TELEMEDICINE MONITORING OF NOCTURNAL INCIDENTS OF TREATMENT-REQUIRING HYPOGLYCEMIA IN OLDER ADULTS WITH T1DM (TELE-MONITOR T1DM) A FEASIBILITY STUDY

An observational feasibility study to determine if it is possible to implement an automated system of daily remote monitoring of CGM data to identify and contact patients who are having episodes of hypoglycemia and/or difficulty using their CGM device.

Study Protocol

Version 1.1
06/08/2018

Table of Contents

CHAPTER 1: INTRODUCTION

1.1 Background Information

Older adults with type 1 diabetes (T1D), a growing but under-evaluated population (1-4), are prone to hypoglycemia and hypoglycemia unawareness, particularly when diabetes is longstanding. Hypoglycemia, which in addition to producing altered mental status and sometimes seizure or loss of consciousness, can be associated with falls leading to fractures, and cardiac arrhythmias resulting in sudden death (5-7). Hypoglycemia must always be considered a possible contributing factor in older adults with T1D in whom these events occur, especially when a glucose measurement is not available from the time of the event (8). In Medicare beneficiaries with diabetes, hospitalizations related to hypoglycemia are now more frequent than those for hyperglycemia and are associated with high 1-year mortality (6). Emergency room visits due to hypoglycemia also are common (5). These reports likely underestimate the risk of hypoglycemia in older adults with T1D since they include individuals with the more prevalent type 2 diabetes in whom severe hypoglycemic events are likely considerably less frequent than they are in individuals with T1D.

Unlike treatment guidelines in younger individuals with T1D which focus on optimizing glycated hemoglobin (HbA1c) levels, treatment approaches for older adults with T1D often focus on minimizing hypoglycemia rather than attempting to achieve low HbA1c levels (9, 10). Despite these efforts, biochemical hypoglycemia occurs frequently and severe hypoglycemia (SH) occurs more often in older than younger adults with T1D. Data from the T1D Exchange registry has shown a remarkably high frequency of SH in older adults with longstanding T1D: 18% of registry participants >60 years old reported seizure or loss of consciousness due to hypoglycemia in the prior 12 months (11). In addition, although there may be less of a push towards tight control in older adults, T1D Exchange registry data indicate that SH is just as common with HbA1c levels >8.0% as it is for HbA1c levels <7.0% (11). A T1D Exchange study (12) of 201 adults ≥60 years old with T1D duration ≥20 years (101 with SH in the prior year and 100 without SH in the prior 3 years) found that glucose concentrations measured with blinded continuous glucose monitoring (CGM) were <70 mg/dL for a median of 91 minutes per day and <50 mg/dL for 31 minutes per day. Furthermore, mean HbA1c was similar in the individuals who had experienced SH in the prior year compared with those who had not experienced SH in the prior 3 years (7.8% versus 7.7%). These data do not support the strategy of "raising the HbA1c" an effective approach for hypoglycemia prevention in older adults with T1D.

Hypoglycemia unawareness, or the loss of physiological symptoms associated with a low blood glucose level, is associated with duration of diabetes, making it particularly prevalent in older adults. The presence of hypoglycemia unawareness is associated with a 20-fold increased risk for experiencing SH (13). The prevalence of hypoglycemia unawareness was remarkably high in the T1D Exchange of older adults (12), 147 with 58% of those with SH within the prior year having hypoglycemic unawareness compared with 25% in those with no SH in the prior 3 years. Furthermore, glycemic variability was significantly greater for those having experienced SH within the prior year, supporting mechanisms beyond awareness of hypoglycemia contributing to risk for SH in older adults with T1D.

The occurrence of hypoglycemia and fear of hypoglycemia have adverse effects on quality of life of both the individuals with T1D (14) and their families (15). Hypoglycemia fear and associated behaviors impact participation in activities that are beneficial to emotional and physical well-being

(e.g., exercise, socializing, and travelling), and may lead to intentional hyperglycemia. Diabetes-related distress (i.e., the emotions, stresses and worries associated with diabetes) is also an important component of QOL for people with T1D and is associated with poor glycemic control, longer duration of diabetes, higher rates of depression, and prior SH (16).

