

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

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KEY ROLES

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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 use of decision support technology.
Study Design	Single-arm prospective longitudinal study
Eligibility Criteria	<p>Inclusion Criteria</p> <ul style="list-style-type: none"> • 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) <i>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</i> • 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 <i>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.</i> • 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 <p>Exclusion Criteria</p> <ul style="list-style-type: none"> • 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) <i>Use of such medications during the study will also be prohibited.</i> • 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. <i>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.</i>

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PARTICIPANT AREA	DESCRIPTION
Sample Size	The recruitment target is 300 initiating CGM.
Outcomes	<p>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</p> <p>Safety Outcomes: Severe hypoglycemia, diabetic ketoacidosis, hospitalizations, and emergency room visits</p>
Participant Duration	Study participation will be up to 12 months.
Protocol Overview/Synopsis	<p><u>Patient Population</u> Adults ≥ 18 years with type 1 diabetes or type 2 diabetes using insulin therapy who are not CGM users will be enrolled. Potential participants may be recruited through insurance providers, primary care networks, or health care providers.</p> <p><u>Baseline Data Collection</u> 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.</p> <p><u>HbA1c</u> 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.</p> <p><u>Contact between Study Team and Participant</u> 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.</p> <p>Virtual clinic team members will check in with participants during study follow up to review CGM data and recommendations related to diabetes management.</p> <p><u>CGM Use</u> 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.</p> <p><u>Changes in Insulin Dosing</u> 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.</p>

SCHEDULE OF STUDY VISITS AND PROCEDURES

1

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

3

				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		<i>Examples: CGM Overview Parts of CGM</i>	<i>Examples: HbA1c Sample Collection CGM Setup</i>	<i>Examples: Understanding Your Real-Time Data How to Change Sensor</i>	<i>Examples: How to Upload CGM Data How to View Reports Understanding Your Ambulatory Glucose Profile / Data Patterns</i>	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	
<p>*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.</p>										

4

Chapter 1: Background Information

1.1 Introduction

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

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

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

25 The efficacy of CGM has been demonstrated in randomized trials of adults and youth with type 1
26 diabetes (T1D)³⁻¹⁰, adults with type 2 diabetes (T2D) using insulin¹¹⁻¹³, and in a registry of adults
27 and youth with T1D¹⁴; including reductions in HbA1c levels, duration of hyperglycemia and
28 hypoglycemia, and increased time spent with glucose levels between 70 and 180 mg/dL, which is
29 the target range. Studies not only demonstrated improvement in HbA1c and reduction in
30 hypoglycemia but also showed that after six months, approximately 90% of individuals were
31 using CGM on a daily or near-daily basis. CGM users have reported substantial satisfaction with
32 use of the device and improved quality of life.^{3,9,15-18}

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

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

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

46 the compelling evidence of the benefits of CGM, many individuals with T1D or insulin-using
 47 T2D have not incorporated CGM into their diabetes management. Although there are not
 48 specific data to cite, it is likely that the low rate of CGM adoption partially reflects a lack of
 49 awareness about CGM among primary care providers, who are responsible for the care of not
 50 only most adults with type 2 diabetes but also those with type 1 diabetes¹⁹⁻²¹. Lack of provider
 51 resources to introduce and incorporate CGM into patient diabetes self-management may also be
 52 a limiting factor to technology adoption, as usage is low even among some leading diabetes
 53 centers^{14,22}. Although demand for endocrinology care continues to grow, access to specialized
 54 care may be impacted by geographic isolation and a shortage in the number of endocrinologists
 55 in the United States.

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

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

73 **1.2 Rationale**

74 The objective of this study is to evaluate a virtual diabetes clinic model, for adults with either
 75 T1D or T2D, that supports integration of CGM into diabetes self-management and use of
 76 decision support technology. The virtual diabetes clinic model will also include mental health
 77 screening and support services, particularly for diabetes-related issues.

