infusion set failure is defined as the number of infusion set removals associated with unexplained hyperglycemia divided by total number of infusion sets inserted.

The hypothesis is that the overall rate of infusion set failure due to unexplained hyperglycemia (i.e. suspected occlusion) at the end of day 7 is not inferior to 20%, with two sided 0.05 significance level, which will ensure the mean rate of infusion set failure due to unexplained hyperglycemia is $\leq 16\%$. The hypothesis is mathematically expressed as:

$$H_0: \mu \geq 0.20$$

$$H_a: \mu < 0.20$$

Where μ is the mean rate of infusion set failure due to unexplained hyperglycemia at the end of day 7.

A generalized estimating equation method model will be used. The one sided 97.5% upper confidence limit of the failure rate will be tested against the threshold of 20%.

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

13.5.4. Descriptive Endpoints

- Descriptive summary of all infusion set failures and the day they failed. All causes of infusion set failures, such as removal due to discomfort of site, accidental removals, kinked or bent cannula, leakage, loss of insertion (e.g. patient does not appear to be receiving insulin within 12 hours after infusion set is inserted), mechanical failure, and adhesive issue will be collected and analyzed.
- HbA1c changes from baseline to the end of study.
- All severe hyperglycemic events as defined in Section 10.2 will be summarized whether they are device related or not or whether they are associated with infusion set failure or not.
- Descriptive summary of infusion set change at baseline

13.5.5. Device Deficiencies

Descriptive summary will be used to characterize device deficiencies.

13.5.6. Subject Feedback

Descriptive summary will be used to characterize study questionnaire results.

13.6. Sample Size Considerations

The infusion set failure rate due to unexplained hyperglycemia (i.e. suspected occlusion) of 16% (FDA response Q180616/S001), around 20% upper limit, was used when generating simulation dataset for Day 6 and Day 7 evaluations, as supported by discussions with the Agency. Sample size estimation was performed based on data from Dr. Buckingham EWIS data in 2018 (20 subjects each wore 2 EWIS infusion sets with no missing data). The suspected occlusion occurrence rate was 12.5%. Subjects were sampled to enter the simulation dataset with a vector of 12 measurements (12 EWIS wears). The resulting simulation datasets have correlated occurrence rates. Therefore, a repeated-measure Generalized Linear Model (GENMOD) was used to determine the upper boundary of the occurrence rate. Using all available data for each subject, the intercept of a null GLM model, with a repeated factor for infusion set wear day, was used to estimate the overall occurrence rates. A simulation was performed 1000 times and the upper boundary of the intercept of the GENMOD was tested against the critical value of 20%. The results of the simulation indicated that a sample size of 100 per insulin group will yield power of over 80% to demonstrate that the infusion set failure rate due to unexplained hyperglycemia is not inferior to 20%, with two sided 0.05 significance level, which will ensure that $\leq 16\%$ rate is achieved.

14. Ethics

14.1. Statement(s) of Compliance

IRB

This CIP, any subsequent amendments to this CIP, the ICF, 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 investigational center will not initiate any subject activities until IRB approval has been granted, the sponsor has cleared the investigational center to begin the study, and the investigational center staff has been appropriately trained to conduct the study.

Regulatory Compliance

This clinical study will be conducted in compliance with the Clinical Investigation Agreement; US CFR Title 21 Part 11 (Electronic Records; Electronic Signatures), Part 50 (Informed consents), Part 54 (Financial Disclosure by Clinical Investigators), Part 56 (IRBs), Part 812 (Investigational Device Exemptions), and all other applicable federal and local regulatory requirements.

The study will also be conducted in compliance with the principles of good clinical practice (GCP) meaning that the study design, conduct, performance, monitoring, auditing, recording, analysis and reporting will assure that the data and results are credible and accurate and that the rights, safety and well-being of subjects are protected. GCP includes review and approval by an independent ethic committee (IEC)/ IRB before initiating the investigation, ongoing review of the investigation by an IEC/IRB and obtaining and documenting the freely given informed consent of the subject (or the subject's legally authorized representative) before their participation in the investigation.

The ethical principles that have their origin in the Declaration of Helsinki have been implemented in this clinical study by means of the informed consent process, IRB approval, study training, clinical trial registration, preclinical testing, risk benefit assessment, publication policy, etc.