Aging is associated with normative decline in cognitive functioning independent of any disease process. Thus, older adults often have more difficulty learning and adopting new technologies and following complex medication regimens. Older adults with T1D have additional risk for more substantial cognitive impairment given increased rates of microvascular and macrovascular complications from longstanding diabetes. We previously found that mild cognitive impairment is common in community dwelling older adults with T1D (see preliminary data) and that it is related to activities of daily living and everyday diabetes related tasks (17). Further, those with SH perform poorer in some areas of cognitive function than those without SH (12) making it possible that cognitive impairment increases the risk of a SH event. While it is possible that SH results in greater cognitive impairment, this has not been supported in a younger T1D cohort in DCCT/EDIC followed for over 18 years (18). The combination of cognitive difficulties and blunting of the alerting symptoms of hypoglycemia may put older adults at high risk for hypoglycemia (19).

1.2 Continuous Glucose Monitoring

CGM measures interstitial glucose concentrations and provides for real-time observation of glucose levels, trend direction and alarms for when glucose drops to low levels. The components or CGM include a receiver, a transmitter and a sensor. In December 2016, the FDA expanded the indications for the Dexcom G5 sensor to allow for replacement of fingerstick blood glucose testing for diabetes treatment decisions.

Several randomized trials have demonstrated the efficacy of CGM when it is used on a regular basis by individuals with T1D, particularly adults (20-23). Among individuals with HbA1c levels above target, improvement has been demonstrated in HbA1c levels and in a reduction in biochemical hypoglycemia. Among individuals with HbA1c levels at or below target, CGM has been demonstrated to reduce biochemical hypoglycemia while at the same time maintaining excellent HbA1c levels better than a control group (24). While these trials have found consistent glycemic benefit with CGM use, it is clear that the amount of benefit is related to the amount of CGM use (22, 23).

In addition, regular CGM users have reported substantial satisfaction with use of the device and improved QOL (25). The JDRF funded RCT of CGM in children and adults showed a modest improvement in hypoglycemia fear associated with CGM use in the adult cohort, but no changes in other more general measures of QOL (23). Langendam et al. found no benefit of continuous glucose monitoring on QOL in their Cochrane Review, although only 5 of 22 studies included QOL outcomes (26). However, all of these studies used earlier generation CGM devices. Based on the extremely high compliance with daily CGM use in recently completed trials coordinated by the Jaeb Center for Health Research using the Dexcom G4 or G5 sensor, substantially higher patient satisfaction and improvement in QOL is likely with the current generation Dexcom device.

CGM can alert when blood glucose is low or trending downward and this information can be automatically shared with others; features that may be particularly helpful for those at risk for SH.

Polonsky and Hessler surveyed existing CGM users and found that older age was associated with a greater perceived benefit in hypoglycemia safety and interpersonal support, although the mean age of this sample was 41 years (25). Despite its potential benefits to reduce hypoglycemia and hypoglycemia fear, CGM is used by only a small proportion of older adults with T1D. In the T1D Exchange registry, only 19% of adults over the age of 60 are using CGM, a percentage that likely over-represents CGM use in this age group since all of the registry participants, by selection, are seen by an endocrinologist who has a practice focused on T1D.

1.3 Preliminary Studies

The USC research team has experience in conducting CGM and hypoglycemia studies in older adults with T1D. They were part of study funded by the T1D Exchange Clinic Network which was a case-control study of 201 individuals >60 years old with T1D for ≥20 years at 18 clinical sites (12). The objective of the study was to assess potential contributory factors for the occurrence of severe hypoglycemia, including cognitive functioning, social support, depression, hypoglycemia unawareness, various aspects of diabetes management, residual insulin secretion (as measured by C-peptide levels), frequency of biochemical hypoglycemia, and glycemic control and variability. Cases (N=101) had at least one severe hypoglycemic event in the prior 12 months while controls (N=100), frequency-matched to cases on age, had no severe hypoglycemia in the prior 3 years. HbA1c levels (mean 7.8% versus 7.7%) and CGM-measured mean glucose (175 mg/dL versus 175 mg/dL) were similar between cases and controls. More cases than controls had hypoglycemia unawareness; only 11% of cases compared with 43% of controls reported always having symptoms associated with low blood glucose levels ($p<0.001$). Cases had greater glucose variability than controls ($p=0.008$) and experienced CGM glucose levels <60 mg/dL more often than in controls ($p=0.04$). Cases scored worse than controls on measures of general mental status, processing speed and executive functioning. As expected, hypoglycemia fear was higher in cases compared with controls.

