Study Title: Improving type 2 diabetes management in primary care through periodic continuous glucose monitoring (T2D INSIGHT)

Protocol (COMIRB) Number: 25-1116

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1. Study Rationale

Diabetes is the eighth leading cause of death in the U.S.[1] and increased in prevalence between 2000 and 2023[2] to 14.7% of adults.[1] During this same time period, the proportion of adults with diabetes achieving glycemic control declined from 57.4% (2007 to 2010) to 50.5% (2015 to 2018)[3] following more than a decade of improvements in this measure.[3] The economic burden of diagnosed diabetes as of 2022 was $412.9 billion in direct medical costs, reduced employment, presenteeism, and lost productivity resulting from premature deaths.[4] Lowering A1C can significantly reduce total healthcare and diabetes-related costs.[5]

Usual care for glycemic measurement to inform clinical diabetes management often consists of frequent self-monitoring of blood glucose. Continuous glucose monitoring (CGM) can help improve diabetes management, clinical care, and clinical outcomes for people with diabetes by providing immediate feedback on the influence of lifestyle factors and medication on glucose levels. Randomized controlled trials and observational studies have demonstrated its effectiveness to improve glycemic outcomes and patient satisfaction for people with type 2 diabetes not treated with insulin, mostly outside of primary care settings.[6-9]

Use of OTC CGM at periodic intervals for people with non-insulin treated T2D has the potential to improve diabetes care and management in primary care settings by reducing and eliminating insurance- and cost-related barriers to CGM adoption. Additionally, recent FDA clearance of over-the-counter (OTC) CGM for people with type 2 diabetes not treated with insulin at a fraction of the cost of prescription CGM has the potential to address many of the biggest barriers to CGM use in primary care settings. However, previous studies on the effectiveness of periodic CGM to improve glycemic outcomes for people with non-insulin treated type 2 diabetes are lacking: They do not compare intervals of periodic use to identify the ideal interval to maintain effectiveness, were conducted outside of the U.S., were not specific to primary care, or were not specific to people with diabetes not treated with insulin. None of the previous studies have examined the use of OTC CGM. **Our study will compare glycemic outcomes (A1C, CGM metrics such as percent time-in-range) associated with use of periodic, OTC CGM Dexcom Stelo) at 30- and 90-day** intervals to usual care for **people with non-insulin treated type 2 diabetes**. It will also assess **feasibility, acceptability, and reach** of this intervention for patients and clinicians.

This study originally proposed to recruit 4 practice sites from which to recruit 188 patient participants. We have since increased to a total of 6 practice sites to ensure we can recruit a sufficient number of participants with non-insulin-treated type 2 diabetes, given that 2 sites from the originally recruited group are fairly small practices.

2. Background

Primary care practices are uniquely positioned to improve diabetes care and management, as they provide care for 50% of adults with type 1 diabetes and 90% of adults with type 2 diabetes.[10-12] However, CGM uptake has been slower in primary care than other specialty care settings due to limited insurance coverage (particularly for people with type 2 diabetes not treated with insulin), burdensome and time-consuming insurance authorization processes, and high costs to patients.[13 14]

Limited but promising evidence suggests that periodic CGM use, at intervals from three weeks to three months (e.g. 15-day use every three months), can support improved glycemic outcomes compared to self-monitoring of blood glucose.[15-19] Periodic CGM use requires fewer sensors for any given timeframe, lowering patients' cost of using CGM. Periodic use of OTC CGM would require fewer sensors than all-the-time use for a given timeframe, and costs about $50 per sensor compared to over $100 per sensor for prescription devices when not covered by insurance. Additionally, OTC CGM negates the need for burdensome and time-consuming ordering and insurance authorization processes on the part of clinicians. The device's self-directed education alleviates the need for primary care practice teams to expend resources such as training and time related to initiating the device with patients.

Understanding whether use of periodic OTC CGM is effective at improving glycemic outcomes in primary care settings and understanding evidence behind specific intervals of use would allow primary care providers to make evidence-based recommendations to their patients with T2D not on insulin. Demonstrating effectiveness of use of CGM at less than $20 or $50/month without prior authorization or insurance barriers could increase access to this evidence-based technology for people who previously could not access or afford it.

3. Objectives and Endpoints

Specific Aim 1: Conduct a two-arm, 1:1 randomized trial to determine the effectiveness of two intervals of periodic use of a CGM on A1C, time-in-range (TIR), and time-in-tight-range (TITR) among people with T2D not treated with insulin and who receive diabetes treatment in primary care settings.

- **Primary and secondary outcomes:**
  - Change in A1C
  - Percent time in range (TIR): Percent of glucose values between 70 and 180 mg/dL.
  - Percent time in tight range (TITR): Percent of glucose values between 70 and 140 mg/dL.

Specific Aim 2: Determine feasibility, acceptability, and reach of periodic use of OTC CGM among 1) primary care clinicians and 2) people with T2D not treated with insulin.

- **Secondary outcomes:**
  - Feasibility (clinicians): Feasibility of Intervention Measure (FIM)[20]
  - Acceptability
    - Clinicians: Acceptability of intervention measure (AIM)[21]
    - Patients:
      - Days of wear
      - Glucose monitoring satisfaction[22]
      - Attrition
      - Percentage approached who agreed to participate.
      - Willingness to pay / affordability: (e.g. Percent of participants willing to pay to continue periodic, OTC CGM use following study completion.)
  - Reach (patients): (e.g. participant demographics (age, race, gender, income, insurance)).
  - Adoption (practices and clinicians): practice characteristics, clinician professional characteristics and demographics
  - Reasons and context for implementation, feasibility, acceptability (qualitative interviews)
  - Intentions to continue, resources and changes needed to continue recommending periodic OTC CGM (qualitative interviews)

4. Study Design

This **single-site, two-arm, 1:1 randomized clinical trial** will examine the use of periodic, OTC CGM **over a six-month period** among people with T2D who do not use insulin in primary care practices. We seek to

determine the frequency of use needed to affect key glycemic control metrics of A1C, time in range (TIR) and time in tight range (TITR), as well as feasibility, acceptability, and affordability of these devices in primary care.

