Virtual Diabetes Specialty Clinic: A Study Evaluating Remote Initiation of Continuous Glucose Monitoring

VDiSC Study

Statistical Analysis Plan

Version: 1.0

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Based on Protocol Version: 2.0

Note: The table shells are included in a separate document.

Revision History

The following table outlines changes made to the Statistical Analysis Plan.

Version Number	Author	Approver	Effective Date	Study Stage
1.0	Dan Raghinaru	Peter Calhoun	12/30/2020	Study Enrollment

Version Number	Revision Description

Approvals

Role	Digital Signature or Handwritten Signature/Date
Author: Dan Raghinaru	
Senior Statistician: Peter Calhoun	
JCHR Sponsor Representative: Robin Gal	

1 Statistical and Analytical Plans

This document summarizes the proposed analyses to be performed for the Virtual Diabetes Specialty Clinic (VDiSC) study. All analyses are exploratory and additional analyses and outcomes not pre-specified here may be performed in the future. The table shells detailing how the results will be displayed will be shown in a separate document.

2 Study Overview

The following two tables gives an overview of the VDiSC study.

Table 1. Study Overview

PARTICIPANT AREA	DESCRIPTION
Title	Virtual Diabetes Specialty Clinic: A Study Evaluating Remote Initiation of Continuous Glucose Monitoring
Précis	This study will assess feasibility and efficacy of establishing a virtual diabetes clinic with a focus on introduction of CGM technology and ongoing CGM use to minimize such rate-limiting factors as geography, cost and access to specialty care
Objectives	The objective of this study is to evaluate a virtual diabetes clinic model, for adults with either T1D or T2D, that supports integration of CGM into diabetes self-management and use of decision support technology.
Study Design	Single-arm prospective longitudinal study

PARTICIPANT AREA	DESCRIPTION
Eligibility Criteria	**Inclusion Criteria** • Age ≥18 years old • Diagnosis of type 1 diabetes or type 2 diabetes and using insulin therapy (at least 3 injections of insulin per day or insulin pump that is compatible with Tidepool software) *Multiple daily injection (MDI) users must be willing to use a device provided by the study that records the injection dosages and/or enter insulin dosing information through an app* • See a healthcare provider at least once a year • Resident of United States and plan to reside in the U.S. for the duration of the study *This requirement is due to virtual clinic license requirements and U.S. use restrictions for some study software and devices. Not all U.S. states may be eligible for inclusion due to virtual clinic license status.* • Use either an Android or iOS smartphone that is compatible with app requirements that are needed for the study • Access to a compatible computer with internet • Understand written and spoken English • Willing and able to follow the study procedures as instructed **Exclusion Criteria** • Use of real-time CGM (including Abbott Libre or integrated pump system) in last 12 months (interval blinded CGM use is acceptable) • Current use of any off-label glucose-lowering medications for diabetes type (Example: T1D use of non-insulin, anti-diabetic medications including SGLT2 inhibitors) *Use of such medications during the study will also be prohibited.* • Females who are pregnant, intending to become pregnant, or breastfeeding during the study • Current renal dialysis or plan to begin renal dialysis during the study • Active cancer treatment • Extreme visual or hearing impairment that would impair ability to use real-time CGM • Known adhesive allergy/prior skin reaction or skin reaction identified during the blinded CGM use phase that would preclude continued CGM use • Participation in a different diabetes management study during the study • Planned relocation to a state other than current state of residence during the study if virtual clinic is not licensed in the new state. *Individuals working routinely in a state other than current state of residence in the next six months are also ineligible if the virtual clinic is not licensed in that state.*
Sample Size	The recruitment target is 300 initiating CGM.
Outcomes	**Efficacy Outcomes:** CGM use; CGM metrics for hypoglycemia (<54 and <70 mg/dL), hyperglycemia (>180 and >250 mg/dL), time in range (70-180 mg/dL), mean glucose, and glycemic variability (coefficient of variation); HbA1c; participant- reported outcomes including psychosocial and diabetes treatment satisfaction questionnaires **Safety Outcomes:** Severe hypoglycemia, diabetic ketoacidosis, hospitalizations, and emergency room visits
Participant Duration	Study participation will be up to 12 months.
Protocol Overview/Synopsis	Patient Population Adults ≥ 18 years with type 1 diabetes or type 2 diabetes using insulin therapy who are not CGM users will be enrolled. Potential participants