Ethical Considerations

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

14.2. Investigator's Responsibilities

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

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

- Conduct of the investigation in accordance with the signed Investigator Agreement for clinical investigations of medical devices, CIP applicable regulations set forth in 21 CFR Part 812 and all other applicable and other applicable FDA regulations, and any conditions of approval imposed by the reviewing IRB or FDA regulatory requirements
- Conduct of investigation in accordance to draft guidance from FDA, "Protecting the Rights, Safety, and Welfare of Study Subjects - Supervisory Responsibilities of Investigators", to meet responsibilities with respect to protect human subjects and ensuring the integrity of the data from clinical investigations. This guidance is also intended to clarify FDA's expectations concerning the investigator's responsibility:
 - 1) to supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other third parties, and
 - 2) to protect the rights, safety, and welfare of study subjects.
- Protecting the rights, safety, and welfare of subjects under the investigator's care
 - Providing reasonable medical care for study subjects for medical problems that arise during participation in the trial that are, or could be, related to the study intervention
 - Providing reasonable access to needed medical care, either by the investigator or by another identified, qualified individual (e.g., when the investigator is unavailable, when specialized care is needed)
 - Adhering to the CIP so that study subjects are not exposed to unreasonable risks
- Controlling devices under investigation (21 CFR 812.100)
- Providing adequate supervision of those to whom tasks have been delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of a clinical study.
- Ensuring that the requirements for obtaining informed consent are met in accordance with 21 CFR 50
- Supervising the use of investigational device. An investigator shall permit an investigational device to be used only with subjects under the investigator's supervision. An investigator shall not supply an investigational device to any person not authorized under 21 CFR Part 812 to receive it.
- Disposing of device properly. Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.
- Allowing study devices to be used only with subjects under the investigator's supervision and to supply study devices only to persons authorized to receive it

- Ensuring that investigational center staff are adequately trained to perform their assigned duties
- Maintenance of accurate, complete, and current records relating to the investigator's part of an investigation (21 CFR 812.140), to include:
 - all relevant correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.
 - records of receipt, use or disposition of study devices
 - records of each subject's case history and exposure to the device
 - the CIP, with documents showing the dates of and reasons for each deviation from the CIP
 - Any other records the FDA requires to be maintained by regulations or by specific requirement for a category of investigations or a particular investigation
- Preparation and submission to Medtronic and, when required, FDA and the reviewing IRB, the following complete, accurate, and timely reports:
 - any reportable AEs (see Section 10) occurring during an investigation
 - progress reports on the investigation as required by the FDA and IRB
 - any deviation from the CIP made to protect the life or physical well-being of a subject in an emergency
 - any use of the device without obtaining informed consent
 - any further information requested by the FDA and IRB about any aspect of the investigation
- Permitting FDA to inspect and copy any records pertaining to the investigation including, in certain situations, those which identify subjects (21 CFR 812.145)
- Meeting with the monitor to discuss study progress and findings
- Ensuring that investigational center resources are adequate to fulfill the obligations of the study
- Ensuring completion of eCRF to include entry and addressing discrepancies in a timely fashion and approving selected eCRFs.

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

The investigator's signature on the Investigator Agreement confirms that the investigator is familiar with the CIP in its entirety and agrees to conduct this study in accordance with the provisions of the CIP and all applicable regulations. The investigator, prior to the initiation of any study related activity, will sign the Investigator Agreement. If the sponsor discovers that an investigator is not complying with the

Investigator Agreement, CIP, or other regulatory requirements, the sponsor shall promptly secure compliance or discontinue that investigator's participation in the study.

15. Study Administration

15.1. Training of Clinical Staff

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

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

15.2. Monitoring

Monitoring visits may be conducted at the start, during and at the closure of the clinical study in accordance with Medtronic SOPs and the Monitoring Plan. At minimum, it will be verified whether signed and dated ICFs have been obtained from each subject at the point of enrollment and that AEs discussed in Section 10.3 were reported via completion of the AE eCRFs. More details regarding the monitoring activities (frequency of monitoring visits, planned extent of source data verification) are described in the Monitoring Plan.