In this sample of non-demented, community dwelling and functionally independent older adults with T1D, 55% of the combined sample was at least mildly impaired (compared to demographically corrected normative data) on a brief neuropsychological test battery, with 35% in the moderate to severely impaired range. This was clinically relevant, as cognitive performance was associated with simulated diabetes task performance (e.g., calculating an insulin dose based on a nutritional label) and instrumental activities of daily living (17). Due to the cross-sectional nature of this work, however, it is not known if cognitive impairment is a cause or consequence (or both) of hypoglycemia. In those with mild or moderate cognitive impairment, falling glucose alert and threshold alarm features of CGM may be particularly useful to “remind” patients to check their blood glucose when the glucose level is decreasing and approaching the hypoglycemic range.

Additionally, we are investigators on the WISDM Trial, which is a multi-center study on the use of CGM in individuals with type 1 diabetes who are 60 years of age and older. It is an RCT in which patients are randomized to CGM vs. no CGM for 6 months and then all participants will wear a CGM for the second 6 months of the study.

1.4 Summary of Study Rationale

Reducing hypoglycemia is an important aspect of management of T1D in older adults, many of whom have hypoglycemic unawareness, cognitive impairment, or both. CGM offers the opportunity to reduce hypoglycemia and its related complications such as fractures from falls and hospitalizations and improve QOL including reducing hypoglycemic fear and diabetes distress. Despite these potential benefits, CGM is used by only a small proportion of older adults with T1D (19% in the T1D Exchange registry). Previous studies assessing CGM efficacy have included only a small number of adults ≥ 60 years of age, excluded patients most prone to SH, focused on improving HbA1c rather than hypoglycemia, and used older generation CGM sensors. These studies are not generalizable to the population of older adults with T1D. The potential benefit of CGM in reducing hypoglycemia in the older adult population has not been well studied. Prior and on-going trials compare CGM to self-monitoring of blood glucose levels, but none look at remote daily monitoring of CGM data. Moreover, in none of the studies is education standardized. The follow-up of patients is done only at routine clinic visits, without any particular oversight of glucose values on an on-going basis. In some cases individual patients may share their data with a family member, but these are generally not trained medical personnel and the Dexcom provided by Medicare has the "share" feature disabled.

1.5 Study Objectives

1.5.1 Primary Objectives

Primary Aim 1: To determine the effect of continuous remote CGM reporting coupled with a telemedicine intervention (Tele-CGM program) on rates of hypoglycemia in adults with T1D ≥65 years old.

Working Hypothesis: Participants using the Tele-CGM program will have a reduction in hypoglycemia (as measured by the amount of time spent with glucose both below 54 mg/dl and in the range of 54-70 mg/dl) compared with participants followed in usual care using CGM.

1.5.2 Secondary Objectives

Secondary Aim 1: To determine the effect of the Tele-CGM program on rates of CGM adherence and successful use in adults with T1D ≥65 years old.

Working Hypothesis: Participants using the Tele-CGM program will have an increase in weekly time spent wearing functional CGM devices compared with participants followed in usual care using CGM. This should improve CGM-based outcomes due to the relationship between CGM weekly utilization and CGM benefits.

Secondary Aim 2: To determine the effect of the Tele-CGM program on quality of life (as measured by reduction in hypoglycemic fear and improved diabetes specific distress, emotional wellbeing, and ratings of global health), in adults with T1D ≥ 65 years of age.

Working Hypothesis: Participants using the Tele-CGM program will have an improved quality of life compared with participants followed in standard care without it.

Secondary Aim 3: To determine the effect of the Tele-CGM program on costs for the care of adults with T1D ≥65 years old.

Working Hypothesis: Participants using the Tele-CGM program will have a reduction in the need for emergency department or urgent clinic visits, as well as paramedic services. Telemedicine visits and automated remote monitoring are much less expensive and potentially more effective than in-person visits.

Additional Secondary and Exploratory Aims: Secondary analyses of CGM data will be performed to look for patterns and trends will to assess whether changes in metrics such as glucose variability or time in range can predict episodes of hypoglycemia. Rates of SH events, ER visits, hospitalizations, falls, and fractures will be assessed. The study will provide the opportunity to explore factors that may mediate or moderate the relationships between CGM glucose levels and study outcomes, including method of insulin administration (pump versus injection), presence of cognitive impairment, frailty, hypoglycemic unawareness, glycemic variability, and scores on baseline and subsequent QOL and cognitive function measures.

