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Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	Performance Evaluation of an Advanced Algorithm with CGM in Adults, Adolescents, and Pediatrics
Clinical Investigation Plan Identifier	CIP324
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Document Version	30-SEP-2019

Table of Contents

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0 30-SEP-2019	New Document	[redacted]

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
A1C	Glycosylated hemoglobin
AE	Adverse Event
BG	Blood Glucose
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
CGMS	Continuous Glucose Monitoring System
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FST	frequent sample testing
iCGM	integrated Continuous Glucose Monitoring
RF	Radio Frequency
SG	Sensor Glucose
SGV	Sensor Glucose Values
SQ	Subcutaneous
SMBG	Self-Monitoring of Blood Glucose
YSI™*	Yellow Springs Instrument

3. Introduction

Current methods of continuous glucose monitoring (CGM) include the use of subcutaneous (SQ) glucose sensors worn by the user, which convert glucose from the subject's interstitial fluid into an electronic signal, the strength of which is proportional to the amount of glucose present in the fluid. A CGM sensor is typically attached to a transmitter, which sends interstitial glucose information to a monitor (e.g. the Guardian™ Connect App) as radio frequency (RF) signals. The sensor is composed of a microelectrode with a thin coating of glucose oxidase beneath several layers of biocompatible membrane. The monitor is the data collection/user interface of the system and provides continuous real-time glucose values to the user, as well as the option to set high/low glucose alerts according to the individual patient's needs.

The Medtronic MiniMed™, Inc. (d/b/a "Medtronic Diabetes") family of Continuous Glucose Monitoring Systems (CGMS) measures SQ glucose continuously over various ranges of time. The newest generation Medtronic MiniMed™ SQ Glucose Sensor (Guardian™ Sensor 3) was approved by the United States Food and Drug Administration (FDA) for commercialization as part of the MiniMed™ 670G System in September 2016. The Medtronic MiniMed Glucose Sensor is a glucose sensor designed to work in Medtronic CGM systems to help users manage their diabetes.

Medtronic has developed a new advanced sensor calibration algorithm, called the "Zeus" algorithm, for use with Guardian™ Sensor (3). The "Zeus" algorithm is intended to minimize or eliminate required calibrations, which will reduce user burden. This algorithm will be implemented into a new Transmitter based on the Guardian™ Connect transmitter.

In this study, sensor data from Guardian™ Sensor (3) will be collected in a blinded approach, where commercial Guardian™ Connect Transmitters will be used as a recorder for the purposes of data collection. There will not be any live data communication during the study as no mobile application will be used. At the end of the study, raw sensor data collected by the Guardian™ Connect Transmitters will be processed using the Zeus algorithm and various calibration schemes.

Testing on human subjects is necessary to characterize the accuracy of this sensor algorithm. For purposes of this study, subjects will wear the study devices with Guardian™ Sensor (3). Subjects will manage their diabetes independent of the Guardian™ Sensor (3) values. During YSI™*/SMBG FST, venous blood glucose concentrations or SMBG (subjects 2-6 years only) will be measured periodically; these values will be compared to sensor glucose values (SGVs) in order to determine sensor accuracy.

Accuracy data will be calculated based on comparing calibrated glucose sensor values to a "gold standard" (Yellow Springs Instrument [YSI™*] plasma glucose values) in subjects during YSI™* frequent sample testing (FST). The YSI™* glucose analyzer, Model 2300, has been the recognized standard for the measurement of blood glucose and will be utilized across the investigational centers for the tests.

4. Study Objectives

The primary objective of the study is to demonstrate the accuracy of Guardian™ Sensor (3) when used over a period of 7 days (i.e., 170 hours) with the system in subjects 2-80 years of age.

5. Investigation Plan

The study is a multi-center, randomly assigned, prospective, single-sample correlational design without controls. Subjects will be randomly assigned to sensor location, FST day, and FST time.

A total of up to 460 previously-diagnosed type 1 and 2 diabetes subjects will be enrolled in order to have 244 subjects (122 adults and 122 pediatrics) complete study.

- Cohort1 (Adults): N= 122 subjects 18-80 years old
  - N= 15 minimum subjects age 18-29 years old
  - N= 15 minimum subjects age 30-60 years old
  - N= 15 minimum subjects age 61-80 years old
- Cohort2 (Pediatrics): N= 122 subjects 2-17 years old
  - N= 15 minimum subjects 2-4 years old
  - N= 15 minimum subjects 5-6 years old
  - N= 20 minimum subjects 7-10 years old
  - N= 20 minimum subjects 11-13 years old
  - N= 24 minimum subjects 14-17 years old

6. Determination of Sample Size

6.1 Guardian™ Sensor (3) accuracy, Threshold of 75%

The sample size selected is based on the primary effectiveness endpoint, which is the within 20% mean agreement rate (±20 mg/dL when Reference BG less than (<) 80 mg/dL) in comparative readings of paired Guardian™ Sensor (3) and YSI™* glucose readings in FST days. On those 4 FST days, 8 hours of paired testing will be recorded.

