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

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
BGM	Blood Glucose Meter
CDC	Centers for Disease Control and Prevention
CDCES	Certified Diabetes Care and Education Specialist
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitor
DKA	Diabetic Ketoacidosis
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
IRB	Institutional Review Board
MDI	Multiple Daily Injections
SH	Severe Hypoglycemia
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes

PROTOCOL SUMMARY

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 evaluates use of decision support technology within the virtual clinic model.
Study Design	Single-arm prospective longitudinal study
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** • Current use of a closed loop system where an insulin pump and CGM share information and insulin dose is automatically adjusted based on glucose reading • Current CGM use where Time in Range is ≥60% or Time <54% ≤1.0%). • 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

PARTICIPANT AREA	DESCRIPTION
	• 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 will be enrolled. Although the primary focus of the study is to enroll non-CGM users, CGM users whose glycemic control is suboptimal can be enrolled. Potential participants 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 the initial six months of study follow up to review CGM data and recommendations related to diabetes management. Participants who continue in the optional extended follow-up phase after the first six months can contact the virtual clinic as needed. CGM Use Participants who do not currently use a CGM 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. Current CGM users will be asked to share their CGM data to confirm that they meet study eligibility criteria and 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

PARTICIPANT AREA	DESCRIPTION
	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.

SCHEDULE OF STUDY VISITS AND PROCEDURES

This is a remote study design with virtual visits; eligibility and other study questionnaires are by participant self-report.

				Virtual Clinic Training Phase (0-13 Weeks)					Virtual Clinic Follow Up Phase	Optional Extended 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	X
Contact with Study Team†		X	X	CGM Initiation	CGM Data Interpretation	CGM Data Review Goal Setting	X	X	X	X
CGM Use††			~2 Week Blinded CGM Use†††	Start of 26-Week Unblinded CGM Use	X	X	X	X	X	X

*. Participants 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. Virtual Clinic follow up will be available to participants on an as-needed basis 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.

†††Current CGM users are not required to wear blinded CGM unless current CGM data cannot be shared to establish baseline.

Chapter 1: Background Information

1.1 Introduction

The advent of home blood glucose meter (BGM) testing from a fingerstick in the 1980s had a major impact on the management of diabetes, particularly in individuals using insulin. While BGMs remain the method of glucose monitoring for most people with diabetes, continuous glucose monitoring (CGM) systems are now available and have replaced BGM testing for primary glucose monitoring in an increasing number of adults and children with type 1 diabetes (T1D) and some with type 2 diabetes (T2D).

The CGM device has a sensor that is inserted in the subcutaneous space and measures the interstitial fluid glucose concentration. Some CGMs, such as the Dexcom G6, provide real-time glucose measurements every five minutes with alerts for rising or dropping glucose levels and threshold alarms when a preset hyperglycemia or hypoglycemia level is reached. Other CGMs such as the Abbott FreeStyle Libre, which also has been referred to as flash glucose monitoring, show glucose levels only when the user passes the receiver over the sensor to transmit the glucose data to the receiver; glucose recordings are every 15 minutes.

The accuracy of current generation CGMs approaches that of blood glucose meters. For the current generation of the Dexcom and Abbott sensor, the mean absolute relative difference, a common metric for assessing accuracy when sensor glucose values are compared with reference glucose values, is about 10% or lower, which is in about the middle of the range of accuracy of current blood glucose meters[1,2]. This accuracy is what led the FDA to approve the device for non-adjunctive use in dosing insulin.

The efficacy of CGM has been demonstrated in randomized trials of adults and youth with type 1 diabetes (T1D)[3-10], adults with type 2 diabetes (T2D) using insulin[11-13], and in a registry of adults and youth with T1D [14]; including reductions in HbA1c levels, duration of hyperglycemia and hypoglycemia, and increased time spent with glucose levels between 70 and 180 mg/dL, which is the target range. Studies not only demonstrated improvement in HbA1c and reduction in hypoglycemia but also showed that after six months, approximately 90% of individuals were using CGM on a daily or near-daily basis. CGM users have reported substantial satisfaction with use of the device and improved quality of life.[3,9,15-18]

Studies have demonstrated the benefits of CGM in individuals with T1D or T2D treated with multiple daily injections of insulin[3,5,6,9,15,16]. In the T1D Exchange registry, CGM use (predominately Dexcom) was associated with lower HbA1c levels irrespective of whether a pump or injections are used for insulin delivery. Mean HbA1c was 9.1% in individuals not using a pump or CGM, 8.6% in those using a pump but not a CGM, 7.9% in those using both a pump and CGM, and 8.0% in those using injections and CGM.