PARTICIPANT AREA	DESCRIPTION
	may be recruited through insurance providers, primary care networks, or health care providers. Baseline Data Collection Baseline data collected will include demographics, height and weight, socioeconomic status, diabetes history, knowledge of and experience with diabetes devices, medical history and medications, and health-related physical activity. Questionnaires will collect information related to hypoglycemia awareness, treatment satisfaction, and psychosocial issues. Participant contact information will be collected. Contact information for the participant's diabetes healthcare provider will also be collected. HbA1c Participant will receive fingerstick HbA1c kits that will be sent to a central lab for measurement after enrollment and at 13 weeks, 26 weeks, 39 weeks, and 52 weeks. Contact between Study Team and Participant Each participant will be assigned to work with virtual clinic team members. Mental health service support options for diabetes-related mental health issues will be discussed as needed. Virtual clinic team members will check in with participants during study follow up to review CGM data and recommendations related to diabetes management. CGM Use Participants will use a blinded CGM device for a single sensor wear period prior to CGM initiation. Participants may be asked to use a blinded CGM for an additional sensor wear period(s) if enough CGM data are not available to establish a baseline that can be used as baseline comparator data. Virtual training will include CGM set up, sensor insertion, alerts and alarms, uploading data, and visualizing data. Changes in Insulin Dosing If the virtual clinic team believes that changes in insulin type or dosing should be considered, they will work with the participant to implement any such changes. Decision support tools, which include use of a mobile application, may be used if available to provide the virtual clinic team with potential recommendations regarding insulin use.

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Table 2. Schedule of Visits and Procedures

				Virtual Clinic Training Phase (0-13 Weeks)					Extended Virtual Clinic Follow Up Phase	Optional Participant Follow Up
	Enrollment	**Initial Virtual Clinic Contact**	**Baseline CGM Data Collection**	**Training 1 (Week 0)**	**Training 2 (Week 1)**	**Training 3 (Week 3)**	**CGM Follow Up (Weeks 4, 8)**	**CGM Follow Up (Week 13)**	**Follow up (>13-26 Weeks)**	**Follow Up (>26-52 Weeks)**
TARGET WINDOW		Within 7 Days from Completion of Enrollment Questionnaires		Day 0	Day 7-14	Day 21-28		Weeks 12-14		
ICF • **Eligibility Confirmation**	X								X*	X*
Baseline Data Collection • **Contact Information** • **Demographics** • **Medical History** • **Questionnaires**	X		X							
Follow-Up Data Collection**					X	X	X	X	X	X
HbA1c***			X					X	X	X
Video Tutorials / Access to Resource Materials		*Examples:* *CGM Overview* *Parts of CGM*	*Examples:* *HbA1c Sample Collection* *CGM Setup*	*Examples:* *Understanding Your Real-Time Data* *How to Change Sensor*	*Examples:* *How to Upload CGM Data* *How to View Reports* *Understanding Your Ambulatory Glucose Profile / Data Patterns*	X	X	X	X	
Contact with Study Team†		X	X	CGM Initiation	CGM Data Interpretation	CGM Data Review Goal Setting	X	X	X	
CGM Use††			~2 Week Blinded CGM Use	Start of 26-Week Unblinded CGM Use	X	X	X	X	X	

*Virtual Clinic Training and Follow up phase ends at 26 weeks. Participant will be asked to extend follow up for an additional 26 weeks and sign an addendum ICF if they plan to continue to use CGM after the first 26 weeks.
**Participants will be asked to complete questionnaires monthly after CGM Initiation. A final questionnaire will be elicited at the earlier of CGM discontinuation or completion of study follow up (~52 weeks).
***HbA1c checks prior to unblinded CGM initiation, and at 3-month intervals following CGM initiation (~13 weeks, 26 weeks, 39 weeks, and 52 weeks)
†Follow up may be via phone, text, virtual (i.e. Skype), or app. outside of scheduled training. Additional follow up may be conducted as needed. Participants may follow up with study team as needed.
††CGM supplied for blinded data collection will be provided. CGM supplies for six months of unblinded use will be provided for those who successfully complete blinded data collection.