Randomization: In a 1:1 ratio, participants will be randomly assigned to use one 15-day OTC CGM every 30 or 90 days. Randomization block sizes of 4 and 6 will be used randomly to maximize uniform distribution of participant characteristics while minimizing the possibility of predicting an assignment. Randomization will be stratified by clinical practice and GLP-1 or GLP-1/GIP dual agonist use. To minimize an imbalance in the number of participants assigned to each group, randomization will not be stratified by age, A1c, or other factors because of the small number per clinic that is possible. Any imbalances will be adjusted for in the analysis.

Blinding: Baseline data from blinded CGM will be used as a comparator for usual care. Blinded CGM devices will be applied at the screening visit or within approximately one week if remote study visit) to collect a 10-day blinded CGM run-in and again at 3- and 6-month study visits (within approximately one week if remote study visit). Participants will be instructed to not apply a blinded device if they are wearing an OTC CGM.

The aims of the proposed study are:

Specific Aim 1: Conduct a two-arm, 1:1 randomized trial to determine the effectiveness of two intervals of periodic use of a CGM on A1C, time-in-range (TIR), and time-in-tight-range (TITR) among people with T2D not treated with insulin and who receive diabetes treatment in primary care settings. Baseline data from blinded CGM will be used as a comparator for usual care (UC). Our hypotheses are as follows:

1a: Periodic CGM use (one 15-day sensor) once every 30 days or once every 90 days will be associated with lower A1C compared to UC at 3 and 6 months.

1b: Periodic CGM use (one 15-day sensor) once every 90 days will be associated with non-inferior A1C reduction at 3 and 6 months compared to periodic CGM use once every 30 days.

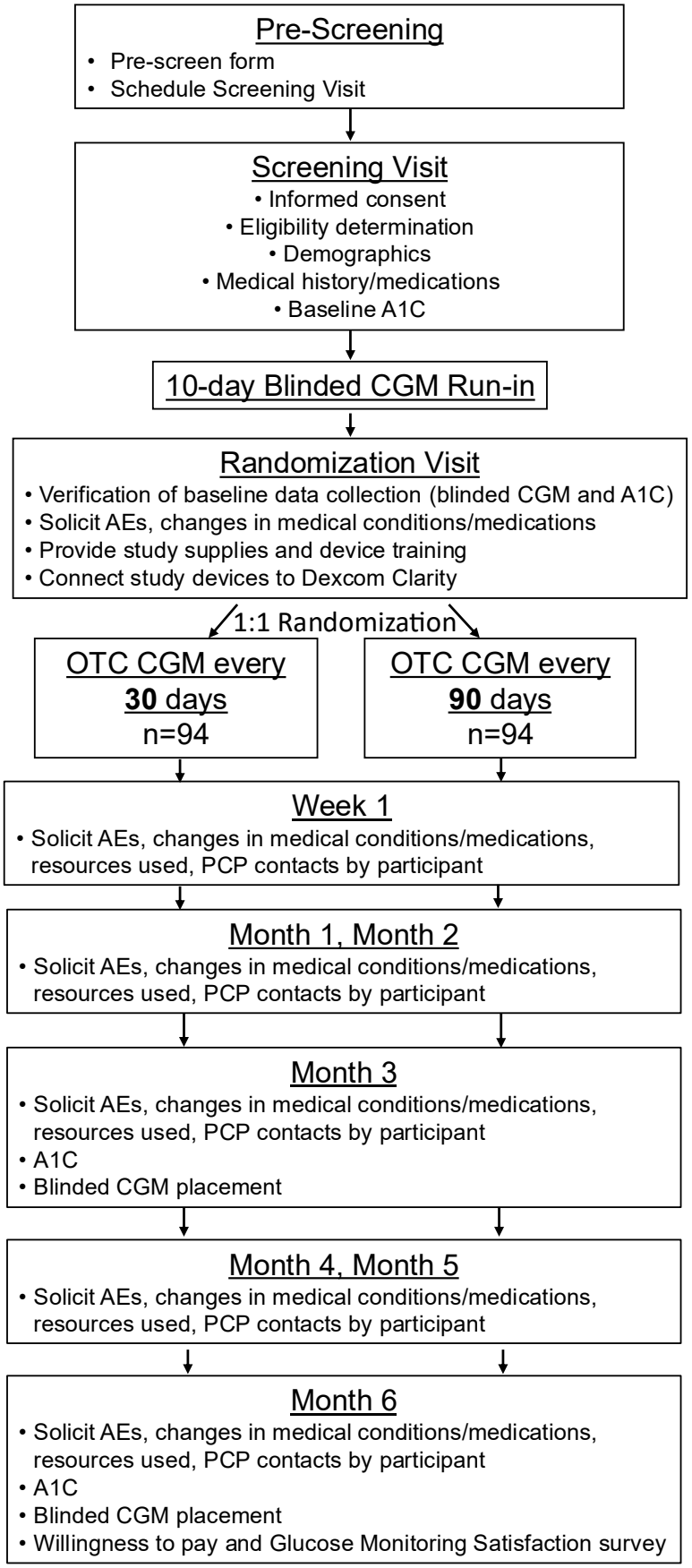
1c: Periodic CGM use (one 15-day sensor) once every 30 days or once every 90 days will be associated with greater TIR and TITR compared to baseline.

Specific Aim 2: Determine feasibility, acceptability, and reach of periodic use of OTC CGM among 1) primary care clinicians and 2) people with T2D not treated with insulin. Hypotheses are as follows:

2a: Measures of feasibility and acceptability will be higher for OTC CGM implementation than for prescription CGM implementation among primary care clinicians.

2b: Periodic OTC CGM use will have higher and more equitable reach and will be acceptable to participants (demographics, % recommended days worn, willingness to pay).

Figure 1. Study Diagram



5. Study Population

Population:

Practices: This project will take place at up to six primary care practices in Colorado recruited through the Practice Innovation Program at the University of Colorado Anschutz Medical Campus.

Practice Inclusion Criteria include:

- Primary care specialty (e.g. family medicine, internal medicine)
- Located within the state of Colorado
- Practice staff and/or providers willing to answer surveys and interviews about their experience caring for patients using the Stelo

Practice Exclusion Criteria include:

- Already participating in CGM- or diabetes-focused initiative that could interfere with intervention and outcomes of the present study, in the opinion of study investigators

Practice Members: Clinicians and staff, including physicians, PAs, NPs, diabetes care and education specialists/diabetes educators, pharmacists, and other team members who care for patients with diabetes, from participating practices will be invited to complete baseline and follow-up surveys and semi-structured interviews to describe implementation, feasibility, and acceptability of periodic OTC CGM in primary care settings. We will recruit 30-40 practice members for surveys (~5-7 per practice), with 30 required to achieve statistical power for planned aim 2 analyses. We will recruit 2-4 practice members from each practice for interviews, up to a possible total of 20. This will result in a total of up to 60 practice member participants, though this will likely be closer to 40 given extensive overlap between survey and interview participants.