Current generation CGMs have been shown to have a good safety profile. The ease of insertion, lack of need for calibration or routine blood glucose meter testing, and extension of sensor life have all made the initiation of CGM easier. Thus, the time has come to consider initiation of CGM use as similar to BGM use.

CGM use has been endorsed for individuals with T1D by the American Diabetes Association, the American Association of Clinical Endocrinologists, the Endocrine Society, and the International Society for Pediatric and Adolescent Diabetes. Despite these recommendations and

the compelling evidence of the benefits of CGM, many individuals with T1D or insulin-using T2D have not incorporated CGM into their diabetes management. Although there are not specific data to cite, it is likely that the low rate of CGM adoption partially reflects a lack of awareness about CGM among primary care providers, who are responsible for the care of not only most adults with type 2 diabetes but also those with type 1 diabetes [19-21]. Lack of provider resources to introduce and incorporate CGM into patient diabetes self-management may also be a limiting factor to technology adoption, as usage is low even among some leading diabetes centers[14,22]. Although demand for endocrinology care continues to grow, access to specialized care may be impacted by geographic isolation and a shortage in the number of endocrinologists in the United States.

A recently completed feasibility study assessed whether adults with T1D or T2D using insulin could be trained virtually, outside of the clinic, to initiate and use CGM as part of their diabetes self-management. This study demonstrated that a virtual approach outside of the clinic can be used for successful CGM initiation and incorporation into diabetes self-management for adults with T1D or T2D using insulin. There was a substantial reduction in HbA1c in most participants, as well as a reduction in estimated mean glucose, with an increase in the amount of time in range spent with glucose levels between 70 and 180 mg/dL, which is the generally accepted target range for most adults with T1D or T2D (excluding pregnancy)[23]. Further, participant-reported outcomes evaluated before and after exposure to the virtual clinic revealed improvements in glucose monitoring satisfaction, confidence in treating hypoglycemia, and reductions in diabetes distress.

It is important for those using CGM to understand how to use the data from the CGM. This includes looking at patterns and trends to understand what their glucose is doing and how it changes while sleeping, in between meals, and during periods of exercise and stress. Understanding CGM data extends beyond responding to alerts and warnings when levels are too high and too low. Current CGM users may benefit from virtual clinic support to better understand their CGM data, as not all CGM users meet goals for time in range or HbA1c target.

We plan to assess feasibility and efficacy of establishing a virtual diabetes clinic with a focus on introduction and training related to use of CGM technology and ongoing CGM use to minimize such rate-limiting factors as geography, cost and access to specialty care. The virtual diabetes clinic model will include a comprehensive care team with support for diabetes technology such as CGM and decision support to align with current recommendations in diabetes care. Screening for and access to diabetes-related mental health support will also be included.

1.2 Rationale

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 evaluates use of decision support technology within the virtual clinic model. The virtual diabetes clinic model will also include mental health screening and support services, particularly for diabetes-related issues.

1.3 Potential Risks and Benefits

1.3.1 Known Potential Risks

The fingerstick to collect the HbA1c sample could cause bruising and/or pain at the collection site.

The CGM sensor may produce pain when it is inserted into the skin. There is a low risk for developing a local skin infection at the site of the sensor needle placement. Itchiness, redness, bleeding, and bruising at the insertion site may occur as well as local tape allergies. On rare occasions, the sensor may break and leave a small portion of the sensor under the skin that may cause redness, swelling, or pain at the insertion site.

There is a small risk of hypoglycemia when using CGM for insulin dosing if the CGM glucose value is substantially higher than the true glucose level. There also is a small risk of hyperglycemia if the CGM glucose is substantially lower than the true glucose.