Data from CIP318 and ERP2018-11254 study was used for power estimation via simulation.

The simulation was performed 1000 times and the 95% lower confidence limit of 75%. The results of the simulation indicated that a sample size of 122 will yield greater than 80% power.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

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

7.1.2 Clinical Investigation Plan (CIP) Deviations

All protocol deviations will be presented in the listings.

7.1.3 Analysis Sets

All enrolled subjects who have at least one paired Guardian™ Sensor (3) and YSI™* measurement will be included in the efficacy analysis population. All enrolled subjects who have a Guardian™ Sensor (3) inserted will be included in the safety analysis population.

7.2 General Methodology

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

7.3 Center Pooling

Data will be pooled per cohort for analysis.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

All available data will be included in the data listings and tabulations. No imputation for missing data will be performed.

7.5 Adjustments for Multiple Comparisons

Secondary endpoints will be evaluated in a fixed sequence of testing for adjustment of multiplicity.

7.6 Demographic and Other Baseline Characteristics

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

7.7 Treatment Characteristics

The number of Guardian™ Sensor (3) insertions and Guardian™ Sensor (3) removals for every subject enrolled in the study will be presented.

A descriptive analysis of Guardian™ Sensor (3) disposition including Guardian™ Sensor (3) dislodgement and reasons why it dislodged will be included in the Final Report. Guardian™ Sensor (3) insertion and removals will be characterized by the following:

- Guardian™ Sensor (3) location
- Duration of Guardian™ Sensor (3) wear by investigational center subject report
- The number and percentage of Guardian™ Sensor (3)s remaining in place at study end.
- Duration of Guardian™ Sensor (3) wear (subject report) by insertion site.
- Reason for removal: for example, scheduled removal, adverse event, fell out.

The functional life of the Guardian™ Sensor (3) will also be characterized. The duration of Guardian™ Sensor (3) performance from the time of first valid Interstitial Signal (ISIG) to the last glucose reading (i.e., time to end of Guardian™ Sensor (3) life) will be described with Kaplan-Meier curves.

7.8 Interim Analyses

Interim Analysis will be performed for primary effectiveness endpoint to provide direction for continuing enrollment. If primary endpoint is met, secondary endpoints will also be evaluated. Two interim analyses will be conducted after there are 40 and 100 adult subjects complete the study, and separate two interim analyses will be conducted after there are 40 and 100 pediatric subjects complete the study.

The standard group sequential O'Brien-Fleming's approach will be used to estimate of significance level at interim analysis.

Number of Planned Analyses	Number of Interim Analyses	Number of Subjects	P-value threshold (alpha)
3	1	40	N/A*
	2	100	0.031
	3 (final)	122	0.041

*N/A: No intention to stop for efficacy at the first interim analysis (N = 40). Therefore, p-value threshold (alpha) is Not Applicable (N/A)

For this three stage design, hypothesis testing (primary and secondary endpoints) will be conducted at p = 0.031 and p = 0.041 for the second (N = 100) and final analyses (N = 122), using O'Brien-Fleming's approach. If significance is found at the second interim analysis at N = 100 complete subject, Medtronic may request to stop the study because endpoints are met. Otherwise, the study will continue up to the planned enrollment.

7.9 Evaluation of Objectives

7.9.1 Primary Endpoints

A total of 16 primary endpoints will be independently evaluated in blocks of 16 in the study. Analysis will be done in the blocks of 16 as:

- Adult (18 – 80 years), abdomen insertion location and 0 Calibration of Zeus algorithm
- Adult (18 – 80 years), abdomen insertion location and two Calibrations of Zeus algorithm (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Adult (18 – 80 years), abdomen insertion location and three Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Adult (18 – 80 years), abdomen insertion location and daily Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, 14 hours after second calibration and 24 hours after the previous calibration until end of wear)
- Adult (18 – 80 years), arm insertion location and 0 Calibration of Zeus algorithm