Practice Member Inclusion Criteria include:

- Employed in a primary care practice participating in this study
- Care for patients with diabetes

Practice Member Exclusion Criteria include:

- Lack of knowledge about clinical care and operations related to care for patients with diabetes

Patients: We will enroll up to 188 people with type 2 diabetes who are not using insulin from up to six Colorado primary care practices, with the goal of 150 participants completing the study. Enrolling up to 188 participants provides a buffer of 25% to the target completion number of 150 to ensure that a sufficient number of participants remain to achieve adequate power to detect target effect sizes after accounting for screen failures, withdrawals, and other participant attrition.

There will be approximate recruitment goals for the following:

Approximate maximum:

- 10% with screening A1c <7.0%
- 25% with screening A1c >10%

Patient Inclusion Criteria include:

1) Age ≥ 18 years at time of enrollment
2) Diagnosis of type 2 diabetes
3) Able to read and understand English (Dexcom Stelo is currently only available in English)
4) No real-time or intermittently scanned (Flash) CGM use 12 months prior to enrollment

5) Stable medication regimen (medication classes) and dose (equivalent dose if medication has been changed within the same medication class) for any glucose lowering or weight loss medications for 30 days prior to enrollment and willing to not change medications prior to randomization unless safety concerns.
6) Cell phone meeting minimum required OS compatibility with Stelo
7) Willing to use the study device and download the Stelo app
8) Willing and able to complete all study procedures per investigator discretion, including willingness to accept either experimental group (q30 or q90).
9) A1C value (from lab data or chart review) greater than or equal to 6.5 in the 6 months prior to enrollment
10) Currently receiving primary care in a participating study practice

Patient Exclusion Criteria include:

1) Use of insulin in the 12 months prior to screening or planning to initiate insulin during the next 12 months (short-term use of insulin in an inpatient setting is acceptable)
2) Concomitant disease or condition that in the opinion of the investigator may compromise patient safety including but not limited to severe mental illness, a diagnosed or suspected eating disorder, or any uncontrolled or chronic medical condition that would interfere with study related tasks or visits
3) Use within 30 days of screening visit of any medication that in the opinion of the investigator may exacerbate glucose dysfunction (e.g. systemic corticosteroids)
4) Current or planned use of hydroxyurea (due to interference with CGM)
5) Known presence of a hemoglobinopathy or other condition that is expected to affect the measurement of A1C in the judgment of the investigator
6) Known severe allergy to medical grade adhesive, a serious skin condition that could interfere with CGM placement, or extensive tattoos that precludes the use of CGM in an FDA approved location
7) End stage renal disease currently managed by dialysis or eGFR <30 mL/min/1.73m^2
8) Current participation in another interventional study protocol that could impact participation in this study per investigator discretion
9) Pregnant or planning to become pregnant within the next 6 months.
10) Planning to switch primary care practices in the next 6 months.

Strategies for Recruitment and Retention:

Patient participants will be recruited from up to six participating primary care clinics. Potential patient participants will be identified using the UCHealth RECRUIT tool, or by participating clinics (e.g. using patient registries and/or reports from the electronic health record system to identify potential patients). Unaffiliated, non-UCHealth clinics are recruitment sites only, as they are not engaged in research, obtaining informed consent, or performing study procedures. Potential participants will be provided with a recruitment flyer from their primary care provider and/or by email containing an overview of the study's purpose, eligibility criteria, expectations of participants, and study incentives. Flyers will also be placed within the clinic waiting area and exam rooms. This flyer will include a link for a prescreening questionnaire. Additionally, study team members will review the Primary Care Diabetes Lab patient registry (COMIRB # 20-2497) for patients meeting inclusion criteria from participating clinics. The PCDL registry is a list of individuals who have previously engaged with the PCDL through study screening, study participation, or other outreach, and have consented to being contacted with future study opportunities for which they may be eligible. The study team will text, email, call, and/or mail referred patients to explain the study, offer an opportunity to ask questions, and schedule a screening visit. We will contact potential participants up to three times total by phone call, text, email, or mail for recruitment purposes.

The phone script will be used to reach out by phone call to past research participants (PCDL patient registry), RECRUIT referrals who do not complete online prescreening, patients who provide HIPAA authorization for their provider to share contact information for study recruitment purposes, and participants who reach out by phone via the flyer or other modes of advertisement.

Other potential recruitment strategies may include:

- IRB-approved paper and digital advertisements, brochures, postcards, flyers, and/or newsprint advertisements
- IRB-approved digital advertisements posted on social media sites
- In-person recruitment and telephone recruitment by individual clinical sites
- Site specific EHR portal messaging

Incentives will be delivered in the form of electronic gift card using a secure, online gift card platform (e.g. Tango, Amazon) or physical gift card to Walmart or Amazon.

Patient participants will receive up to the following incentives:

Completion of baseline study visit tasks (e.g. demographics, A1c, blinded CGM collection): $30
Completion of 3-month study visit tasks (e.g. A1c, blinded CGM data collection): $30
Completion of 6-month study visit tasks (e.g. surveys completion, A1c, blinded CGM data collection): $50

Clinician participants will receive up to the following incentives:

Completion of baseline survey: $25
Completion of end of study survey: $25
Completion of interview: $50

6. Study Intervention

Patients participating in this study will be randomized 1:1 to receive a 15-day session of periodic, OTC CGM either every 30 days or every 90 days for a six-month period at intervals of 30 or 90 days. Three- and six-month outcomes associated with periodic, OTC CGM use will be compared to participants' own baseline usual care, measured through A1c and blinded 10-day CGM data collection.

Dexcom Stelo is a 15-day OTC (over-the-counter available without a prescription) CGM that is built on the same technology used in the prescription-only Dexcom G7 CGM.[23] It is intended for adults who do not use insulin, which includes most people diagnosed with T2D.[23,24] It is the first OTC CGM to be cleared by the U.S. Food and Drug Administration.[24] The Dexcom Stelo does not have any alarms, and only reads from 70-250 mg/dL. Dexcom Stelo uses an applicator applied to the skin of the upper arm containing a small sensor inserted into the interstitial fluid directly under the skin, from which glucose levels are measured and transmitted to the user's phone application. It is based on the Dexcom G7 platform described below.