There is a risk of breach of confidentiality. All data will be maintained in a secure database with restricted access to help assure confidentiality. Data downloaded from diabetes devices will be collected for the study. Some people may be uncomfortable with the researchers having such detailed information about their daily diabetes habits.

There is the possibility that completion of questionnaires could make the participant feel uncomfortable.

The study may include other risks that are unknown at this time.

1.3.2 Known Potential Benefits

It is likely that the participants will benefit from access to a virtual diabetes specialty clinic and using CGM in the study. However, it is possible that participants will not directly benefit from being a part of this study.

1.3.3 Risk Assessment

The protocol risk assessment for this study has been categorized as not greater than minimal risk.

1.4 General Considerations

The study is being conducted in compliance with the policies described in the study policies document, with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice (GCP).

Chapter 2: Study Enrollment and Baseline Data Collection

2.1 Participant Recruitment and Informed Consent

Adults (age ≥18 years) with type 1 diabetes or type 2 diabetes using insulin therapy (Tidepool-compatible pump or injections) will be enrolled. Although the primary focus of the study is to enroll non-CGM users, CGM users whose glycemic control is suboptimal can be enrolled. Participation will be limited to U.S. residents in states where the virtual clinic is licensed; state eligibility will be verified as part of screening. Potential participants may be recruited through insurance providers, primary care networks, or health care providers. Potential participants also may become aware of the study by other means, such as another study participant.

Up to 800 individuals may sign the informed consent form to initiate screening. Enrollment will proceed with the goal of at least 300 participants initiating training for CGM use with the Virtual Clinic. The goal will be to limit T2D enrollment to no more than 100. Recruitment efforts will be focused on participants who receive diabetes care in a primary care setting rather than through an endocrinologist, with a goal of having at least 225 who have not seen an endocrinologist in the past six months. Eligible participants will be included without regard to gender, race, or ethnicity.

The goal will be to include at least 50 participants <25 years of age and at least 50 participants >65 years of age.

2.1.1 Informed Consent and Authorization Procedures

Individuals who indicate that they are interested will be directed to a website with information about the study. Interested individuals will be able to communicate with study staff who can answer questions about the study as part of the informed consent process. Individuals who want to participate in the study will sign the Institutional Review Board (IRB) approved electronic consent form. As part of the informed consent process, each participant will be asked to sign an authorization for release of personal information. Participants will be asked to sign an addendum consent for follow up after the first 6 months if they plan to continue use of CGM.

2.2 Participant Inclusion Criteria

Individuals must meet all the following inclusion criteria in order to be eligible to participate in the study:

1. Age ≥18 years old
2. 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 enter insulin dosing information through an app
3. See a healthcare provider at least once a year
4. 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.

5. Use either an Android or iOS smartphone that is compatible with app requirements that are needed for the study
6. Access to a compatible computer with internet
7. Understand written and spoken English
8. Willing and able to follow the study procedures as instructed

2.3 Participant Exclusion Criteria

Individuals meeting any of the following exclusion criteria at baseline will be excluded from study participation:

1. Current use of a closed loop system where an insulin pump and CGM share information and insulin dose is automatically adjusted based on glucose reading
2. Current CGM use where Time in Range is ≥60.0% or Time <54% is ≤1.0%.
3. 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.
4. Females who are pregnant, intending to become pregnant, or breastfeeding during the study
5. Current renal dialysis or plan to begin renal dialysis during the study
6. Active cancer treatment
7. Extreme visual or hearing impairment that would impair ability to use real-time CGM
8. Known adhesive allergy/prior skin reaction or skin reaction identified during the blinded CGM use phase that would preclude continued CGM use
9. Participation in a different diabetes management study during the study
10. 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.