- Adult (18 – 80 years), arm insertion location and two Calibrations of Zeus algorithm (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Adult (18 – 80 years), arm insertion location and three Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Adult (18 – 80 years), arm insertion location and daily Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, 14 hours after second calibration and 24 hours after the previous calibration until end of wear)
- Peds (2 to 17 years), buttock insertion location and 0 Calibration of Zeus algorithm
- Peds (2 to 17 years), buttock insertion location and two Calibrations of Zeus algorithm (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Peds (2 to 17 years), buttock insertion location and three Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Peds (2 to 17 years), buttock insertion location and daily Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, 14 hours after second calibration and 24 hours after the previous calibration until end of wear)
- Peds (2 to 17 years), arm insertion location and 0 Calibration of Zeus algorithm
- Peds (2 to 17 years), arm insertion location and two Calibrations of Zeus algorithm (first calibration at 2 hours after insertion and second calibration at 8 hours after first calibration)
- Peds (2 to 17 years), arm insertion location and three Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, and 14 hours after second calibration)
- Peds (2 to 17 years), arm insertion location and daily Calibrations of Zeus algorithm (first calibration at 2 hours after insertion, second calibration at 8 hours after first calibration, 14 hours after second calibration and 24 hours after the previous calibration until end of wear)

Guardian™ Sensor (3) accuracy for *ZEUS Algorithms*

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 20% mean agreement rate (±20 mg/dL when SG less than (<) 80 mg/dL), μ, between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated against the null Hypothesis:

H0: $\mu \leq 75\%$

H1: $\mu > 75\%$

- Statistical testing

  A generalized estimating equation method model will be used. The one sided 95% lower confidence limit of the mean agreement rate will be tested against the threshold of 75%. For the GEE model, Exchangable (exch) or Auto-regressive (AR1) or Independence (IND) correlation structure will be used, based on quasi-AIC (QIC). Confidence intervals from bias-corrected and accelerated percentile bootstrap approaches will be provided, if applicable. In addition, the confidence intervals from GEE model and bootstrap approaches will be adjusted based on the proposed alpha level at the interim analyses. 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.

7.9.2 Secondary Endpoints

Within each block of 16, secondary endpoints (a total of 176) will be evaluated in a fixed sequence of testing for adjustment of multiplicity. The results will be compared to the iCGM Special Control criteria for sensor accuracy (SG limit of **50-400** mg/dL). For each of the endpoints, iCGM measurement refers to the sensor glucose value:

- % of iCGM measurements that indicate a positive glucose rate of change greater than 1 mg/dL/min when the corresponding true negative glucose rate of change is less than -2 mg/dL/min as determined by the corresponding blood glucose measurements
- % of iCGM measurements that indicate a negative glucose rate of change less than -1 mg/dL/min when the corresponding true positive glucose rate of change is greater than 2 mg/dL/min as determined by the corresponding blood glucose measurements
- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 20% mean agreement rate between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated
- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 15% mean agreement rate when SG >180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated
- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 40% mean agreement rate when SG >180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

- When iCGM values are greater than 180 mg/dL, corresponding blood glucose value read less than 70 mg/dL.
- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 15% mean agreement rate when SG between 70 and 180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated
- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 40% mean agreement rate when SG between 70 and 180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated
- When iCGM values are less than 70 mg/dL, no corresponding blood glucose value shall read above 180 mg/dL.
- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±15 mg/dL mean agreement rate when SG less than (<) 70 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated
- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±40mg/dL mean agreement rate when SG less than (<) 70 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

Within each block of 16, secondary endpoints (a total of 176) will be evaluated in a fixed sequence of testing for adjustment of multiplicity. The results will be compared to the iCGM Special Control criteria for sensor accuracy (SG limit of **40-400** mg/dL). For each of the endpoints, iCGM measurement refers to the sensor glucose value:

- % of iCGM measurements that indicate a positive glucose rate of change greater than 1 mg/dL/min when the corresponding true negative glucose rate of change is less than -2 mg/dL/min as determined by the corresponding blood glucose measurements
- % of iCGM measurements that indicate a negative glucose rate of change less than -1 mg/dL/min when the corresponding true positive glucose rate of change is greater than 2 mg/dL/min as determined by the corresponding blood glucose measurements
- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 20% mean agreement rate between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated
- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 15% mean agreement rate when SG >180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 40% mean agreement rate when SG >180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

- When iCGM values are greater than 180 mg/dL, corresponding blood glucose value read less than 70 mg/dL.

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 15% mean agreement rate when SG between 70 and 180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within 40% mean agreement rate when SG between 70 and 180 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

- When iCGM values are less than 70 mg/dL, no corresponding blood glucose value shall read above 180 mg/dL.

