Medtronic

Study Title	Use of the Guardian™ Connect System With Smart Connected Devices
NCT Number	NCT04809285
Document Description	Clinical Biostatistical Plan (Version 1.0)
Document Date	13-JAN-2022

Medtronic Statistical Analysis Plan	
Clinical Investigation Plan Title	**Use of the Guardian™ Connect system with Smart Connected Devices**
Clinical Investigation Plan Identifier	**331**
Statistical Analysis Plan Version Date	**13-Jan-2022**
Sponsor/Local Sponsor	**Medtronic MiniMed, Inc.** **(“Medtronic”)** **18000 Devonshire St** **Northridge, CA 91325** **866.948.6633**

Table of Contents

1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	[redacted]

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
BMI	Body Mass Index
CGM	Continuous Glucose Monitoring
CIP	Clinical Investigation Plan
DKA	Diabetic Ketoacidosis
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice

3. Introduction

In patients with insulin dependent diabetes mellitus, glycemic control is influenced by numerous factors, such as insulin dosage, insulin absorption, timing, physiological/lifestyle factors such as exercise, food intake, sleep, hormones and illness. These factors may contribute to significant variability in insulin requirements, which makes self-management of diabetes challenging.

Today, there are 55 million patients globally taking insulin through injections as compared to the 1 million administering insulin via pump therapy. Some of these patients will move to insulin pump therapy over the course of their lifetime, but the majority will continue using injections. Their rationale to continue with insulin injections include the following reasons:

- There is higher patient out-of-pocket cost associated with pump therapy;
- The physical experience of wearing a pump device is not appealing; and
- There has been growth in new therapy options available to injection users, such as CGM, smart pens, and decision support apps.[1]

While CGM has greatly improved a patient's ability to get rapid and accurate glucose readings, patients are still required to make hundreds of decisions a day with little guidance on what to eat, what to dose, when to dose, and how to manage activities such as exercise. Without actionable therapy guidance, the following key needs remain unmet for these patients:

- Understanding how specific foods, physical activity, sleep patterns, and other routines affect their personal glucose levels;
- Recovering quickly from low and high glucose levels;

- Avoiding overnight lows;
- Optimizing physical exercise to stay in range; and
- Knowing exactly how much insulin to take, and when, at mealtime and throughout the day.[2]

Due to the lack of guidance on the key needs listed above, multiple daily injections (MDI) patients on the current state of the art therapies spend an average of 45-51% of their time within a healthy glycemic range, known as Time in Range (TIR)[3], which is well below the TIR outcomes for pump users[4, 5]. The overall goal of the Smart CGM system is to significantly improve TIR and quality of life (QOL) for injection-based insulin users by improving the user experience in three key areas:

(1) Personalizing dosing recommendations that are tailored to the patient's own physiology, lifestyle, and diabetes state;

(2) Providing holistic decision support to the user in point-of-care situations; and,

(3) Reducing the burden of logging information relevant to diabetes management.

The Smart CGM system will accomplish this by providing the patient with intelligent automation, detection, insights, and recommendations that will enable them to achieve significantly improved TIR and QOL as an MDI user.

4. Study Objectives

The primary objective of this feasibility study is to collect data to be used for development of Medtronic Diabetes and Cardiac Diagnostics devices and products.

5. Investigation Plan

The study is a multi-center, prospective single-arm design without controls. All subjects will participate for a minimum of 90 days (Phase 1) and some subjects 18 years of age or older will participate for up to 9 months (Phase 2). All subjects will wear the Guardian Connect system (real-time continuous glucose monitoring (CGM)) continuously and use smart insulin pens or insulin pens with smart caps for multiple daily injections and continue their standard therapy throughout the duration of the study.

See CIP Section 5 for additional details on Study Design.

The purpose of this study is to collect sensor, insulin, sleep, activity and food/meal data for a minimum of 90 days of wear (Phase 1) and up to a maximum of 9 months of device wear (Phase 2) with optional insulin injection video capture and/or menstrual cycle tracking and/or cardiac monitoring in subjects with insulin requiring diabetes 2-80 years of age.

6. Determination of Sample Size

Up to 500 subjects with insulin-requiring type 1 or type 2 diabetes age 2-80 who use multiple daily injections (MDI) insulin therapy will be enrolled.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

The number of subjects screened, enrolled, completed and withdrawn in the study will be presented. The reasons for subject's withdrawal 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 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 uploading 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 the case of partially missing day and/or month, 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.

In the case of partially missing time, 12am will be used for event times with known day but unknown time, if applicable.

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, type of diabetes mellitus, and BMI (calculated based on provided height and weight) will be summarized by descriptive statistics

7.7 Treatment Characteristics

Not applicable.

7.8 Interim Analyses

No interim analysis will be conducted.

7.9 Evaluation of Objectives

7.9.1 Endpoints

Descriptive statistics will be performed; no statistically powered analyses or hypothesis testing will be performed.

- Glycemic control: Percentage of Time in Range (SG <70 mg/dL, 70-180 mg/dL, and >180 mg/dL)

7.9.2 Other descriptive Endpoints

- Summary of completed data collection/available data
- Summary of study questionnaire results

7.10 Safety Evaluation

7.10.1 Adverse Events (AE)

Descriptive summary will be used to characterize adverse events:

- Serious Adverse Events (SAE)
- Device Related AEs
- Procedure Related AEs
- Serious Adverse Device Effect (SADE)
- Unanticipated Adverse Device Effect (UADE)
- Severe hypoglycemia
- Diabetic Ketoacidosis (DKA)

7.10.2 Device Deficiencies

Descriptive summary will be used to characterize device deficiencies.

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

1. Tanenbaum ML, H.S., Miller KM, Naranjo D, Bensen R, Hood KK, *Diabetes Device Use in Adults with Type 1 Diabetes: Barriers to Uptake and Potential Intervention Targets.* Diabetes Care, 2017. **40**(2): p. 181-187.
2. *Medtronic data on file.*
3. Beck RW, R.T., Ruedy K, et al., *Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections.* JAMA, 2017. **317**: p. 371-378.
4. Garg SK, W.S., Tamborlane WV, et al., *Glucose outcomes with the in-home use hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes.* Diabetes Technology Therapeutics, 2017. **19**: p. 1-9.
5. Bergenstal RM, G.S., Weinzimer SA, et al., *Safety of a hybrid closed-loop insulin delivery system in Patients with type 1 diabetes.* JAMA, 2016. **316**: p. 1407-1408.