2.4 Screening Procedures

Participants will be asked to confirm eligibility by completing a screening questionnaire. Participants who pass screening will be asked to provide baseline data. Current CGM users will also be asked to share their CGM data to confirm eligibility. If current data cannot be shared, current CGM users will be asked to complete blinded CGM data collection. Non-CGM users will also be asked to complete blinded CGM data collection. Participants will be asked to submit a baseline HbA1c sample

2.5 Collection of Baseline Data and Testing

After informed consent is signed, baseline data will be collected, including the following:

- Contact information
- Date of birth

- Demographics
- Height and weight
- Socio-economic information such as education, income, and insurance
- Name and contact information of healthcare provider for diabetes management
- Diabetes history, including diabetes duration, prior management, insulin delivery method, meal bolus determination method, prior severe hypoglycemia (SH), prior diabetic ketoacidosis (DKA)
- Medical history
- Medications, including but not limited to medications other than insulin being used for glycemic control
- Prior CGM experience and knowledge, including why CGM is not used
- General health
- Questionnaires (see Chapter 4)
- Finger stick to measure HbA1c
- Blinded CGM Data Collection

2.5.1 HbA1c

HbA1c will be measured at a central laboratory. The participant will be sent a kit, which will include a blood collection tube and shipping materials, to obtain a finger stick blood sample. The sample will be returned to the lab in a prepaid mailer. Participants will be able to view their HbA1c results through the study website.

2.6 CGM System

Participants will use the Dexcom G6, which is a commercially available CGM system. CGM data will be shared with CDCES and study team members.

Other sensors that become FDA approved during the course of the study may be included as an option for participants. If additional sensors are included, the participants will be given information about CGM system options and will review the CGM systems with a study team member. A recommendation may be provided for one of the systems based on discussion with the participant, or there may be an indication that there is no specific recommendation. Participants will be able to select the CGM system that they prefer, regardless of recommendation. After a CGM system is selected, the participant may be asked why that system was selected.

2.7 Blinded CGM

Non-CGM users will use a blinded CGM device for a single sensor wear period (usually at least 10 days) prior to CGM initiation. Current CGM users will be asked to use a blinded CGM device for a single sensor wear period if their current CGM data cannot be successfully shared to confirm eligibility. Study supplies required for blinded CGM data collection will be sent to the participant by mail. An Android phone may be provided which is used as a receiver to collect data from the blinded Dexcom G6 Pro. Current non-Dexcom CGM users, including pump users with integrated CGM should continue to use their personal CGM for glucose management.

A virtual clinic team member will be available to answer questions about blinded CGM use. The participants will not be able to see the glucose values and will be expected to follow their normal diabetes management practice during this blinded CGM use period. The goal will be to obtain ten days of blinded data. Participants may be asked to use a blinded CGM for an additional sensor wear period if enough CGM data are not available to establish baseline comparator data. Participants will be dropped from the study if blinded data cannot be obtained. Participants who have a serious skin reaction to the sensor during blinded CGM wear that precludes continued use of a sensor will be dropped. If additional FDA-approved CGM options are available for use in this study, the participant may be offered the opportunity to try the other CGM system; in this case blinded data collection would be repeated with another system.

2.8 Psychosocial Screening Questionnaires

Separate from the patient-reported outcome questionnaires, psychosocial screening questionnaires are administered to study participants 4 times during the study: as part of baseline data collection and 1, 2, and 3 months after unblinded CGM initiation. These screening questionnaires are validated tools to evaluate depression, diabetes distress, and hypoglycemia fears. Questionnaire administration is repeated to ensure that the virtual clinic team delivering diabetes care is aware of any mental health issues that may make diabetes management harder for the study participant. An elevated score on any of these questionnaires prompts an automated alert to the virtual clinic team (See section 3.2).

Chapter 3: Study Procedures and Data Collection

3.1 Overview

Training and data collection for the study will be completed remotely. Study supplies will be sent to the participant by mail. Participants will be followed for up to 12 months or until they discontinue CGM use. After initial CGM training has been completed, participants will continue to be followed by the virtual clinic team for six months. After the initial six months of follow up, participants who decide to continue to use CGM will be asked to extend follow up for an additional 6 months and complete questionnaires, submit HbA1c samples, and share CGM data. During the extended follow up phase, participants will be able to contact the virtual clinic with questions or to request assistance as needed.

3.2 Virtual Clinic Team Interactions with Study Participant

Each participant will be assigned to work with virtual clinic team members who are able to provide clinical care for diabetes management in the state where the participant resides. The virtual clinic team members will teach participants to use and incorporate CGM into self-management practices. Mental health service support options for diabetes-related mental health issues will be discussed as needed.