3 Statistical Hypotheses

There are no primary outcomes and additional analyses not pre-specified here may be performed. In this study, we expect that most hypothesis testing will involve testing whether the change from baseline for various outcomes is significantly different from zero. This will primarily be for the CGM metrics, HbA1c, and the questionnaires. In those cases, the null hypothesis of the change from baseline being equal to zero will be tested against the alternative hypothesis that the change from baseline is nonzero. Analyses will be stratified by type of diabetes.

4 Sample Size

The goal for the study is to include at least 300 participants who initiate CGM. This is a convenience sample and not based on statistical principles.

5 Outcome Measures

The following quantitative study outcome measures will be tabulated by diabetes type using summary statistics appropriate to the distribution:

- HbA1c
- Percentage of time using the CGM
- Hours of CGM use
- Mean of sensor glucose levels
- Percentage of time spent with sensor glucose levels <54 and <70 mg/dL
- Percentage of time spent with sensor glucose levels >180 and >250 mg/dL
- Percentage of time spent with sensor glucose levels in the target range (70-180 mg/dL)
- Glycemic variability measured by the coefficient of variation
- Total daily insulin (units/kg)
- Total daily basal insulin (units/kg)
- Total daily bolus insulin (units/kg)
- Patient Health Questionnaire-8
- Diabetes Distress Scale Management Distress Subscale
- Hypoglycemia Fear Survey Worry Subscale
- CDC Healthy Days
- Hypoglycemia Confidence Survey
- Diabetes Technology Attitudes Survey
- Glucose Monitoring Satisfaction Survey
    - Openness Subscale
    - Emotional Burden Subscale
    - Behavioral Burden Subscale
    - Trust Subscale
- Sleep Quality Scale
- Benefits and Barriers of CGM Survey
- Percentage of CGM discontinuations
- CGM Discontinuation Survey (only administered to subjects who discontinue CGM)
- Positive screen for mental health

    - Positive screen triggered by Patient Health Questionnaire-8
    - Positive screen triggered by Diabetes Distress Scale
    - Positive screen triggered by Hypoglycemic Fear Survey Worry Scale
- Behavioral health service utilization
- Behavioral health metrics
- Cost of care over time
- Service utilization such as hospitalizations, ER visits, prescriptions filled

CGM, HbA1c, and insulin outcomes will be evaluated at baseline and 13, 26, 39, and 52 weeks. CGM and insulin outcomes will also be evaluated over the first 26 weeks and last 26 weeks. Questionnaires will be evaluated at all time points they are collected.

6 Description of Statistical Methods

6.1 Analysis Cohorts

- All subjects enrolled in the study who initiate the CGM and have at least 168 hours of CGM data will be included in the tabulations of demographics and the glycemic outcome measures listed in Section 5
- CGM use assessment will include all subjects who stayed in the study at least one week following CGM initiation.
- HbA1c, questionnaires, insulin, and other analyses will include all subjects with any amount of corresponding data following CGM initiation.
- The tabulations of the safety outcomes will include all participants who enrolled, regardless of how much data is available.

7 Analysis of Study Endpoints

7.1 Calculation of CGM Metrics

7.1.1 Calculation of 13 Week CGM Metrics

All CGM metrics listed in Section 5 will be calculated on a 13-week period for each subject level. The windows for the 13-week periods are defined as follows:

Time Point	Window
1-13 Weeks	0 to 91 days after the CGM initiation date
14-26 Weeks	92 to 183 days after the CGM initiation date
27-39 Weeks	184 to 274 days after the CGM initiation date
40-52 Weeks	275 to 365 days after the CGM initiation date

For each 13-week period, CGM metrics will be calculated by pooling all CGM readings occurring from 12:00 AM on the first day of the 13-week period up until 11:59PM on the last day of the 13-week period. For the first 13-week period, the first CGM reading will be the start datetime of the period. If a participant discontinues CGM prior to the last day of the 13-week period, then CGM data will include readings up to the last CGM reading on the discontinuation date. Calibrations will be excluded from all these calculations. CGM metrics for 13-week periods with less than 168 hours of CGM data will be set to missing.

