Medtronic

Clinical Investigation Plan Title	Impact of Acetaminophen on Performance of Guardian™ Sensor (3) in Adults
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Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	Impact of Acetaminophen on Performance of Guardian™ Sensor (3) in Adults
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Table of Contents

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0 13-JUL-2020	• New Document	[redacted]

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
HbA1c	Glycosylated hemoglobin
AE	Adverse Event
BG	Blood Glucose
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
CGMS	Continuous Glucose Monitoring System
CI	Confidence Interval
CIP	Clinical Investigation Plan
DKA	Diabetic Ketoacidosis
eCRF	Electronic Case Report Form
FST	Frequent Sample Testing
GST	Glucose Sensor Transmitter
MARD	Mean Absolute Relative Difference
RF	Radio Frequency
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SG	Sensor Glucose
SMBG	Self-Monitoring of Blood Glucose
SQ	Subcutaneous
UADE	Unanticipated Adverse Device Effect
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 attached to a transmitter, which typically 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.

Previous in vitro testing has demonstrated that the presence of acetaminophen can be associated with a minimal increase in the positive bias of the sensor glucose reading relative to the true glucose concentration in the test solution. Clinical studies will further characterize the in vivo impact of acetaminophen ingestion on sensor accuracy.

Following completion of the study, raw sensor data collected by the Guardian™ Connect Transmitters will be processed using the C and Zeus algorithms. For the C algorithm, sensor glucose will be generated based on 2 calibrations per day. For the Zeus algorithm, sensor glucose will be generated based on 0 calibration and 2 calibrations on Day 1.

4. Study Objectives

Error! Reference source not found. The primary objective of the study is to characterize the impact of acetaminophen ingestion on the accuracy of Guardian™ Sensor (3) (i.e., C algorithm and Zeus algorithm) with the system in subjects 18-80 years of age.

5. Investigation Plan

The study is a multi-center, prospective, single-arm study without controls.

See CIP Section 5 for additional details on Study Design.

A total of up to 150 previously-diagnosed type 1 or type 2 diabetes subjects will be enrolled in order to have 75 subjects complete the study. Up to 9 investigational centers in the US will be used during the study.

Subjects will wear two sensors (one sensor in the abdomen and one in the arm location) and undergo 6 hours of FST on Day 4 (74-98 hours) or Day 5 (98-122 hours). No randomization or blinding will be used.

6. Determination of Sample Size

Given that this study is not statistically powered, no sample size calculation is performed. Due to potential attritions of sensor data, up to 150 subjects will be enrolled at up to 9 investigational centers in order to have 75 subjects who complete the study.

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 CIP deviations will be presented in the listings.

7.1.3 Analysis Sets

The primary study population consists of all enrolled subjects who have at least one paired sensor and YSI™* measurement. In addition, subjects who are not qualified (e.g., fail to meet the fasting requirement or are impacted by unexpected conditions during FST) will be determined and excluded from the analysis.

All enrolled subjects 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 for analysis.

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

In determining the phase of adverse events and protocol deviations or in calculating the duration of diabetes, the first day of the month will be used for event dates with known year and month but unknown day, unless specified otherwise in the description; similarly, the first day of the year will be used for event dates with known year but unknown month and day, unless specified otherwise.

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

7.5 Adjustments for Multiple Comparisons

No adjustments will be made.

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

Baseline and 1-hour post-ingestion serum acetaminophen concentration will be summarized.

7.8 Interim Analyses

No interim analysis will be conducted.

7.9 Evaluation of Objectives

7.9.1 Primary Endpoints

Bias between the Guardian™ Sensor (3) values and YSI™* plasma glucose values during the 1 hour before and 5 hours after ingestion of acetaminophen will be described by each hour. Summary statistics will include its mean, standard deviation, median, 95% confidence interval (CI), minimum, and maximum.

7.9.2 Secondary Endpoints

Mean absolute relative difference (MARD) between the Guardian™ Sensor (3) values and YSI™* plasma glucose values during the 1 hour before and 5 hours after ingestion of acetaminophen will be described by each hour. Summary statistics will include its mean, standard deviation, median, 95% CI, minimum, and maximum.

20% mean agreement rate (±20 mg/dL (1.1 mmol/L) when reference YSI™* plasma glucose value less than or equal to (≤) 80 mg/dL (4.4 mmol/L) between the Guardian™ Sensor (3) values and YSI™* plasma glucose values during the 1 hour before and 5 hours after ingestion of acetaminophen will be described by each hour. Summary statistics will include its mean, standard deviation, median, 95% CI, minimum, and maximum.

7.10 Safety Evaluation

7.10.1 Adverse Events (AE)

Descriptive summary will be used to characterize all adverse events (AE):

- Serious Adverse Events (SAEs)
- Adverse Device Effects
- Procedure Related AEs
- Serious Adverse Device Effect (SADEs)
- Unanticipated Adverse Device Effects (UADEs)
- Severe hypoglycemia
- Diabetic Ketoacidosis (DKA)
- Deaths

7.10.2 Device Deficiencies

Descriptive summary will be used to characterize device deficiencies:

- All Investigational Center/subject reports of sensor damage, breakage or fracture will be included

7.11 Health Outcomes Analyses

Not Applicable

7.12 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

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. 28:1245-1249, 2005