15.2.1. Accessibility of Investigational Center Staff and Study Materials

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

15.2.2. Audits and Investigational Center Inspections

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

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

15.2.3. Investigational Center Disqualification

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

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

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

15.3. Data Management

15.3.1. Data collection

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

15.3.1.1. Electronic Case Report Forms (eCRFs)

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

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

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

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

15.3.1.2. CareLink™ Personal For Clinical Research Software

During the course of the study, subject's BG values may be assessed from the CONTOUR® NEXT LINK 2.4 study meter and the SG values may be assessed from the MiniMed™ 670G insulin pump. The MiniMed™ 670G insulin pump and the CONTOUR® NEXT LINK 2.4 study meter data will be uploaded in CareLink™ Personal For Clinical Research software by the investigator or designated investigational center staff. The system uses TLS technology, which encrypts all data it stores (21 CFR Part 11 compliant). The data in the different databases are linked to each other via the SIDs to prevent patient identification by the sponsor.

15.3.2. Time windows for completion and submission of Case Report Forms

It is expected that eCRFs are completed in a timely manner with the exception of the reportable adverse events (see Section 10.4). After data entry, eCRFs should be submitted (i.e. saved) so that Monitors can proceed with data verification without delay.

15.3.3. Data review and processing

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

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

15.4. Direct Access to Source Data/Documents

The patient's clinic file, CareLink™ Personal For Clinical Research data, and source worksheets are handled as source data.

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

15.4.1. Quality Audits

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

15.5. Confidentiality

The investigator will ensure that the subject's anonymity is maintained. Subjects will not be identified in any publicly released reports of this study. All records will be kept confidential to the extent provided by federal, state and local law. The study monitors and other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records. The investigator will inform the subjects that the above-named representatives will review their study-related records without violating the confidentiality of the subjects. All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified only by the

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subject ID code in order to maintain subject confidentiality. All records will be kept locked and all computer entry and networking programs will be done with coded numbers only.

15.6. CIP Amendments

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

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

15.7. Records and reports

15.7.1. Investigator Records

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

- All essential study documents and correspondence that pertains to the clinical study
- CIP and, if applicable, any amendments
- Report of Priors and/or user guide
- Medtronic and IRB-approved Patient ICF
- IRB and Regulatory authority approval or notification
- Fully signed clinical study agreements (i.e. including Investigator Statement and Signature Page, Clinical Trial Agreement and Confidential Disclosure Agreement)
- Completed Delegation of Authority Log
- Training documentation of all investigational center staff
- Subject screening log and/or SID log
- Signed, dated and fully executed Patient ICFs
- Source document requirements
- Fully executed eCRFs and corrections
- Report of AEs and Device Deficiencies
- Device accountability records
- CIP Deviation/ CIP Non-Compliance, if any
- Clinical Bulletins (if applicable)- A brief official update or summary of current study news on a matter of immediate interest and high importance to investigational center surrounding the CIP.
- Current signed and dated curriculum vitae (CV) of PI (and key study team members if required per local requirements)
- Study reports

15.7.2. Investigator reporting responsibilities

Table 3. Investigator Reporting Requirements

| Report | Submit to | Description/Constraints |
|--|--|--|
| AEs | Sponsor, IRB, and regulatory authority, where applicable | Refer to section 10.3,10.4,10.5, and 12 for reporting requirements. |
| Withdrawal of IRB approval (either suspension or termination) | Sponsor | An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation. |
| Progress report | Sponsor and IRB | The investigator must submit this report to the sponsor and IRB at regular intervals but in no event less than yearly. |
| Study deviations | Sponsor and IRB | Notice of deviations from the CIP to protect the life or physical wellbeing of a subject in an emergency shall be given as soon as possible but no later than 5 working days after the emergency occurred. |
| Failure to obtain informed consent prior to investigational device use | Sponsor and IRBs | If an investigator uses a device without obtaining informed consent, the investigator shall report such use within 5 working days after device use. |
| Final report | Sponsor IRBs Relevant Authorities | This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation. |
| Other | Sponsor, IRB and FDA | An investigator shall, upon request by a reviewing IRB, FDA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation. |

15.8. Record Retention

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

15.9. Suspension or Early Termination

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

15.9.1. Early Investigational Center suspension or termination

Sponsor, IRB or a Regulatory Authority may decide to suspend or prematurely terminate an investigational center (e.g. in case of expiring approval of the reviewing IRB, non-compliance to the CIP, or lack of enrollment). If an investigational center is suspended or prematurely terminated, sponsor shall promptly inform the investigator(s) of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing IRB and the study subjects.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definite outcomes, investigators must assess whether to continue, modify, or immediately stop the clinical study in the respective investigational center and immediately inform the sponsor and IRB, if applicable.