Baseline CGM metrics will be calculated by pooling all blinded CGM readings up to 90 days prior to the date of CGM initiation for each subject. Baseline CGM metrics with less than 72 hours of CGM data will be set to missing.

The amount of time using the CGM will be calculated as the number of CGM values multiplied by the expected CGM measurement frequency (i.e., 5min in general), with the exception that there can only be one value within the CGM measurement frequency. Percentage of time CGM is used will be calculated as the amount of time using the CGM divided by the total possible time the participant could have used the CGM during the same period. Note that this denominator includes sensor warm-up periods with no CGM values, so this metric will serve as a conservative estimate of CGM use.

7.1.2 Calculation of 4 Week CGM Metrics

All CGM metrics listed in Section 5 also will be calculated on a 4-week interval for each subject. The windows of the 4-week periods is defined as follows:

Time Point	Window
1-4 Weeks	0 to 28 days after the CGM initiation date
5-8 Weeks	29 to 56 days after the CGM initiation date
9-12 Weeks	57 to 84 days after the CGM initiation date
13-16 Weeks	85 to 112 days after the CGM initiation date
17-20 Weeks	113 to 140 days after the CGM initiation date
21-24 Weeks	141 to 168 days after the CGM initiation date
25-28 Weeks	169 to 196 days after the CGM initiation date
29-32 Weeks	223 to 224 days after the CGM initiation date
33-36 Weeks	225 to 252 days after the CGM initiation date
37-40 Weeks	253 to 280 days after the CGM initiation date
41-44 Weeks	281 to 308 days after the CGM initiation date
45-48 Weeks	309 to 336 days after the CGM initiation date
49-52 Weeks	337 to 365 days after the CGM initiation date

For each 4-week interval, CGM metrics will be calculated by pooling all CGM readings occurring from 12:00 AM on the first day of the 4-week interval up until 11:59PM on the last day of the 4-week period. For the first 4-week interval, the first day will be the day after CGM initiation date. If a participant discontinues CGM prior to the last day of the 4-week period, then CGM data will include readings up to the day before CGM discontinuation date. Calibrations will be excluded from all these calculations. CGM metrics for 4-week periods with less than 168 hours of CGM data will be set to missing.

7.1.3 Calculation of CGM Metrics during the First and Last 26 Weeks of the Study

All CGM metrics listed in Section 5 also will be calculated for the first and last 26 weeks of the study for each subject. CGM metrics will be calculated by pooling all CGM readings in the first 26 weeks (i.e., 1-13 and 14-26 week periods defined above) and last 26 weeks (i.e., 27-39 and 40-52 week periods defined above). In these calculations, subjects that discontinue use of the CGM during the period of time that is being evaluated will also be handled in the same way as

described above. Calibrations will be excluded from the calculations. CGM metrics for 26-week periods with less than 168 hours of CGM data will be set to missing.

7.2 Calculation of Questionnaire Scores

Data from the following questionnaires will be reported at each time point collected:

- Patient Health Questionnaire-8: This questionnaire consists of 8 items, and it is typically used to screen for depression. Each item is scored on a scale of 0 to 3, with a higher value denoting more depressive symptoms. The total score is calculated by summing the individual responses to each question. Per the scoring instructions, total scores are set to missing for participants who skip more than one question. A total score of ≥10 denotes major depression, and a score of ≥20 denotes severe major depression.
- Diabetes Distress Scale Management Distress Subscale: This questionnaire consists of questions about the participant's distress regarding diabetes management. Items are ranked on a scale of 1 to 6, where a 1 denotes that the item is not a problem at all and a 6 denotes that it is a very serious problem. For this questionnaire, a mean score will be calculated across all questions.
- Hypoglycemia Fear Survey Worry Subscale: This questionnaire consists of items asking the participant about his or her worries regarding what may occur as a result of low blood sugar. Items are scored on a scale of 0 to 4. Higher numbers denote responses that are more worrisome. The total score is calculated by summing the responses to each question.
- CDC Healthy Days: This is a questionnaire about the participant's general mental and physical health. It estimates the number of days that the participant's mental and physical health has been adequate over the past month, in addition to the impact that the participant's health has had on his or her daily life. Analyses will report the percentage of participants ranking their general health as either fair or poor. Additionally, the number of unhealthy days over the past 30 days will be calculated by summing the number of reported unhealthy mental and physical days. The sum will be truncated at 30 days if it exceeds 30.
- Hypoglycemia Confidence Survey: This questionnaire asks the participant about their level of confidence regarding the avoidance of problems with daily activities due to hypoglycemia. Items are ranked on a scale of 1 to 4, with higher numbers denoting a higher level of confidence. For this questionnaire, a mean score will be calculated across questions.
- Diabetes Technology Attitudes Survey: This questionnaire consists of 5 questions about diabetes technology. Responses to each question are ranked on a scale of 1 to 5. Higher numbers denote more satisfaction with diabetes technology. A total score is calculated as the sum of the individual responses to each question.
- Glucose Monitoring Satisfaction Survey: This questionnaire asks the participant to provide a response on a scale of 1 to 5 to several questions about their satisfaction with their current glucose monitor. The directionality of the responses varies across questions, so some questions are reverse scored in the calculation of scores. The questionnaire includes four subscales, and the overall score is tabulated as a mean across all questions for the full questionnaire and each subscale.