The Dexcom G7 will be used to collect blinded CGM data. The Dexcom G7 CGM System comprises three subsystems: Glucose Sensing Subsystem (GSS), Mobile Application System, and the Receiver Subsystem. The GSS consists of an applicator and a wearable encompassing a sensor, a transmitter, and an adhesive patch. The GSS houses and deploys a wearable medical device onto a patient's body for the purpose of measuring the concentration of glucose in the patient's interstitial fluid in real-time and wirelessly communicating estimated glucose information to receiving devices (in this study, the Receiver). It consists of an applicator that inserts the sensor, releases the wearable, and places the adhesive patch on the user's skin. The wearable is composed of the sensor, transmitter, and an

adhesive patch as one unit. All the wearable components can be used for one single session. The sensor is a small, flexible wire sensor that can continuously measure glucose levels in the interstitial fluid for up to 10 days, plus an extra 12-hour grace period at the end. The transmitter is attached to the sensor, and employs an algorithm to calculate estimated glucose values. After insertion, the transmitter automatically detects deployment, verifies wake-up, and begins a sensor session. The sensor's built-in transmitter connects to the Receiver via a Bluetooth Low Energy(BLE). The transmitter logs/saves the data to internal memory and does not transmit any information to a display device when used to collect blinded data, as in this study. The supplemental Dexcom Overlay Patch ("Overpatch") is a standalone, single-use, polyurethane medical tape provided with the System to accompany the wearable device and increase adherence to the skin. Participants will be provided with overpatches for use during the study during both the blinded data collection and use of the OTC CGM.
Device accountability procedures will be followed throughout the study in accordance with SOPs of the Primary Care Diabetes Lab (e.g. inventory, shipping).

Regulatory Concerns:
This study is FDA regulated but is considered IDE exempt because it does not seek to determine the safety or effectiveness of a device. The effectiveness of CGM as a device has been established. Further, periodic use of CGM is within the label of FDA approval for OTC CGM for people with non-insulin treated T2D and this would qualify as testing a modification of the device (periodic use vs. more traditional continuous use). As a result, we are investigating the OTC CGM device in accordance with its FDA labeling, and the study is exempt from IDE regulations. The intervention (the Dexcom Stelo) is an over-the-counter device available without a prescription.

7. Discontinuation and Participant Withdrawal

Discontinuation of study intervention: Participants who discontinue the study intervention will not be discontinued from study participation and will be encouraged to complete study activities (e.g. A1C collection, surveys) through the end of their originally planned participation period.

Use of the Stelo or blinded Dexcom G7 by a participant will be discontinued if any of the following occur:

- The investigator believes it is unsafe for the participant to continue on the intervention. This could be due to the development of a new medical condition or worsening of an existing condition; or participant behavior contrary to the indications for use of the device that imposes on the participant's safety.
- The participant requests that the treatment be stopped
- Pregnancy

Participant discontinuation/withdrawal from the study: Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study non-compliance (e.g. refusal to follow randomized interval for CGM use, not following study procedures)
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant, in the judgment of the PI.
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

The reason for participant discontinuation or withdrawal from the study will be recorded. Subjects who sign the informed consent form and are randomized but do not receive the study intervention

may be replaced if needed to assure that 150 participants complete the study. Subjects who sign the informed consent form and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, may be replaced if needed to assure that 150 participants complete the study.

Lost to follow-up: Substantial effort will be made to contact a participant in the case of a missed scheduled visit, as detailed below. A participant will be considered lost to follow-up if he or she fails to present for two scheduled visits and is unable to be contacted by the study site staff via two or more different methods (e.g., email, telephone, text message).

The study team will take the following actions if a participant fails to present for a required study visit:

- The study team will attempt to contact the participant to reschedule the missed visit, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant. This may include email, telephone call, text message (up to 5 attempts each), outreach to the patient's primary care clinician, and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods. These contact attempts should be documented in the participant's study file.
- Should the participant continue to be unreachable two weeks after the certified letter is sent, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8. Study Assessments and Procedures

Outcome Measures: Primary and secondary outcomes of effectiveness are changes in 1) *A1C* and 2) CGM metrics of *time-in-range (TIR)*, *time-in-tight-range (TITR)*, *mean glucose*, and *time >180 mg/dL (T>180)* from baseline to 3 and 6 months. *TIR* measures the percentage of time that a person spends with their CGM glucose levels between 70 and 180 mg/dL, with a consensus target of over 70% TIR for most people with diabetes.[25 26] *TITR* measures the percentage of time spent within a narrower blood glucose range of 70 to 140 mg/dL. *Mean glucose* measures the mean CGM glucose levels. *T>180* measures the percentage of time that a person spends with their CGM glucose above 180 mg/dL.

Secondary outcomes of implementation are *feasibility*, *acceptability*, and *equitable reach*. These measures provide insight into factors that may affect successful implementation of intermittent CGM in primary care settings. *Feasibility* refers to the extent to which an intervention can be successfully utilized in a particular setting.[20] *Acceptability* is defined as the perception of stakeholders that the intervention is agreeable or satisfactory.[20] **Clinician**-level outcomes of *feasibility* and *acceptability* will be collected through a mixed methods assessment consisting of clinician surveys and semi-structured interviews. Survey measures of **clinician**-level *feasibility* and *acceptability* will be assessed using validated measures--the 4-item Feasibility of Intervention Measure (FIM) and the 4-item Acceptability of Intervention Measure (AIM).[20] Clinician interviews will provide additional context about *acceptability*, *feasibility*, and *implementation* affecting recommendation of periodic use of CGM and its use for diabetes management among people with T2D not using insulin. Semi-structured clinician interviews will include questions assessing barriers and facilitators associated with implementation, including reasons for (in)feasibility, (un)acceptability, and intention to continue to use/not use OTC CGM after the study ends. **Patient-**level *acceptability* will be measured using the proportion of approached participants who agree to participate**,** days of wear, attrition rates, and

surveys collected at 6 months, including questions assessing willingness to pay and affordability, and Glucose Monitoring Satisfaction Survey (type 2 diabetes version) measures.[22] *Reach* refers to the number, proportion, and representativeness of intervention participants.[27] *Equitable Reach* to historically marginalized and economically vulnerable groups will be measured through participant demographics (age, gender, race, income, insurance).