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±15 mg/dL mean agreement rate when SG less than (<) 70 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

- Guardian™ Sensor (3) values will be compared to YSI™* plasma glucose values during YSI™* FSTs. A within ±40mg/dL mean agreement rate when SG less than (<) 70 mg/dL between Guardian™ Sensor (3) values and YSI™* plasma glucose values during YSI™* FST days will be evaluated

7.9.3 Numbers of Readings in the Low and High Ranges

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

7.9.4 Difference Tables Comparing Sensor and Reference Readings

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

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

7.9.5 Sensor Calibration

Characteristics of Guardian™ Sensor (3) calibration will be evaluated by:

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

7.9.6 Clarke Error Grid Analysis (EGA) of Paired Sensor and YSI™* and Reference Values

1) Description

Clarke Error Grid Analysis (EGA) separates paired observations into five zones of clinical significance. The presence and severity of possible treatment error based on interstitial glucose assay evaluated by the sensor defines the five zones. Zone A represents the absence of treatment error, where the evaluation method and the reference method are within 20% of one another or in which both methods indicate hypoglycemia. Zone B represents cases where the two methods disagree by more than 20%, but do not lead to treatment error. Zones C, D, and E represent increasingly large and potentially harmful discrepancies between the evaluation and the reference method. If the method under evaluation has a high percentage (greater than (>)90%) of its pairs in Zones A and B, then it is considered clinically acceptable [Clarke et al, 1987].

2) Statistical analysis

Summary statistics (N, %) for each of the zones, as well as combined Zones A and B, will be calculated.

In order to evaluate differing levels of accuracy at various YSI™* defined glucose levels, the number and percentage of paired observations falling into Zones A, B, A+B, C, D, and E will be provided by YSI™* glucose ranges of 40-80 mg/dL, greater than (>) 80-120 mg/dL, greater than (>) 120-240 mg/dL, and greater than (>) 240 mg/dL.

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

7.9.7 Precision Analysis

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

7.9.8 Comparison of CGM Performance to Reference under conditions leadings to Alert

The alert will be triggered when the sensor BG value reaches the threshold glucose value. Predictive alerts will be evaluated by using the predicted sensor BG value based on current sensor BG and sensor BG readings within the previous 30 minutes.

In the in-clinic portion, the threshold and predictive alert analysis will be performed retrospectively with theoretical hypoglycemia threshold setting at 50 mg/dL, 60 mg/dL, 70 mg/dL, 80 mg/dL, 90 mg/dL and 100 mg/dL and theoretical hyperglycemia threshold setting at 180 mg/dL, 220 mg/dL, 250 mg/dL and 300 mg/dL.

The threshold alert performance will be evaluated for in-clinic portion by true alert rate, missed alert rate and false alert rate within 15 and 30 minute windows of the reference event. Predictive alert performance will only be evaluated for the in-clinic portion by true predictive alert rate, missed predictive alert rate and false predictive alert rate within 15 and 30 minute windows. All reference BG values will be used, including those less than (<) 40 mg/dL and greater than (>) 400 mg/dL.

The comparison of CGM performance to reference under conditions leading to alert will be evaluated by true alert rate, missed alert rate and false alert rate within 15 and 30 minutes window of the reference event.

The alert rates will be defined as follows:

Alert Rate Type	Column Label	Label Definition
Detection Rate	Hypo/Hyper Events Correctly Detected (%)	The device alarmed at the specified CGM settings within 30 minutes (or 15 minutes) before or after the reference blood glucose value (YSI™* or SMBG) goes below (for hypo) or above (for hyper) the specified CGM setting levels.

Alert Rate Type	Column Label	Label Definition
Missed Detection Rate	Hypo/Hyper Events Not Detected (%)	The device did not alarm at the specified CGM settings within 30 minutes (or 15 minutes) before or after the reference blood glucose value (YSI™* or SMBG) goes below (for hypo) or above (for hyper) the specified CGM setting levels.
True Alert	Alerts Verified by Hypo/Hyper Events (%)	There is at least one reference blood glucose value (YSI™* or SMBG) goes below (for hypo) or above (for hyper) the specified CGM setting levels within 30 minutes (or 15 minutes) before or after the sensor alarmed at the specified alert settings.
False Alert	False Alerts (%)	There is no reference blood glucose value (YSI™* or SMBG) goes below (for hypo) or above (for hyper) the specified CGM setting levels within 30 minutes (or 15 minutes) before or after the sensor alarmed at the specified alert settings.

7.9.9 Other Accuracy Analyses

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

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

A correlation between the sensor and YSI™* values will be performed. As this statistic ignores any data dependency, it will be used only as a descriptive measure of association.

A linear model, in which YSI™* is predicted by sensor values, using a repeated measures model, will be performed. The models solution will provide the intercept and slope, while adjusting for dependence in the data within day. An intercept of 0, along with a slope of 1, would indicate the absence of bias in predicting YSI™* from sensor readings. The residuals of the model will be inspected to determine if transformation of either variable is required.