- Sleep Quality Scale: This questionnaire consists of a single item asking the participant to rank their sleep quality on a scale of 0 to 10, with a higher number denoting better sleep. For this questionnaire, a mean score will be calculated across questions.
- Benefit of CGM Survey: This questionnaire asks the participants questions about things that are good about wearing a CGM. The participants are asked to rank their agreement with each statement on a scale of 1 to 5. A higher number indicates more agreement, which would imply more satisfaction with using a CGM. For this questionnaire, a mean score will be calculated across questions.
- Barriers of CGM Survey: This questionnaire asks the participants questions about things that are bad about wearing a CGM. The participants are asked to rank their agreement with each statement on a scale of 1 to 5. A higher number indicates more agreement, which would imply less satisfaction with using a CGM. For this questionnaire, a mean score will be calculated across questions.
- CGM Discontinuation Survey (only administered to subjects who discontinue CGM): This questionnaire asks the participants several questions about why they discontinued CGM. For this survey, only responses to each individual question will be tabulated.

The electronic data capture system for this study will allow the subjects to skip questions on the questionnaires. For all questionnaires, at least 75% of questions must be answered in order to be included in the analyses (unless specified otherwise above). The 75% rule described above will be applied separately for the mean score and each subscale so it is possible that the sample size will be different for some subscales. The score used for the analyses will only be based on the questions that were answered. Analyses will be limited to subjects who are included in the primary cohort (no imputation).

7.3 Missing Data

Missing data will not be imputed for any outcomes in this study and will be handled by means of direct likelihood analyses.

7.4 Statistical Methods

For all outcomes, summary statistics appropriate to the distribution will be tabulated on a subject level overall and within the subgroups defined in Section 12. For the CGM metrics, summary statistics appropriate to the distribution also will be tabulated for each 4-week interval and for the first and last 26 weeks of the study. For the questionnaires, summary statistics will be reported for the mean scores in addition to the individual responses for each question.

For all outcomes, a linear mixed model with a random subject effect will be used to test whether the mean change from baseline significantly differs from zero. These models will be fit for each of the subject level CGM metrics and HbA1c at 13, 26, 39, and 52 weeks. They also will be fit for the questionnaires at 26 and 52 weeks. If values are skewed, then winsorization will be utilized. Point estimates and 95% confidence intervals for change in glycemic outcomes will be reported.

For the three mental health screening questionnaires, only summary statistics will be tabulated. The three mental health screening questionnaires falling under this umbrella are the Patient

Health Questionnaire-8, the Diabetes Distress Scale (Management Distress Subscale), and the Fear of Hypoglycemia Survey (Worry Subscale).

7.5 Analyses Windows

For HbA1c, only measurements occurring within ±45 days of the target measurement date at a given time point will be included in the tabulation of summary statistics. The windows for glycemic metrics were defined above in Section 7.1.

7.6 Sensitivity Analyses

For CGM and HbA1c outcomes, a complete-case analysis restricting to non-missing outcomes will also be assessed. A paired t-test (for normally distributed outcomes) or a Wilcoxon signed rank test (for skewed outcomes) will be used.