1.6 Study Synopsis

1.6.1 Study Design

This study is a single center pilot study

1.6.2 Sample Size: 10 subjects

1.6.3 Eligibility

1) Diagnosis of type 1 diabetes
2) Age ≥65 years old
3) No serious illnesses where life expectancy is <1 year
4) Insulin regimen involves either use of an insulin pump or multiple daily injections of insulin.
5) Understand the study requirements and agree to comply with all study visits and procedures, including the use of the study CGM.
6) Fluent in English or Spanish
7) Must have a smart phone

1.6.4 Visit and Phone Contact Schedule

Participants from our clinic population who fit the entry criteria will be asked to join the study.

Baseline Visit—Visit 0

1. Obtain informed consent
2. Administer questionnaires
3. Measure point of care A1C
4. Start study Dexcom CGM device (those already on CGM will change to the study device).
5. The patient will be signed into Tidepool using a research code name and email.

Visit 1—2 weeks

1. 14 days worth of data will be downloaded from the patient's CGM device.
2. Systems will be checked to be sure they are functioning
3. Remote monitoring program will be activated.

4. Telemedicine procedure will be discussed with patient; emergency contact numbers will be obtained in case patient cannot be reached

Visit 2—14 weeks

1. Administer questionnaires
2. Measure point of care A1C.
3. Collect CGM data and compare to baseline

1.6.5 Testing and Assessments:

- Continuous glucose monitoring (CGM)
- Tidepool cloud upload
- Laboratory testing: Point of care HbA1c
- Telemedicine outreach
- T1D REDEEM diabetes distress questionnaire
- Hypoglycemia Fear Survey
- Assessment of Severe Hypoglycemia and Diabetic Ketoacidosis

1.6.6 Main Outcome Measures

Primary Outcome: Rates of hypoglycemia

Second Outcome: Adherence to CGM

Secondary Outcome: Changes in quality of life (as measured by reduction in hypoglycemic fear and improved diabetes specific distress, emotional wellbeing, and ratings of global health)

Secondary Outcome: Change in A1C

Secondary Outcome: Change in time in range

1.6.7 General Considerations

The study is being conducted in compliance with the ethical principles that have their origin in the Declaration of Helsinki and with the standards of Good Clinical Practice.

CHAPTER 2: ELIGIBILITY CRITERIA AND ENROLLMENT

2.1 Study Population

Participants in the study must meet criteria as described below.

2.2 Eligibility Criteria

2.1.1 Eligibility

1) Diagnosis of type 1 diabetes
2) Age 65 - 75 years old
3) No serious illnesses where life expectancy is <1 year
4) Insulin regimen involves either use of an insulin pump or multiple daily injections of insulin.

5) Understand the study requirements and agree to comply with all study visits and procedures, including the use of the study CGM.
6) Fluent in English or Spanish
7) Use of an iPhone that can stream data into Tidepool

2.1.2 Exclusions

1) Subject anticipates the need to use Tylenol or other pain-relieving medications containing acetaminophen.
2) Subject is currently pregnant or lactating or plan on becoming pregnant during the course of the study.
3) Subject is blind
4) Subject cannot follow instructions due to a medical condition or mental illness.
5) Subject has a known allergy to medical adhesive.

2.1.3 Assessment of Eligibility

Eligibility will be assessed as part of usual care and review of clinic records.

2.3 Informed Consent

Individuals who are interested in participating in this study must be willing to sign a written consent in order to participate.

CHAPTER 3: STUDY VISITS

3.1 Study Visits

Study visits will occur at

- Baseline
- 14 days (+3 days)
- 14 weeks (+7 days)

Additional office visits may occur as needed.