Instruments & corresponding measures:

Instrument	Measures	Timing
Patient 6-month survey	Glucose Monitoring Satisfaction Survey (Version: Type 2 Diabetes)[22]	6-month visit
	Willingness to pay	
Practice survey	Organizational characteristics of practice sites (ownership structure, specialty, characteristics of patient population, number of patients with type 2 diabetes)	Practice enrollment
Clinician survey	Clinician demographic characteristics	Year 3
	Feasibility of Intervention Measure (FIM)[20]	
	Acceptability of Intervention Measure (AIM)[20]	
Clinician interview	Reasons and context for implementation, feasibility, acceptability	Year 3
	Intentions to continue, resources and changes needed to continue recommending periodic OTC CGM	

OTC CGM data collection (Dexcom Stelo). We will mail Stelo devices to patients at time points determined by randomization. Participants will apply devices according to instructions and other educational material provided by manufacturer with device. Participants will be provided with study team contact information in case of questions or problems with application.

Blinded CGM data collection (Dexcom G7). We will use Precision Digital Health software to blind Dexcom G7 devices for blinded data collection. This will allow us to collect baseline data without the effect of OTC CGM, and ensure that follow-up data collection at 3 and 6 months is comparable to baseline. Stelo was based on Dexcom G7, but neither are available as blinded devices. Precision Digital Health offers software that blinds G7 receivers so that real-time readings are not available. After the 10-day sensor period, the receiver is returned to the study team and readings are uploaded to study datasets.

De-identified Stelo and G7 data will be shared with Dexcom, Inc. as specified in contract between Dexcom, Inc. and University of Colorado for purchase of study devices. The study team will provide participants with instructional materials developed by the manufacturer providing information on proper use of and contact information for questions and problems with the Stelo and G7 devices.

A1C testing. A1C will be collected using venous point-of-care testing (for in-person visits) or home A1C test kits (for virtual study visits with participants unable to travel to an in-person site). For in-person study visits, venous A1C will be collected in the course of screening, 3-month, and 6-month study visits conducted at the University of Colorado Clinical and Translational Research Center (CTRC). For virtual study visits, capillary A1C will be collected using home test kits through an agreement with the University of Minnesota Advanced Research and Diagnostic Laboratory (ARDL), which is certified by the National Glycohemoglobin Standardization Program (NGSP). The study team will provide participants with instructional sheets for use of A1C home test kits developed by the manufacturer.

Survey data collection. An initial Practice Survey will be completed by a clinician and/or practice administrator at each participating practice site. The Practice Survey will collect practice characteristics such as size (number of clinicians), ownership structure, specialty (e.g. family medicine, internal medicine), and number of people with T2D served. Clinician Surveys will assess

clinician demographics and measures of implementation including feasibility and acceptability. Based on our experience with these practices and prior completion rates, we expect to receive 40 completed Clinician Surveys. Patient Surveys will include questions assessing willingness to pay (affordability) that we have used in previous studies and the 15-item Glucose Monitoring Satisfaction Survey for T2D, a validated scale assessing emotional burden, behavioral burden, openness, and worthwhileness of glucose device satisfaction.[22] Surveys will be administered via REDCap or hard copy and returned via postage-paid envelopes provided to participants. Patient demographics will be collected as part of the baseline study visit.

Interview data collection. The interview guide will consist of semi-structured questions to solicit information about study outcomes across the identified RE-AIM domains while allowing for exploration of additional topics that participants may indicate are important to discuss. Specifically, up to 20 interviews will be conducted with practice providers and staff to explore the frequency and consistency of recommending periodic OTC CGM for patients with non-insulin treated T2D (*Adoption*), descriptions of implementation, feasibility, and acceptability (*Implementation*); perceptions of *Reach* for patients with non-insulin treated T2D; and explanations and context for each of these topics. We will select 2-4 practice members from each practice (up to 20 total, with fewer participants in smaller practices) for interviews using purposive sampling to ensure input from participants with higher and lower adoption of periodic OTC CGM. Interviews will take place in the last year of the study when most participants will have had some opportunity to care for patients using OTC CGM for this study. Interviews will be conducted via Zoom or telephone and audio recorded with participant permission.

Study Visits

Study visits and procedures will be conducted in-person or via HIPAA-compliant Zoom depending on patient preference.

Prescreening (Visit preparation)

1. Participants are recruited and directed to prescreening form to assess eligibility via one of the following methods:
    a. RECRUIT tool
    b. HIPAA authorization form for non-UCHealth provider to share contact information with study team
    c. PCDL registry
    d. Flyers
2. Potential participants complete prescreening form (online or over phone with study team member) to assess eligibility.
3. Participants complete medical records release form (administered and collected by practice according to organizational policies) to authorize release of medical records for research recruitment purposes.
4. Upon receipt of relevant medical records from practice, PI Oser will review medical records to determine participant eligibility.
5. Upon confirmation of participant eligibility, study team member to schedule screening visit with patient, at which participants will first complete informed consent before beginning any study procedures.

Consent and Screening (Visit 1)

Study procedures will be performed by study staff and will include:

1. Complete informed consent process, including verification of understanding of protocol and willingness to accept assignment to either treatment group.
2. Basic demographic information

3. Medical history
4. Current medications taken (prescription and non-prescription), including approximate date of start, last dose change, and reason for taking.
5. Outcome measure collection
    a. A1c (Venous A1c or POC certified by the National Glycohemoglobin Standardization Program (NGSP)) or for remote participants unable to travel to an in-person site, capillary A1C through the University of Minnesota Advanced Research and Diagnostic Laboratory (ARDL) which is a NGSP certified lab). For each participant, the same method will be used for all three time points. For each participant A1c will be collected within 5 days of the visit.
6. Placement of blinded Dexcom CGM sensor (within approximately 7 days if the visit is being conducted remotely)
    a. Set up Dexcom Clarity account for data collection
    b. A minimum of 2400 glucose values must be collected prior to randomization. Additional blinded sensors/and or additional days may be needed if there are technical issues in collecting the blinded data and this will not result in a protocol deviation.
    c. CGM training will be conducted by a qualified trainer and will include instructions in how to insert the sensor, including observation of placement and instructions on care of the sensor. Glucose readings will not be visible to the participant during blinded wear.