15.9.2. Subject follow-up in case of termination

In case of early investigational center suspension or termination, all subjects should be contacted to plan an early Termination visit at the investigational center. All efforts will be made to complete and report all study observations at the time of termination. The subject will return the study devices to the investigational center.

15.10. Study Close Out

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

15.11. Publication and Use of Information

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

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

16. References

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

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

17. Appendices

17.1. Names and addresses

17.1.1. Investigational Centers

At the time of this CIP was finalized, a list of the names and addresses of the participating investigational centers were not identified. Refer to ClinicalTrials.gov for the names and address of the participating Investigational Centers.

17.1.2. IRB

| IRB Name | Address | Chairperson |
|----------|--|-----------------------------------|
| Advarra | 1501 Fourth Avenue Suite 800 Seattle, WA 98101 | See current IRB Membership Roster |

At the time of this CIP was finalized, the names and addresses of other IRBs were not all identified.

17.1.3. Monitors Contact Information

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


Clinical Monitoring Manager, MC2 Global Monitoring

Medtronic

710 Medtronic Parkway
Minneapolis, MN 55432

At the time of this CIP was finalized, the names and addresses of the monitors were not identified.

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17.2. Labeling and IFUs of Devices

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


17.3. Sample Consent Materials

Samples of the following consent forms/materials will be provided in a separate cover which includes the California Experimental Subject's Bill of Rights (if applicable), ICF, and the HIPAA Authorization.

18. Version History

| Version | Summary of Changes | Author(s)/Title |
|---------------------------|---|-------------------------------------|
| A | <ul style="list-style-type: none"> Initial release | ██████████ Principal Medical Writer |
| B (Equivalent to FDA B.1) | <ul style="list-style-type: none"> Unexplained hyperglycemia definition updated Increased subject replacement of infusion sets up to 16 Updated inclusion criteria #2 and #3 Added inclusion criteria #6 (subject can afford use of Guardian Sensor[3]) Updated exclusion criteria #11 Added exclusion criteria #23 (subject has history of cardiovascular disease) | ██████████ Principal Medical Writer |
| FDA B.2 | <ul style="list-style-type: none"> Updated to include patients with type 1 diabetes (replaced insulin-requiring) Added IDE# Updated Glossary Updated Non-investigational devices to list out devices owned by subjects (pump) and those not provided by study | ██████████ Principal Medical Writer |

| | | |
|--|--|--|
| | <ul style="list-style-type: none">• Updated protocol relating to the approach relating to correction dose(s) of insulin that can be administered in the mentioned scenarios and additional clarification around infusion set failure and severe hyperglycemia• Updated instructions to not do ketone measurements if it is less than 3 hours post-prandial• Removed replacements of infusion sets• Updated study duration and study timeline• Updated inclusion criteria #2, 3, and #5, and specified those that are study specific inclusion criteria• Removed inclusion criteria #6• Updated all exclusion criteria as study specific exclusion criteria• Updated exclusion criteria #5, 12, and 21• Added exclusion criteria#24• Added Success Criteria• Updated Stopping Rules• Updated Device Accountability• Updated Visit Details Table:<ul style="list-style-type: none">○ Obtain TSH and retest○ Disburse and collect use of acetaminophen from subjects○ Updated name of questionnaires○ Added site procedures to complete study end questionnaire for user guide and instructional materials assessment.• Updated Reuse Risk• Updated Deviation Handling• Added Risk with Closed Loop Therapy and its Prevention and Mitigation | |
|--|--|--|

| | | |
|---------------------------|---|--|
| | <ul style="list-style-type: none">• Updated Descriptive Endpoints• Added hypothesis for primary and secondary effectiveness endpoints• Updated Sample Size Justification/Considerations• Added Interim Analysis• Removed subjects less than 18 years under Statement(s) of Compliance• Updated Direct Access to Source Data/Documents• Updated IRB name and chairperson contact information• Updated MC2 name under Monitors Contact information | |
| C (Equivalent to FDA C.1) | <ul style="list-style-type: none">• Updated Glossary• Corrected time of infusion set insertion will be taken from Daily Log• Allowed replacement of subjects who have early withdrawal• Updated primary and secondary effectiveness endpoints• Updated Sample Size Considerations• Added Study Population under Statistical Section• Removed Interim Analysis |  Principal Medical Writer |