3.1.1 Baseline Visit

After informed consent is obtained, the following will be done:

1) Information will be collected from the chart and solicited from the participant with respect to: emergency contact information, medications, medical conditions, physical exam, management, demographics, exercise, nutrition, insulin use, and other diabetes management factors.
2) HbA1c
3) Questionnaires:
   - T1D REDEEM diabetes distress questionnaire
   - Hypoglycemia Fear Survey
   - Simplified Diabetes Knowledge Test
   - Assessment of Severe Hypoglycemia and Diabetic Ketoacidosis
4) CGM device will be provided and sensor will be inserted and instructions on calibration, use, and maintenance issues will be provided
5) Tidepool account set-up and training

3.1.2 Procedures at Post Baseline Study Visits

The following procedures will be performed at each visit, unless otherwise specified:

- Assessment of compliance with CGM
- Solicitation of the occurrence of adverse events, including falls, hospitalizations, emergency department visits, severe hypoglycemia, and diabetic ketoacidosis
- Assessment of device issues
- CGM skin assessment
- Review of glucose data and insulin dosing and recommendations for changes in diabetes management
- HbA1c determination using a point of care device at 14 weeks

3.1.3 Daily Uploading of CGM Data to Tidepool

CGM data will automatically upload to the Tidepool system through the subject's existing iPhone via the iPhone Health app.

3.2 TeleMonitoring

This will consist of an out going call/email to the patient if one of the following occur has occurred in the past 24 hours: ≥4 hours without CGM signal, ≥2 hours 54 – 70 mg/dl and/or 15 minutes <54 mg/dl. The study coordinator will be alerted each morning though the Tidepool program to patients who fit these criteria. The outgoing call/email will consist of questions to find out why the event happened and then suggestions on how to trouble shoot to avoid issues in the future. If needed the participant will be seen in person for an education/training session.

If the patient cannot be reached within 6 hours, the patient's emergency contact will be notified if the PI feels that such out reach is warranted.

CHAPTER 4: DATA COLLECTION AND TESTING PROCEDURES

4.1 HbA1c

HbA1c will be obtained using the point of care Siemens DCA Vantage Analyzer at Baseline, and at 14 weeks.

4.2 Continuous Glucose Monitoring (CGM)

A commercially available DexCom G5 or G6 CGM device will be provided and a sensor will be inserted. The participant will receive instructions on calibration, insertions, maintenance, use, and removal of the sensor.

4.3 T1D REDEEM Diabetes Distress Questionnaire

The T1D REDEEM Diabetes Distress Questionnaire (9) measures several dimensions of stress related to having type 1 diabetes. It consists of the following 7 subscales: Subscale 1 - Powerlessness (5 items); Subscale 2 – Management Distress (4 items); Subscale 3 – Hypoglycemia Distress (4 items); Subscale 4 – Negative Social Perceptions (4 items); Subscale 5 – Eating Distress (3 items); Subscale 6 – Physician Distress (4 items); Subscale 7 – Friend/Family Distress (4 items). Each question has a 6-choice Likert response format. Administration time is approximately 10 minutes.

4.4 Hypoglycemia Fear Survey

The Hypoglycemia Fear Survey measures several dimensions of fear of hypoglycemia among adults with type 1 diabetes (10). It consists of a 10-item Behavior subscale that measured behaviors involved in avoidance and over-treatment of hypoglycemia and a 13-item Worry subscale that measures anxiety and fear surrounding hypoglycemia, each with a 5-choice Likert response format. Administration time is approximately 10 minutes.

4.5 Simplified Diabetes Knowledge Test

The Simplified Diabetes Knowledge Test (11) consists of 23 knowledge test items developed by the Michigan Diabetes Research Training Center (MDRTC). These items represent a test of general knowledge of diabetes and are answered in a true/false/don't know format. The psychometric properties provide information regarding the reliability of the various groups of items, as well as a difficulty index (percent of patients who scored this item correctly), and an item to group total correlation for each item. These data can be reported when describing the use of the test. Administration time is approximately 15 minutes.

4.6 Assessment of Sever Hypoglycemia and Diabetic Ketoacidosis

The Assessment of Severe Hypoglycemia and Diabetic Ketoacidosis is an interviewer administered survey assessing if the subject had any episodes of severe hypoglycemia and/or diabetic ketoacidosis since their last study visit. Events are recorded to assess frequency, as is type of assistance required to treat the event. Administration time is approximately 5 minutes.

4.7 Tidepool. https://tidepool.org/

Tidepool is an open source, not-for-profit company focused on **"**liberating data from diabetes devices, supporting researchers, and providing free software to people with diabetes and their care teams.**" Tidepool is the program that is used routinely in our clinic to assess data from diabetes devices. As part of clinical care all patients are encouraged to upload their data to Tidepool for analysis. Currently we have over 250 patients streaming data into Tidepool. However, data is not analyzed on a daily basis, but rather on as "as needed" basis if a patient contacts the clinic with a problem.**

Tidepool is an open source platform because they want to catalyze innovation, so they make their code and designs openly available. They also believe that the healthcare industry needs more sharing and greater transparency, and being open source is one way to make a difference.