The screening visit may be completed over several days if necessary (e.g. if participant prefers to do informed consent at a separate in-person or remote visit prior to completing the rest of the study visit procedures due to scheduling).

No glucose lowering or weight loss medication changes should occur (removal, addition, change in dose) prior to randomization unless related to safety.

Participants may be rescreened at a later date if they do not initially meet study eligibility per investigator discretion.

Randomization (Visit 2)

During Visit 2, the following study procedures will occur:

1. Study staff will verify that baseline data has been collected (e.g. A1c result available and adequate baseline CGM data obtained).
    a. If more than 45 days elapse between Screening and Randomization Visits, eligibility will be reassessed.
2. Review medical history and medications and record changes and verify no changes to eligibility
3. Assess for and record any adverse events (AEs) that have occurred since Visit 1
4. In a 1:1 ratio, participants will be randomly assigned to use one 15-day OTC CGM every 30 or 90 days.
5. Study staff will provide, or mail OTC CGM supplies to participants (for in-person and remote visits, respectively).
6. Participants will be given information about existing patient education (that is part of the OTC CGM system) for how to use the OTC CGM.
7. Participants will be instructed that OTC CGM devices should not be in place during follow-up blinded data collections.
8. For in-person visits, the first OTC CGM will be placed by the participant. For remote visits, the first OTC CGM will be placed within 7 days.
9. CGM data connection to study account
    a. The study team will assist participants in connecting their OTC CGM to Dexcom Clarity. Although the blinded Dexcom G7 CGM data will be used to analyze the primary outcome of CGM metrics, the OTC CGM data will provide descriptive data such as days of wear,

time within the q30 and q90 time periods that the OTC CGM was used, and provide a further fidelity check to assure that the OTC CGM was not worn at the same time as the blinded Dexcom G7.

Participant contact with the study team for assistance with using the OTC CGM outside of study visits will be tracked to assess feasibility in primary care settings (e.g., percent of participants able to use OTC CGM without additional resources, percent of participants needing additional help).

Mid-Period Follow-up Visits (Phone or Video) (Visits 3, 4, 5, 7, 8)
The schedule for follow-up visits is the same for both treatment groups.

Mid-period visits will be conducted by study staff for the purpose of assessing whether the participant is using the OTC CGM (and reasons for discontinuation if not), AEs, device issues, changes in medical conditions/medications, resources used (provided or additional), and PCP contacts by participants (including whether CGM data was discussed).

Timing for these visits will be based on the day the first OTC CGM was applied.

These visits will occur after:

- 7 days (±2) (Visit 3)
- 30 days (±7) (Visit 4)
- 60 days (±7) (Visit 5)
- 120 days (±7) (Visit 7)
- 150 days (±7) (Visit 8)

3- Month Study Visit (Visit 6)
Prior to Visit 6, study staff will mail remote participants a blinded CGM. This visit will take place 90 days (±7) following application of the first OTC CGM.

During Visit 6, the following study procedures will occur:
1. Review medical history and medications and record changes
2. Assess use and reasons for discontinuation, if applicable
3. Assess for and record any adverse events (AEs) that have occurred since Visit 5
4. Assess for and record device issues
5. Solicit contact with the PCP, existing OTC CGM educational material used, and additional resources used since Visit 5.
6. Assure the participant is not currently using an OTC CGM and solicit date of last use (confirmed by review of Dexcom Clarity data).
7. Outcome measure collection
    a. A1c (Venous A1c or POC certified by the National Glycohemoglobin Standardization Program (NGSP)) or for remote participants unable to travel to an in-person site, capillary A1C through the University of Minnesota Advanced Research and Diagnostic Laboratory (ARDL) which is a NGSP certified lab. For each participant, the same method will be used for all three time points. For each participant A1c will be collected within 5 days of the visit.
8. Placement of blinded Dexcom CGM sensor (within approximately 7 days if the visit is being conducted remotely)

After the collection period, study staff will assure that adequate blinded CGM data has been collected, or the session will be repeated.

6-Month Study Visit (Visit 9)

Prior to Visit 9, study staff will mail remote participants a blinded CGM. This visit will take place 180 days (±7) following application of the first OTC CGM.

During Visit 9, the following study procedures will occur:

1. Review medical history and medications and record changes
2. Assess use and reasons for discontinuation, if applicable
3. Assess for and record any adverse events (AEs) that have occurred since Visit 8
4. Assess for and record device issues
5. Solicit contact with the PCP, existing OTC CGM educational material used, and additional resources used since Visit 8
6. Assure the participant is not currently using an OTC CGM and solicit date of last use (confirmed by review of Dexcom Clarity data).
7. Outcome measure collection
    a. A1c (Venous A1c or POC certified by the National Glycohemoglobin Standardization Program (NGSP)) or for remote participants unable to travel to an in-person site, capillary A1C through the University of Minnesota Advanced Research and Diagnostic Laboratory (ARDL) which is a NGSP certified lab. For each participant, the same method will be used for all three time points. For each participant A1c will be collected within 5 days of the visit.
    b. Completion of Glucose Monitoring Satisfaction Survey and the "Willingness to Pay Survey"
8. Placement of blinded Dexcom CGM sensor (within approximately 7 days if the visit is being conducted remotely)

After the collection period, study staff will assure that adequate blinded CGM data has been collected, or the session will be repeated.

Schedule of patient study visits and procedures:

	Visits																	
Procedures	Screening Visit 1	Randomization Visit 2 (≥+10 days)	[Between]	Follow-up Visit 3, day 7 (±2)	1-month Visit 4, day 30 (±7)	[Between]	2-month Visit 5, day 60 (±7)	[Between]	3-month Visit 6, day 90 (±7)	[Between]	4-month Visit 7, 120 days (±7)	[Between]	5-month Visit 8, 150 days (±7)	[Between]	6-month Visit 9, 180 days (±7)	[Follow-up]
Assess eligibility, informed consent	X																	
Demographics	X																	
A1C	X								X						X			
Blinded CGM	X								X						X			
Verify collection of A1C, blinded CGM		X								X							X	
Assess for AEs		X		X	X		X		X		X		X		X			
Medical history		X		X	X		X		X		X		X		X			
Randomization		X																
Guidance on frequency of OTC CGM use		X																
OTC device application *(within 7 days*		X				X *		X *		X		X *		X *				

for remote participants)							
Assess OTC CGM use/discontinuation	X	X	X*	X*	X	X*	X*
Record contacts with PCP	X	X	X	X	X	X	X
Record resources used	X	X	X	X	X	X	X
Patient survey: glucose monitoring satisfaction, affordability/ willingness to pay							X

Note: X = both study arms, X* = 30-day study arm only.