78 **1.3 Potential Risks and Benefits**

79 **1.3.1 Known Potential Risks**

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

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

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

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

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

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

97 **1.3.2 Known Potential Benefits**

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

101 **1.3.3 Risk Assessment**

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

103 **1.4 General Considerations**

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

107 Chapter 2: Study Enrollment and Baseline Data Collection

108 2.1 Participant Recruitment and Informed Consent

109 Adults (age ≥ 18 years) with type 1 diabetes or type 2 diabetes using insulin therapy (Tidepool-
110 compatible pump or injections) who are not using CGM will be enrolled. Participation will be
111 limited to U.S. residents in states where the virtual clinic is licensed; state eligibility will be
112 verified as part of screening. Potential participants may be recruited through insurance
113 providers, primary care networks, or health care providers. Potential participants also may
114 become aware of the study by other means, such as another study participant.

115 Up to 600 individuals may sign the informed consent form to initiate screening. Enrollment will
116 proceed with the goal of at least 300 participants initiating CGM use. The goal will be to limit
117 T2D enrollment to no more than 100. Recruitment efforts will be focused on participants who
118 receive diabetes care in a primary care setting rather than through an endocrinologist, with a goal
119 of having at least 225 who have not seen an endocrinologist in the past six months. Eligible
120 participants will be included without regard to gender, race, or ethnicity.

121 The goal will be to include at least 50 participants < 25 years of age and at least 50 participants
122 > 65 years of age.

123 2.1.1 Informed Consent and Authorization Procedures

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

131 2.2 Participant Inclusion Criteria

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

- 134 1. Age ≥ 18 years old
- 135 2. Diagnosis of type 1 diabetes or type 2 diabetes and using insulin therapy (at least 3 injections
136 of insulin per day or insulin pump that is compatible with Tidepool software)
137 *Multiple daily injection (MDI) users must be willing to use a device provided by the study*
138 *that records the injection dosages and/or enter insulin dosing information through an app*
- 139 3. See a healthcare provider at least once a year
- 140 4. Resident of United States and plan to reside in the U.S. for the duration of the study
141 *This requirement is due to virtual clinic license requirements and U.S. use restrictions for*
142 *some study software and devices. Not all U.S. states may be eligible for inclusion due to*
143 *virtual clinic license status.*
- 144 5. Use either an Android or iOS smartphone that is compatible with app requirements that are
145 needed for the study

- 146 6. Access to a compatible computer with internet
147 7. Understand written and spoken English
148 8. Willing and able to follow the study procedures as instructed

149 **2.3 Participant Exclusion Criteria**

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

- 152 1. Use of real-time CGM (including Abbott Libre or integrated pump system) in last 12 months
153 (interval blinded CGM use is acceptable)
154 2. Current use of any off-label glucose-lowering medications for diabetes type (Example: T1D
155 use of non-insulin, anti-diabetic medications including SGLT2 inhibitors)
156 *Use of such medications during the study will also be prohibited.*
157 3. Females who are pregnant, intending to become pregnant, or breastfeeding during the study
158 4. Current renal dialysis or plan to begin renal dialysis during the study
159 5. Active cancer treatment
160 6. Extreme visual or hearing impairment that would impair ability to use real-time CGM
161 7. Known adhesive allergy/prior skin reaction or skin reaction identified during the blinded
162 CGM use phase that would preclude continued CGM use
163 8. Participation in a different diabetes management study during the study
164 9. Planned relocation to a state other than current state of residence during the study if virtual
165 clinic is not licensed in the new state.
166 *Individuals working routinely in a state other than current state of residence in the next six*
167 *months are also ineligible if the virtual clinic is not licensed in that state.*

168 **2.4 Screening Procedures**

169 Participants will be asked to confirm eligibility by completing a screening questionnaire. Based
170 upon participant self-reported responses to screening questionnaire, participants who pass
171 screening will be asked to provide baseline data, submit a baseline HbA1c sample, and complete
172 blinded CGM data collection.