Tidepool complies with all HIPAA privacy, security and breach notification regulations. Tidepool enters into Business Associate Agreements (BAAs) with requesting clinics, and also has subcontractor BAAs with our underlying technology service providers (e.g., Amazon Web Services and Google).

Tidepool is an FDA registered entity. The software is listed with the FDA under regulations 880.6310 and 862.2120 as Class I/Exempt medical devices and Medical Data Display Systems. Tidepool complies with all applicable FDA regulations including 21 CFR 820 Quality System Regulations. Class I/Exempt and MDDS software are exempt from FDA part 510(k) filing and approval requirements.

CHAPTER 5: MISCELLANEOUS CONSIDERATIONS

5.1 Adverse Events and Risks

5.1.1 Definition

Reportable adverse events will include the following: severe hypoglycemia as defined below, hyperglycemia/diabetic ketoacidosis (DKA) as defined below, all device-related events with potential impact on participant safety, all falls or fractures, emergency room visits, and all events meeting criteria for a serious adverse event. Skin reactions from sensor placement are only reportable if severe and/or required treatment.

Hypoglycemic events are recorded as Adverse Events only if the event required assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that 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 coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Hyperglycemic events are recorded as Adverse Events if evaluation or treatment was obtained from a 801 health care provider or if the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT), and had all of the following:

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Serum ketones >1.5 mmol/L or large/moderate urine ketones;
- Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15; and
- Treatment provided in a health care facility

In addition, hyperglycemia not meeting the definition of DKA will be reported as an adverse event if emergency evaluation or treatment was obtained at a health care facility; these events are considered Adverse Events and not Serious Adverse Events (SAE) unless one of the criteria for SAE is met.

5.2 Recording of Adverse Events

Throughout the course of the study, all efforts will be made to remain alert to possible adverse events or untoward findings. The first concern will be the safety of the study participant, and appropriate medical intervention will be made.

All reportable adverse events whether volunteered by the participant, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported on an adverse event form. Since the goal of the study is to provide unique daily monitoring, AE's may be noted by the study coordinator before the patient would routinely report them. The study investigator reviews each adverse event form.

The study investigator will assess the relationship of any adverse event to be related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by the

study intervention. To ensure consistency of adverse event causality assessments, investigators should apply the following general guideline when determining whether an adverse event is related:

Yes

There is a plausible temporal relationship between the onset of the adverse event and the study intervention, and the adverse event cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study intervention; and/or the adverse event abates or resolves upon discontinuation of the study intervention or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the adverse event has an etiology other than the study intervention (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to study intervention.

The intensity of adverse events will be rated on a three-point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity: thus, a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

Adverse events will be coded using the MedDRA dictionary.

Adverse events that continue after the study participant's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

5.3 Reporting Serious Adverse Events and Unexpected Adverse Device Events

A serious adverse event is any untoward occurrence that:

- Results in death.
- Is life-threatening (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions (sight threatening).
- Is a congenital anomaly or birth defect.
- Is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above).

An *Unanticipated Adverse Device Event* is defined as an adverse event caused by, or associated with, a device, if that effect or problem was not previously identified in nature, severity, or degree of incidence.

Serious or unexpected device-related adverse events must be reported to the IRB within 24 hours.

Other reportable adverse events and device malfunctions (with or without an adverse event) will be reported within 3 days of the investigator becoming aware of the event to the IRB.
Device complaints not associated with device malfunction or an adverse event must be reported within 7 days of the investigator becoming aware of the event.

5.3 Risks and Discomforts

5.3.1 Risk of Hypoglycemia and Hyperglycemia

As a patient with diabetes, there is always a risk of having a low blood sugar (hypoglycemia) or high blood sugar (hyperglycemia). Symptoms of low blood sugar can include sweating, weakness, shaking, and not feeling well. Symptoms of high blood sugar may include increased thirst, tiredness, blurred vision, and irritability. Instructions will be given to you to make diabetes management decisions based on the study BGM or CGM. You should check your blood glucose with the study provided meter whenever you question the symptoms or expectations do not match the CGM reading.