- 7 days (±2) (Visit 3)
- 30 days (±7) (Visit 4)
- 60 days (±7) (Visit 5)
- 120 days (±7) (Visit 7)
- 150 days (±7) (Visit 8)

9. Risk/Benefit Assessment

Risks:

This study represents no greater than minimal risk to participants. All devices (blinded Dexcom G7, OTC Stelo) will be used consistently with FDA guidelines and approvals. People with non-insulin treated type 2 diabetes (T2D) will be randomized to over-the-counter CGM use for periodic 15-day sessions every 30 or 90 days for six months. Use of the OTC CGM device, Stelo, has been approved by the FDA for people with T2D not using insulin. Use of CGM is consistent with American Diabetes Association Standards of Care for this study's target population: ADA Standards of Care for Diabetes recommend periodic use of CGM for people with non-insulin-treated type 2 diabetes when all-the-time use is not available or not preferred by the patient.[28] Study participation would not expose participants to any greater risk than usual care for their diabetes. Data collection will include A1C and CGM device metrics of time in range (TIR) and time in tight range (TITR), all of which are collected in the normal course of clinical care for people with diabetes using CGM devices. Patients will continue to receive routine care from their usual providers and practice teams. Other patient-level data collection will include surveys (e.g. device satisfaction, willingness to pay). It is possible people may find these questionnaires to be mildly upsetting, but these have been used in previous research, and these types of reactions have been very uncommon.

Loss of confidentiality is a potential risk; however, data are handled to minimize this risk.
Minor potential risks to participants are minor discomfort and skin rash associated with CGM use for some people. However, this risk is no greater than the risk associated with FDA-approved use of the device outside of the study. Further, participants in both study arms will be monitored through study visits on a monthly basis in which study team members will solicit information about any adverse events (AEs) and relevant changes to medical treatment or medications. This will provide the opportunity to promptly discontinue study participation if concerns arise and direct the participant to their primary care or other healthcare provider as appropriate. The greatest potential risk of this study is the inadvertent loss of confidentiality.

Similarly, for practice staff and clinicians, surveys and interviews will cover topics consistent with those encountered in the normal course of clinical operations, presenting no greater risk than their normal workday. These minor risks are outweighed by the potential benefits of this study, which include evidence to support increased and more affordable access to evidence-based technology to control A1C for people with diabetes.

The following risks of Stelo are identified in the manufacturer's package insert:

- Sensor insertion issues (adhesive reactions, retained sensor wire): In rare cases, inserting the sensor can cause infection, bleeding, or pain, and wearing the adhesive patch can irritate your skin. For most people, the adhesive reactions are mild and resolve within a week. Only a few participants in the clinical studies got slight redness and swelling. Although uncommon, some people get a significant reaction from the sensor adhesive that may take weeks to resolve. If a sensor wire breaks off or detaches under your skin and you can't see it, don't try to remove it. Contact your healthcare provider if you have symptoms of infection or inflammation — redness, swelling, or pain — at the insertion site.
- Interfering substances:
    - Acetaminophen: With the Stelo Glucose Biosensor System you can take a standard or maximum acetaminophen dose of 1 gram (1,000mg) every 6 hours and still use the Stelo Glucose Biosensor System. Taking higher than the maximum dose of acetaminophen (e.g. > 1 gram every 6 hours in adults) may affect the sensor readings and make them look higher than they really are.
    - Hydroxyurea: Hydroxyurea makes your sensor readings look higher than they really are. How much higher depends on the amount of hydroxyurea in your body. If you are taking hydroxyurea, talk to your healthcare provider about alternative glucose monitoring approaches. However, it should be noted that taking hydroxyurea is exclusion criteria for this study.
- Inaccurate sensor readings: Inaccurate sensor readings may lead to inappropriate lifestyle decisions. For more reliable decisions, review your readings and trends over time. Always consult your healthcare provider before making any changes to your medication based on your sensor readings.

Benefits: Potential benefits of this study to society in general are knowledge generation to improve care and management for type 2 diabetes. Potential benefits to patient participants are improved clinical health outcomes related to glycemic management (e.g. A1C, time-in-range) and improved satisfaction with glycemic monitoring and management resulting from periodic, OTC CGM use. Potential benefits to participating clinicians and clinical staff are an improved understanding of effective and accessible strategies to improve access to technology to improve diabetes care and management for their patients.

The following benefits of Stelo are identified in the manufacturer's package insert:

- No fingersticks: There is no need to take fingersticks to track your glucose levels as Stelo Glucose Biosensor System provides accurate and reliable glucose measurements. In addition, the Stelo Glucose Biosensor provides functions not feasible using traditional blood glucose monitoring. Traditional blood glucose meters only provide information about discrete, intermittent blood glucose levels and therefore are unable to provide information regarding patterns of glycemic excursions throughout the day and night when people may be unable to test their blood glucose (go to Glucose to find out more).
- Knowing your glucose trends: The Stelo Glucose Biosensor System can help you analyze past glucose data. You can look at trends and patterns over days, weeks, and even months to better understand how your glucose changes over time. This lets you see the overall picture and how changes to your daily habits impact your glucose levels over time. This information may prompt you to discuss your glucose trends with your healthcare provider which can be useful for early detection of abnormal glucose control and behavior modification which may lead to potential avoidance of prediabetes management.[29]
- Making healthy lifestyle decisions: The Stelo Glucose Biosensor System empowers you to make lifestyle decisions on your own. Clinical studies suggest that continuous glucose monitoring can be helpful for people with or without diabetes in connecting the dots of an individual's lifestyle choices and their glucose control.[29 30] Many users felt that continuous glucose monitoring contributed to a healthier lifestyle, such as being more likely to go for a walk or do physical activity if they saw a rise in their glucose, and modifying their food choices. Monitoring the way food, physical activity, medication adherence, stress and emotions, sleep, or other behavioral and lifestyle factors that impact your glucose can also help inform a conversation with your healthcare provider.