The virtual clinic team will assist with initiation of CGM, as needed, after CGM supplies are received and will provide additional training after approximately one week of CGM use, and after approximately three weeks of CGM use. Virtual clinic team members will check in with participants during study follow up to review CGM data and recommendations related to diabetes management, and additional virtual visits may be scheduled. Contact with a virtual clinic team member may be requested by the participant at any time.

In addition, the virtual clinical team member will follow up with the study participant if there is an elevated score on the psychosocial screening questionnaires (section 2.8). The virtual clinic team will follow their internal processes for diabetes related mental health services support. Participants may be offered the opportunity to work with a behavioral health coach from the virtual clinic team at no cost. Follow up communication with a personal healthcare provider is at the discretion of the virtual clinic for any issues which may require additional support.

The virtual clinic team member(s) may interact with the participant through texts, emails, phone calls and/or virtual training sessions. Phone calls may be recorded. Additional mobile applications may be required to facilitate communications between participant and virtual clinic team member(s) depending on program enrollment.

3.2.1 Virtual Clinic Team Interactions with Personal Healthcare Provider

Communications will be provided to the health care provider whom the participant designates for diabetes management, so that the provider is aware of the participant's study participation and of information related to care or treatment (See section 3.5.2).

3.3 CGM Initiation (Unblinded Use)

CGM supplies will be sent to the participant by mail. Device user manuals will be provided along with study instructions. The study website will include a resources page which may

include device user manuals, study instructions and tutorials, and links to standard of care diabetes-related educational information recommended by the study team. Live webinars may be available for those who want to receive additional education about diabetes management and use of CGM technology.

A virtual training session will be arranged with the participant's virtual clinic team member to answer questions regarding CGM set up, sensor insertion, alerts and alarms, uploading data, and visualizing data.

3.4 CGM Use and Data Interpretation

After the initial training to initiate CGM use, participants will receive additional training on how to use data visualization tools and how to use the CGM data to make self-management changes in insulin dosing, meals, exercise, etc. The training approach may vary by participants' age and/or comfort with technology.

3.5 Insulin Dose Changes

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.

3.5.1 Decision Support

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. The virtual clinic team will review all data, including any available decision support recommendations, before making recommendations. Use of decision support for T1D is approved for recommendations to providers. Use for T2D is investigational. For both T1D and T2D, use of decision support would be classified as a Non-Significant Risk as the decision support recommendation is made to the provider and does not replace virtual clinic team review of all available CGM and insulin data when considering management decisions.

3.5.2 Personal Healthcare Provider Notification

The health care provider whom the participant designates for diabetes management will be informed of insulin dose and other medication changes.

3.6 Follow-up Data Collection

Data will be collected throughout study follow up and will include information related to diabetes management, psychosocial outcomes, adverse event and device issues, patient-related outcomes and questionnaires, HbA1c measurement, and upload of device data.

3.6.1 HbA1c

HbA1c will be collected at approximately 13, 26, 39, and 52 weeks and measured at a central laboratory. A kit, which will include a blood collection tube and shipping materials, will be sent to the participant to obtain a fingerstick blood sample and return the sample to the lab.

3.7 Data Uploads

Instructions for downloads and data sharing from diabetes-related care devices and applications used for the study will be reviewed with each participant as part of their training.

3.8 Insulin Delivery and Collection of Insulin Data

Participants will use their own insulin during the study. If the participant uses an insulin pump, training will include uploading (or linking) of these devices.

MDI users with a compatible insulin pen may be given a Biocorp Mallya (Mallya) device to use during the study that automatically logs insulin dose. Mallya is a data collection device that automatically captures data such as date of injection, time of injection, insulin type, and dose. Mallya attaches directly to the insulin pen and does not alter how the pen is used. Mallya is intended for data collection purposes only, with minimal information communicated to the participant via the app or device. Mallya is an investigational device, and it is classified as a Non-Significant Risk device by the Sponsor.

An app that is needed to transfer data from the device used to log insulin dose will be installed on the participant's personal smartphone. Participants will be trained on use of the device and app as needed. If a device that automatically logs insulin dose is not available, the participant may be asked to enter insulin doses directly through an app.