5.3.2 CGM Sensor Placement

The CGM sensor may cause pain when it is inserted into the skin, similar to a pump site insertion or insulin injection. Rarely, a skin infection can happen at the site of insertion of the sensor. Itchiness, redness, bleeding, and bruising at the insertion site may occur. An allergy to the tape that holds the sensor to the skin is possible. The risk of skin problems could be greater if you use a sensor for longer than it is supposed to be used. There is a chance that the sensor or needle may break under your skin. This is not expected to occur; but, if it does, you should ask your study doctor what to do.

5.3.3 CGM Sensor Inaccuracy

There is a small risk of using CGM for insulin dosing, without a confirmatory BGM measurement, due to the accuracy of the sensor and the possibility of an adverse event if the CGM glucose value substantially deviates from the true glucose level, particularly when an insulin bolus is given. This risk has been mitigated by advising participants to check the blood glucose when symptoms or expectations do not match the CGM reading. The G5 and G6 are FDA approved with this recommendation in the label.

5.3.4 Skin Reactions

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.

During each follow-up visit, each site where a CGM sensor has been worn will be assessed by study personnel. Both acute and non-acute changes will be assessed. If a skin reaction is classified as severe (the observation is extremely noticeable and bothersome to participant and may indicate infection or risk of infection or potentially life-threatening allergic reaction) an Adverse Event Form will be completed.

5.3.5 Fingerstick HbA1c and Blood Glucose Measurements

Fingersticks may produce pain and/or ecchymosis at the site.

5.3.6 Psychosocial Questionnaires

As part of the study, participants will complete psychosocial questionnaires, which include questions about their private attitudes, feelings and behavior related to diabetes. It is possible that some people may find these questionnaires to be mildly upsetting. Similar questionnaires have been used in previous research and these types of reactions have been uncommon.

5.3.7. Tele-Monitor

The main intervention in this study—daily monitoring of CGM data—could cause some patients more anxiety because someone is "judging them" daily. If someone objects to this approach they will not be recruited into the study; if someone decides they don't like the intensity of observation they can opt out of the Tele-Monitor. It is possible that daily interventions could worsen, rather than improve, glycemic control by insulin dose adjustments that are too frequent. In order to mitigate this risk, all insulin dose adjustments will be made be the PI who is experienced in T1D management and the frequency of adjustments will be reduced as clinically indicated.

5.3.8 Loss of Privacy

The study will collect data downloaded from study provided CGMs. The researchers will have detailed information about daily diabetes habits. Some people may be uncomfortable with this. Tidepool, Inc. will have access to CGM data but it will not be identified under the participant's name. To reduce risk of privacy loss, the Tidepool account will be set up using a study ID number instead of subject names and a study email address. Many of the participants in this study will already have a Tidepool account as part of their clinical care. The research accounts will be kept separately.

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

6.0 MISCELLANEOUS CONSIDERATIONS

6.1 Benefits

It is expected that the Tele-monitor will provide patients with an increased level of security, especially at night and that frequent contacts will help improve their glucose control.

It is possible that participants will not directly benefit from being a part of this study. However, it is also possible that the blood glucose information from the monitor along with the information and instructions provided for management decisions will be useful for participants' diabetes self-management.

6.2 Participant Reimbursement

The study will provide the BG and CGM and related supplies, for the study.

Participants who complete the study will be able to keep the study CGM devices, assuming that the devices are functioning at the end of the study. Sensors for the CGM to be used after the study will be the participant's responsibility.

6.3 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time.

6.4 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 not be shared. All of the Tidepool data will be streaming into to a computer that is secured and password protected. An email address and date of birth will be created for creating an account in Tidepool, which sends the CGM data to Tidepool. This information will be accessible to Tidepool. All files will include only the participant's identifier; no names or personal information will be included.

CHAPTER 7: STATISTICAL CONSIDERATIONS

7.1 Sample Size

10 subjects will be recruited to participate. This number was chosen based on the usual sample size done in pilot studies such as these, which range (in the literature) from 8 – 12 subjects. This study is primarily a proof of concept to show that the Tele-monitor program works effectively.

7.2 Statistical Analyses

The main goal of this project is to determine study feasibility of the intervention thus statistical considerations were not used.