173 **2.5 Collection of Baseline Data and Testing**

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

- 175 • Contact information
176 • Date of birth
177 • Demographics
178 • Height and weight
179 • Socio-economic information such as education, income, and insurance
180 • Name and contact information of healthcare provider for diabetes management

- 181 • Diabetes history, including diabetes duration, prior management, insulin delivery method,
- 182 meal bolus determination method, prior severe hypoglycemia (SH), prior diabetic
- 183 ketoacidosis (DKA)
- 184 • Medical history
- 185 • Medications, including but not limited to medications other than insulin being used for
- 186 glycemic control
- 187 • Prior CGM experience and knowledge, including why CGM is not used
- 188 • General health
- 189 • Questionnaires (see Chapter 4)
- 190 • Finger stick to measure HbA1c
- 191 • Blinded CGM Data Collection

192 **2.5.1 HbA1c**

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

197 **2.6 CGM System**

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

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

208 **2.7 Blinded CGM**

209 Participants will use a blinded CGM device for a single sensor wear period (usually at least 10
 210 days) prior to CGM initiation. Study supplies required for blinded CGM data collection will be
 211 sent to the participant by mail. The participants will not be able to see the glucose values and
 212 will be expected to follow their normal diabetes management practice during this blinded CGM
 213 use period. The goal will be to obtain ten days of blinded data. Participants may be asked to use
 214 a blinded CGM for an additional sensor wear period if enough CGM data are not available to
 215 establish baseline comparator data. Participants will be dropped from the study if blinded data
 216 cannot be obtained. Participants who have a serious skin reaction to the sensor during blinded
 217 CGM wear that precludes continued use of a sensor will be dropped. If additional FDA-approved
 218 CGM options are available for use in this study, the participant may be offered the opportunity to
 219 try the other CGM system; in this case blinded data collection would be repeated with another
 220 system.

221 **2.8 Psychosocial Screening Questionnaires**

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

230

Chapter 3: Study Procedures and Data Collection

231 3.1 Overview

232 Training and data collection for the study will be completed remotely. Study supplies will be
233 sent to the participant by mail. Participants will be followed for up to 12 months or until they
234 discontinue CGM use. After initial CGM training (initiation of unblinded CGM use) has been
235 completed, participants will continue to be followed by the virtual clinic team for six months.
236 After the initial six months of follow up, participants will no longer be followed by the virtual
237 clinic team but those who decide to continue to use CGM will be asked to extend follow up and
238 complete questionnaires, submit HbA1c samples, and share CGM data.

239 3.2 Virtual Clinic Team Interactions with Study Participant

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

245 A virtual clinic team member will be available to answer questions about CGM use and blinded
246 CGM placement. For those who successfully complete blinded data collection, the virtual clinic
247 team will assist with initiation of CGM after CGM supplies are received and will provide
248 additional training after approximately one week of CGM use, and after approximately three
249 weeks of CGM use. Virtual clinic team members will check in with participants during study
250 follow up to review CGM data and recommendations related to diabetes management, and
251 additional virtual visits may be scheduled. Contact with a virtual clinic team member may be
252 requested by the participant at any time.

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

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

263 3.2.1 Virtual Clinic Team Interactions with Personal Healthcare Provider

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

267 **3.3 CGM Initiation (Unblinded Use)**

268 CGM supplies will be sent to the participant by mail. Device user manuals will be provided
 269 along with study instructions. The study website will include a resources page which may
 270 include device user manuals, study instructions and tutorials, and links to standard of care
 271 diabetes-related educational information recommended by the study team. Live webinars may
 272 be available for those who want to receive additional education about diabetes management and
 273 use of CGM technology.

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

277 **3.4 CGM Use and Data Interpretation**

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

282 **3.5 Insulin Dose Changes**

283 If the virtual clinic team believes that changes in insulin type or dosing should be considered,
 284 they will work with the participant to implement any such changes.