Chapter 4: Questionnaires

Questionnaires are completed by all participants on the study website. The responses to the outcome surveys are not monitored in real-time. The procedures for administration are described in the study procedures manual.

Measure	DESCRIPTION
Patient Health Questionnaire- 8	8-item survey to evaluate depression-related symptoms; 3 minutes to complete
Diabetes Distress Scale (Management Distress Items)	17-item management burden scale to measure the degree of distress related to diabetes; 4 minutes to complete.
Fear of Hypoglycemia (Worry)	6- item survey to measure concerns about low blood sugar; 2 minutes to complete
CDC Healthy Days	4 questions developed by the CDC to obtain a general assessment of physical and mental health; 2 minutes to complete
Hypoglycemia Confidence	Presents 8 common situations where hypoglycemia occurs and evaluates level of confidence of how it can be managed in those situations; 4 minutes to complete.
Diabetes Technology Attitudes	5-item survey to measure perceptions about the benefits of diabetes technology and devices; 2 minutes to complete.
Glucose Monitoring Satisfaction	15-item survey to evaluate treatment satisfaction/burden; 4 minutes to complete.
Sleep	1-item sleep survey that measures quality of sleep; 1 minute to complete
Benefits and Burdens of CGM	16 items per section with 2 sections that list situations (e.g. ability to share data, glycemic events, physical activity) and designation of whether they are barriers or benefits; 4 minutes to complete.
CGM Discontinuation	3-item survey; participants who discontinue CGM will be asked to complete this.

Participants may also be asked to answer questions, which have been approved by the IRB, regarding their participation experience.

Chapter 5: Miscellaneous Considerations

5.1 Adverse Events

Participants will be asked to complete questionnaires to report events that have occurred. For each event reported, the participant will be asked if the event could have been related to the use of CGM.

If there is no response, the participant may be contacted again to encourage questionnaire completion.

Participants will be asked to report the following events:

- Severe hypoglycemia
  - Reportable events will be defined as hypoglycemia during which the participant was impaired cognitively to the point that he/she was unable to treat himself/herself, was unable to verbalize his/her needs, was incoherent, disoriented, and/or combative, or experienced seizure or loss of consciousness.
- DKA
  - The participant will be asked if he/she was seen at a health care facility and/or hospitalized and what the ketone level was if known.
- Hospitalizations

Adverse event data reported to virtual clinic team members and study staff will be collected.

5.2 Device Issues

Participants will also be asked to report the following device issues:

- Device-related events with potential impact on participant safety
  - Skin reactions at the sensor site will be reported as adverse events if they are classified as severe and/or required treatment.

5.3 Study Costs

CGM supplies will be provided for the first six months of the study. Participants will be able to keep the provided CGM supplies after follow up has ended. Participants who plan to continue use of CGM after 6 months will need to work with their insurance provider to obtain approval for CGM.

Costs of standard medical care for diabetes that would occur even if the participant were not in this study, including insulin, will be the participant's responsibility.

5.4 Participant Compensation

Participant compensation will be specified in the informed consent form.

5.5 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. The reason for withdrawal will be collected. Additionally, at the time of withdrawal, the participant will be

asked to complete device downloads and questionnaires. For participants who withdraw, their data will be used up until the time of withdrawal.

Participants who do not complete baseline procedures in a timely fashion or are noncompliant with respect to the protocol may be withdrawn.

5.5.1 Pregnancy

If pregnancy occurs, the participant will be withdrawn from the study.

5.6 Contact Information

Contact information for each participant, including name, email address, mobile number, and mailing address will be provided to the coordinating center, the Jaeb Center for Health Research in Tampa, FL. Permission to obtain such information will be included in the Informed Consent Form. The contact information for the study will be maintained in a secure database and will be maintained separately from study data.

Contact information is necessary for shipment of study supplies, set up of certain apps needed for the study on the participant's personal smartphone, and participant payments. Contact information will be used by virtual clinic team members for training and follow up. Participants will receive reminders via text, email, or phone to complete questionnaires or submit study data. Mobile number will be shared with parties involved in processing of data if the mobile number is required to send automated text reminders to minimize missing data.

Communications will be provided to a health care provider designated by the participant.