CHAPTER 8: REFERENCES

1. Graham C, Waldo D. Type 1 Diabetes in Medicare: Use of Services & Program Expenditures in 2010.Diabetes. 2013; 64:A332.
2. Gregg EW, Li Y, Wang J, Burrows NR, Ali MK, Rolka D, et al. Changes in diabetes-related complications in the United States, 1990-2010. N Engl J Med. 2014; 370:1514-23.
3. Ioacara S, Lichiardopol R, Ionescu-Tirgoviste C, Cheta D, Sabau S, Guja C, et al. Improvements in life expectancy in type 1 diabetes patients in the last six decades. Diabetes Res Clin Pract. 2009; 86:146-51.
4. Lawrence JM, Imperatore G, Dabelea D, Mayer-Davis EJ, Linder B, Saydah S, et al. Trends in Incidence of Type 1 Diabetes Among non-Hispanic White Youth in the United States, 2002-2009. Diabetes. 2014.
5. Geller AI, Shehab N, Lovegrove MC, Kegler SR, Weidenbach KN, Ryan GJ, et al. National estimates of insulin-related hypoglycemia and errors leading to emergency department visits and hospitalizations. JAMA Intern Med. 2014; 174:678-86.
6. Lipska KJ, Ross JS, Wang Y, Inzucchi SE, Minges K, Karter AJ, et al. National trends in US hospital admissions for hyperglycemia and hypoglycemia among Medicare beneficiaries, 1999 to 2011. JAMA Intern Med. 2014; 174:1116-24.
7. Stahn A, Pistrosch F, Ganz X, Teige M, Koehler C, Bornstein S, et al. Relationship between hypoglycemic episodes and ventricular arrhythmias in patients with type 2 diabetes and cardiovascular diseases: silent hypoglycemias and silent arrhythmias. Diabetes Care. 2014; 37:516-20.
8. Donnelly LA, Morris AD, Frier BM, Ellis JD, Donnan PT, Durrant R, et al. Frequency and predictors 1215 of hypoglycaemia in Type 1 and insulin-treated Type 2 diabetes: a population-based study. Diabet Med. 2005; 22:749-55.
9. American Diabetes Association. 6. Glycemic Targets. Diabetes Care. 2015; 38:S33-S40.
10. Chiang JL, Kirkman MS, Laffel LM, Peters AL. Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association. Diabetes Care. 2014; 37:2034-54.
11. Weinstock RS, Xing D, Maahs DM, Michels A, Rickels MR, Peters AL, et al. Severe hypoglycemia and diabetic ketoacidosis in adults with type 1 diabetes: results from the T1D Exchange clinic registry. J Clin Endocrinol Metab. 2013; 98:3411-9.
12. Weinstock RS, DuBose SN, Bergenstal RM, Chaytor NS, Peterson C, Olson BA, et al. Risk Factors Associated With Severe Hypoglycemia in Older Adults With Type 1 Diabetes. Diabetes Care. 2015.
13. Pedersen-Bjergaard U, Pramming S, Heller SR, Wallace TM, Rasmussen AK, Jorgensen HV, et al. Severe hypoglycaemia in 1076 adult patients with type 1 diabetes: influence of risk markers and selection. Diabetes Metab Res Rev. 2004; 20:479-86.
14. Martyn-Nemeth P, Schwarz Farabi S, Mihailescu D, Nemeth J, Quinn L. Fear of hypoglycemia in adults with type 1 diabetes: impact of therapeutic advances and strategies for prevention - a review. J Diabetes Complications. 2016; 30:167-77.
15. Jorgensen HV, Pedersen-Bjergaard U, Rasmussen AK, Borch-Johnsen K. The impact of severe hypoglycemia and impaired awareness of hypoglycemia on relatives of patients with type 1 diabetes. Diabetes Care. 2003; 26:1106-9.
16. Sturt J, Dennick K, Due-Christensen M, McCarthy K. The detection and management of diabetes distress in people with type 1 diabetes. Curr Diab Rep. 2015; 15:101.
17. Chaytor NS, Riddlesworth TD, Bzdick S, Odegard PS, Gray SL, Lock JP, et al. The relationship between neuropsychological assessment, numeracy, and functional status in older adults with type 1 diabetes. Neuropsychol Rehabil. 2015:1-15.
18. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research G. Long-Term Effect of Diabetes and Its Treatment on Cognitive Function. N Engl J Med. 2007; 356:1842-52.