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

Descriptive subgroup analysis of Guardian™ Sensor (3) performance (20% mean agreement rate (±20 mg/dL when Reference BG less than (<) 70 mg/dL)) will be performed in the following cohorts:

- **Diabetes cohorts based on insulin requirement**
  - 18-80 years
    - Insulin requiring N = minimum 78 subjects
      - N= minimum of 52 type 1 insulin requiring
      - N= minimum of 26 type 2 insulin requiring
    - Non-Insulin requiring N = minimum 12 subjects
  - 14 - 17 years
    - Insulin requiring N = minimum 24 subjects
  - 2 - 13 years
    - Insulin requiring N = minimum 10 subjects

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

  A description of the following 4 groups will be performed:
  - Underweight subjects (less than (<) 5th percentile): N=minimum of 1 subject
  - Normal weight subjects (5th percentile to less than (<) 85th percentile): N= minimum of 40 subjects
  - Overweight (85th to less than (<) the 95th percentile): N= minimum of 8
  - Obese subjects (greater than or equal to (≥) the 95th percentile): N=minimum of 1 subject

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

  A description of the following 5 groups will be performed:
  - Underweight subjects (BMI less than (<)18.5 kg/m²): N=minimum of 1 subject
  - Normal weight subjects (BMI 18.5 to 24.99 kg/m²): N= minimum of 28 subjects
  - Overweight and obese subjects (BMI 25.00 to 40 kg/m²): N= minimum of 36 subjects

        - Overweight subjects (BMI 25.00 to 29.99 kg/m²)
        - Obese subjects (BMI 30.00 to 39.99 kg/m²)
    - Morbidly obese subjects (BMI greater than or equal to (≥)40 kg/m²): N=minimum of 1 subject

- **Diabetes cohorts based on prior real-time CGM experience (by self report)**
    - CGM naïve: N= minimum of 40 subjects (2-80 years)
    - CGM experienced: N= minimum of 40 subjects (2-80 years)

- **Diabetes cohorts based on HbA1c:**
    - Baseline HbA1c (by certified National Glycohemoglobin Standardization Program, NGSP, method) will be collected:
    - A description of the following 3 groups will be performed: HbA1c less than (<) 7%, HbA1c 7-9%, HbA1c greater than (>) 9%
    - Quartile comparison (lowest to the highest) based on HbA1c

- **Diabetes cohort based on exercise activity:**
    - 18 – 80 years
        - N=minimum of 22 subjects
    - 14 - 17 years
        - N= minimum of 6 subjects
    - 2 - 13 years
        - N= minimum of 20 subjects
    - Sponsor may instruct site for exercise to be performed in order to obtain low glucose values

- **Diabetes cohort based on compression procedure:**
    - 18 – 80 years
        - N=minimum of 22 subjects
    - 14 - 17 years
        - N= minimum of 6 subjects
    - 2 - 13 years
        - N= minimum of 10 subjects

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

7.9.10 Home-Use Portion Data Analysis

Data from the home-use portion will be described. Analysis will include but not be limited to: 20% mean agreement rate (±20 mg/dL when Reference BG less than (<) 70 mg/dL) for all fingersticks (capillary SMBG) collected, Clark Error Grid, other accuracy analysis, ARE, bias, correlation between Guardian™ Sensor (3) and SMBG and Bland-Altman plots. In addition, 30% mean agreement rate (±20 mg/dL when Reference BG less than (<) 70 mg/dL) will be described by subgroups of: age, YSI™* FST, diabetes classification, BMI, CGM experience, HbA1c and exercise activity. The number of actual calibrations performed per day by study subjects will be tabulated and presented.

7.9.11 Exploratory Analysis

Additional adjustment to low SG values may be implemented to further assess the performance of Guardian™ Sensor (3) sensors.

7.9.12 Safety Evaluation

Descriptive summary will be used to characterize safety events

- Skin assessment at Guardian™ Sensor (3) insertion sites
- All adverse events

Device Deficiencies

Descriptive device deficiencies will include all reports of Guardian™ Sensor (3) damage, breakage or fracture.

7.10 Health Outcomes Analyses

Not Applicable

7.11 Changes to Planned Analysis

Not Applicable

8. Validation Requirements

Level I or Level II validation are required for analysis output. Level I requires that the peer reviewer independently programs output and then compares the output with that generated by the original

Statistical Programmer. Level II requires that the peer reviewer reviews the code; where appropriate, performs manual calculations or simple programming checks to verify the output.

9. References

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