5.6.1 Personal Healthcare Provider Information

Participants will be asked to provide the contact information of a health care provider that they designate for their diabetes management. Provider information is necessary so that the provider can be made aware of the participant's study participation and of information related to care or treatment. Permission for communication to the designated health care provider will be included in the Informed Consent Form.

5.7 Confidentiality

For security purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the JCHR coordinating center in Tampa, FL, virtual clinic and study team members involved with participant training and review of CGM data, participating institutions and investigators in the research study, and parties involved in collecting and processing of data in accordance with the terms of the study contracts. Participant calls with the virtual team members may be recorded. The informed consent form will specify entities that will have access to or receive data.

No identifiable health information of an enrolled participant will be released by the coordinating center, except as described above.

5.8 Quality Assurance and Monitoring

Designated personnel from the coordinating center will be responsible for maintaining quality assurance and quality control systems to ensure that the trial is conducted, and that data are

generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

Chapter 6: Statistical Considerations

6.1 Statistical and Analysis Plan

The approach to sample size and statistical analyses are summarized below. A Statistical Analysis Plan (SAP) will be written and finalized prior to the completion of the study. The analysis plan synopsis in this chapter contains the framework of the anticipated final SAP. The SAP will describe the analyses to be performed for the primary manuscript.

6.2 Sample Size

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

6.3 Outcome Measures

The following outcome measures will be stratified by type of diabetes.

Efficacy Outcomes:

- HbA1c
- 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
- Insulin metrics
- Questionnaire scores (and their corresponding subscales)
- Psychosocial metrics
- Healthcare utilization metrics

CGM, HbA1c, and questionnaires outcomes will be evaluated at all time points they are collected.

Safety Outcomes: Severe Hypoglycemia and DKA events, and hospitalizations

6.4 Description of Statistical Methods

6.4.1 Analysis Cohorts

All subjects enrolled in the study who initiate the CGM and have a minimum amount of data as defined in the SAP will be included in the tabulations of baseline and the efficacy analyses. All subjects enrolled in this study will be included in the safety analyses.

6.5 Analysis of Efficacy Outcomes

CGM metrics and HbA1c will be calculated and summarized at 13, 26, 39, and 52 weeks. Summary statistics for questionnaires will be provided at all time points when they are collected.

A linear mixed model with a random subject effect will be used to assess whether the change from baseline significantly differs from zero. If values are highly skewed, then the winsorized mean will be tested or a transformation utilized. A complete-case analysis using a paired t-test or Wilcoxon signed rank test will also be assessed.

6.6 Subgroup Analyses

Subgroup analyses for HbA1c and selected CGM outcomes will be performed by baseline HbA1c group, insulin delivery modality, age, healthcare provider (endocrinologist or primary care provider), and various participant characteristics as described in the SAP.

6.7 Safety Analyses

All adverse events that occur post enrollment will be listed in a table. Additionally, each of the following safety metrics will be tabulated for reported SH and DKA events, hospitalizations and emergency room visits:

- Number of subjects with ≥1 event
- Number of events per subject
- Incidence rate per 100 person-years

6.8 Baseline Descriptive Statistics

Baseline demographic and clinical characteristics of the cohort of all subjects who initiate the CGM will be summarized in a table.

6.9 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons will be made.

6.10 Additional Analyses

Several additional analyses will be performed in this study. These will include the following:

- Tabulations of CGM glycemia and CGM use by month and comparing the first 26 weeks and last 26 weeks of the study (overall and within subgroups)
- Tabulations of CGM glycemia by time of day
- Tabulations of the number of participant contacts with the virtual clinic
- Bivariate relationship between questionnaires and glycemic metrics following CGM initiation

Chapter 7: Ethics/Protection of Human Participants

7.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

7.2 Institutional Review Boards

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

7.3 Informed Consent Process

7.3.1 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Individuals who indicate that they are interested in study participation will be directed to a website with information about the study. Interested individuals will be able to have a live chat or arrange for a phone call to answer questions about the study as part of the informed consent process. Participants who want to participate in the study will sign the IRB-approved electronic consent form.

The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participant may withdraw consent at any time throughout the course of the study. The participant will be able to print a copy of the informed consent document for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Chapter 8: References

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