8 Safety Analyses

All adverse events that occur on or after the date of enrollment will be listed in a table.

For events occurring on or after the date of CGM initiation, the reported safety outcomes include diabetic ketoacidosis (DKA), severe hypoglycemia (SH), hospitalization, and emergency room visits. The following statistics will be tabulated for each safety outcome:

- Total number of events
- Number and proportion of subjects with an event (discretized into bins)
- Incidence rate per 100 person years

The number of person-years for the incidence rate calculations will be inclusively defined as the number of person-years in between the CGM initiation date and the last day of study follow-up (completion date, withdrawal date, etc.).

9 Adherence and Retention Analyses

9.1 Protocol Adherence

The number of and reasons for participant contacts with the virtual clinic will be reported in a table to assess protocol adherence for the study.

10 Baseline Descriptive Statistics

Baseline demographic and clinical characteristics of the cohort of all subjects who initiate the CGM and were included in the glycemic analyses will be summarized in a table. Use of medications and non-insulin therapy will also be reported. For continuous variables, summary statistics appropriate to the distribution will be given. For discrete variables, number and percentage will be reported for each category. Summary statistics for demographics and clinical characteristics will be presented overall, by diabetes type, by insulin modality, by whether the participant was seeing an endocrinologist or a primary care provider at baseline, by baseline HbA1c groups (<7.5%, 7.5% to <9.0%, and ≥9.0%), and by age (<25, 25-65, and >65 years). Cut points for age and baseline HbA1c may be reassessed after data are collected.

11 Planned Interim Analyses

No formal interim analyses or stopping guidelines are planned for this study. Data will be monitored on an ongoing basis including:

- Status of enrolled participants
- Recruitment rates by month and by site
- Baseline demographic and clinical characteristics
- Dropped participants and reasons for discontinuing
- Reportable adverse events

12 Subgroup Analyses

Subgroup analyses for % of time using the CGM, % time in range, % time >180 mg/dL, % time <70 mg/dL, and HbA1c will be performed based on the following factors:

- Baseline HbA1c (categorized as <7.5%, 7.5% to <9.0%, and ≥9.0%)
- Insulin modality
- Age (categorized as <25, 25-65, and >65)
- Type of healthcare provider (endocrinologist or primary care provider)
- Diabetes Duration (categorized as <5, 5-<10, 10-<20, ≥20)
- Race/Ethnicity
- Household income (categorized as <$50,000, $50,000-<$100,000, and ≥$100,000)

For continuous variables, results will be displayed in subgroups based on cut points although the analysis will utilize the variable as continuous. Cut points for age, baseline HbA1c, diabetes duration, and household income may be reassessed after the data are collected.

Within each subgroup, summary statistics will be tabulated. P-values for change from baseline will be calculated within each subgroup using a linear mixed model will be performed as described in Section 7.4.

Percentage of CGM discontinuations will also be tabulated by the factors listed above.

13 Multiple Comparisons

No adjustments for multiple comparisons will be made.

14 Additional Analyses

CGM metrics over 13-week periods will be tabulated on a subject level by time of day. In these analyses, daytime will be defined as 6:00 AM to <12:00 AM and nighttime will be defined as 12:00 AM to <6:00 AM. For this analysis, CGM metrics will only be calculated if the participant has at least 126 hours of CGM data during daytime and at least 42 hours of CGM data during nighttime.

Total scores for questionnaires in Section 7.2 will be stratified by number of mental health service sessions. Additional analyses will be conducted to assess the bivariate relationship between questionnaire responses and glycemic metrics at 26 and 52 weeks. These relationships will be assessed by displaying scatterplots, along with the corresponding Spearman correlation

coefficient. A 95% confidence interval for the Spearman correlation coefficient will be reported. In these analyses, the following relationships will be explored:

- % Time <70 mg/dL vs. Fear of Hypoglycemia Worry Subscale Mean Score
- % Time <70 mg/dL vs. Hypoglycemia Confidence Survey Mean Score
- % Time in Range vs. Glucose Monitoring Satisfaction Survey Mean Score
- % Time in Range vs. Diabetes Distress Scale Management Distress Subscale Mean Score
- CGM use at 26 weeks vs. Diabetes Technology Attitudes Survey Mean Score