285 **3.5.1 Decision Support**

286 Decision support tools, which include use of a mobile application, may be used, if available, to
 287 provide the virtual clinic team with potential recommendations regarding insulin use. The virtual
 288 clinic team will review all data, including any available decision support recommendations,
 289 before making recommendations. Use of decision support for T1D is approved for
 290 recommendations to providers. Use for T2D is investigational. For both T1D and T2D, use of
 291 decision support would be classified as a Non-Significant Risk as the decision support
 292 recommendation is made to the provider and does not replace virtual clinic team review of all
 293 available CGM and insulin data when considering management decisions.

294 **3.5.2 Personal Healthcare Provider Notification**

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

297 **3.6 Follow-up Data Collection**

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

301 **3.6.1 HbA1c**

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

305 **3.7 Data Uploads**

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

308 **3.8 Insulin Delivery and Collection of Insulin Data**

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

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

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

322

323

Chapter 4: Questionnaires

324 Questionnaires are completed by all participants on the study website. The responses to the
 325 outcome surveys are not monitored in real-time. The procedures for administration are described
 326 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.

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

329

Chapter 5: Miscellaneous Considerations

330 5.1 Adverse Events

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

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

336 Participants will be asked to report the following events:

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

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

347 5.2 Device Issues

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

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

352 5.3 Study Costs

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

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

359 5.4 Participant Compensation

360 Participant compensation will be specified in the informed consent form.

361 5.5 Participant Withdrawal

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

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

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

368 **5.5.1 Pregnancy**

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

370 **5.6 Contact Information**

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

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

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

383 **5.6.1 Personal Healthcare Provider Information**

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

389 **5.7 Confidentiality**

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

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

399 **5.8 Quality Assurance and Monitoring**

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

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

404

Chapter 6: Statistical Considerations

405 6.1 Statistical and Analysis Plan

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

410

411 6.2 Sample Size

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

414 6.3 Outcome Measures

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

416 Efficacy Outcomes:

- 417 • HbA1c
- 418 • CGM use
- 419 • Mean of sensor glucose levels
- 420 • Percentage of time spent with sensor glucose levels <54 and <70 mg/dL
- 421 • Percentage of time spent with sensor glucose levels >180 and >250 mg/dL
- 422 • Percentage of time spent with sensor glucose levels in the target range (70-180 mg/dL)
- 423 • Glycemic variability measured by the coefficient of variation
- 424 • Insulin metrics
- 425 • Questionnaire scores (and their corresponding subscales)
- 426 • Psychosocial metrics
- 427 • Healthcare utilization metrics

428

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

431

432 Safety Outcomes: Severe Hypoglycemia and DKA events, and hospitalizations

433

434 6.4 Description of Statistical Methods

435 6.4.1 Analysis Cohorts

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

439 **6.5 Analysis of Efficacy Outcomes**

440 CGM metrics and HbA1c will be calculated and summarized at 13, 26, 39, and 52 weeks.
 441 Summary statistics for questionnaires will be provided at all time points when they are collected.
 442 A linear mixed model with a random subject effect will be used to assess whether the change
 443 from baseline significantly differs from zero. If values are highly skewed, then the winsorized
 444 mean will be tested or a transformation utilized. A complete-case analysis using a paired t-test
 445 or Wilcoxon signed rank test will also be assessed.

446 **6.6 Subgroup Analyses**

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

450 **6.7 Safety Analyses**

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

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

457 **6.8 Baseline Descriptive Statistics**

458 **6.9 Baseline demographic and clinical characteristics of the cohort of all subjects who**
 459 **initiate the CGM will be summarized in a table. Multiple Comparisons/Multiplicity**

460 No adjustments for multiple comparisons will be made.

461 **6.10 Additional Analyses**

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

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

469 **Chapter 7: Ethics/Protection of Human Participants**

470 **7.1 Ethical Standard**

471 The investigator will ensure that this study is conducted in full conformity with Regulations for
 472 the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50,
 473 21 CFR Part 56, and/or the ICH E6.

474 **7.2 Institutional Review Boards**

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

481 **7.3 Informed Consent Process**

482 **7.3.1 Consent Procedures and Documentation**

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

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

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