- Informing a medication regimen: Continuous glucose monitoring can be important in understanding the impact of medications, such as diabetes and non-diabetes related pills or injections and in adherence to those medications.[30] In addition, review of sensor readings with a healthcare provider can address any changes to medication needs, especially if target goals can't be met through lifestyle changes.

10. Safety Monitoring Plan

The study intervention is an over-the-counter product with no greater risk than usual care and therefore minimal risk. No DSMB or external monitor will be utilized for this study. AEs and device issues will be solicited regularly as per above, but because this study poses minimal risk to the subject, adverse events will only be collected or recorded if a causal relationship to the study intervention is suspected. However, any adverse event that is serious and unexpected, will be reported to COMIRB within 5 days of the PI becoming aware of the event, regardless of whether it is related to the intervention.

Adverse Events and Serious Adverse Events

Adverse Event (AE): Any untoward medical occurrence (including laboratory findings) associated with study procedures or occurring during the course of a study in which a device, biologic, or drug is used in humans, including any comparator used, whether or not the event is considered related (i.e., irrespective of the relationship between the adverse event and the device(s) under investigation).

- To further clarify, an adverse event is any unintended disease or injury, or untoward clinically significant clinical sign (including abnormal laboratory findings) in a research participant that manifests while in the study if it was not present before enrolling in the study, or if it was present before enrolling, it has increased in severity, frequency or type since enrolling in the study. For this purpose, a participant is considered enrolled once the participant has signed the consent form. However, abnormalities identified as part of study screening are not considered adverse events (e.g., physical examination abnormalities or laboratory testing abnormalities) even though they may have been identified after consent was signed. Reportable AEs for this protocol are defined in section below.
- Medical interventions such as surgeries, diagnostic procedures, and therapeutic procedures are not AEs but the action taken to treat a particular medical condition. If the medical intervention relates to a pre-existing medical condition that has not worsened since enrollment, the intervention does not need to be reported unless an AE occurs as a result of the procedure or study drug/device needs to be temporarily discontinued due to the procedure. Also, if the intervention is done in the absence of a condition meeting the definition of an AE, such as for prevention (e.g. colonoscopy) or cosmetic surgery, the intervention should not need to be reported as an AE. If a pre-existing medical condition worsens after enrollment, this will be reported as an AE and the medical intervention will be recorded on the AE form as treatment of the AE.

Serious Adverse Event (SAE): Any untoward medical occurrence that results in any of the following outcomes:

- Death.
- A life-threatening adverse event; (a non-life-threatening event which, had it been more severe, might have become life threatening, is not necessarily considered a serious adverse event).
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.

- A congenital anomaly or birth defect.
- An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical and surgical intervention to prevent one of the outcomes listed in this definition.

Study site will document all SAEs that occur (whether or not related to study intervention). These will be reported to COMIRB within 5 days of the PI becoming aware of the event.

Severity of Event

For adverse events (AEs), the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study intervention). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "potentially related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Unanticipated Problem**:**

Any event or information that was unforeseen and indicates that the research procedures caused harm (including physical, psychological, economic, or social harm) to participants or others or indicates that participants or others are at increased risk of harm than was previously known or recognized.

Unanticipated Event:

Any adverse experience where the nature, severity or frequency is not identified in the investigational brochure described in the application form or detailed in the consent form. This can also include non-compliance issues such as over-enrollment of subjects without prior COMIRB approval.

Device Complaints and Malfunctions:

Device complaints and device malfunctions will be reported except in the following circumstances. These occurrences are expected and will not be reported on a Device Issue Form:

- Skin reaction or pain from CGM sensor if not severe and not requiring pharmacologic treatment
- CGM sensor or transmitter needing replacement prior to labelled maximum use duration
- CGM tape adherence issues
- Battery lifespan deficiency due to inadequate charging or extensive wireless communication
- Intermittent device component disconnections/communication failures not requiring system replacement or workaround/resolution not specified in user guide/manual.
- Device issues clearly addressed in the user guide manual that do not require additional troubleshooting

The following will be reported within 5 days to COMIRB:

- An SAE
- An actual unforeseen harmful or unfavorable occurrence to participants or others that relates to the research protocol (injuries, psychological events, drug errors).
- Adverse events which in the opinion of the principal investigator are both unexpected and probably related to the intervention/ drug or device.
- An unforeseen development that potentially increases the likelihood of harm to participants or others in the future.
- A problem involving data collection, data storage, privacy or confidentiality.
- Incarceration of a participant in a protocol not approved to enroll prisoners.
- Pregnancy of a participant or spouse in a protocol that specifically excludes pregnancy due to the potential risks of the intervention or treatment on the fetus.
- Change to the protocol taken without prior COMIRB review to eliminate an apparent immediate hazard to a research participant.
- Complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional change to the COMIRB approved protocol) that harmed participants or others or that indicates participants or others may be at increased risk of harm.

All reportable AEs will be captured on a study case report form (CRF) with documentation of event description, time of onset, clinician's assessment of severity, relationship to study intervention, actions taken, and time of resolution/stabilization of the event. All AEs will be followed to adequate resolution.

Reportable AEs will be compiled and reported to COMIRB as soon as possible, but in no event later than 5 working days after the PI first learns of the event.

11. Data Analysis

We aim to enroll 188 patients in this study to obtain completed data from 150 patients after potential attrition in order to have adequate power to test key study hypotheses. We anticipate that this will require recruitment outreach to approximately 377 patients and screening approximately 257 patients, based on recent similar studies by our team.

Specific Aim 1: ***Conduct a two-arm, 1:1 randomized trial to determine the effectiveness of two intervals of periodic use of a 15-day CGM on A1C, time-in-range (TIR), and time-in-tight-range (TITR) among people with T2D not treated with insulin and who receive diabetes treatment in primary care settings.***

1a: Periodic CGM use (one 15-day sensor) once every 30 days or once every 90 days will be associated with lower A1C compared to UC at 3 and 6 months.
1b: Periodic CGM use (one 15-day sensor) once every 90 days will be associated with non-inferior A1C reduction at 3 and 6 months compared to periodic CGM use once every 30 days.
1c: Periodic CGM use (one 15-day sensor) once every 30 days or once every 90 days will be associated with greater TIR and TITR compared to baseline.

Primary Outcome
The primary outcome is the change from baseline to 6-month A1C. This outcome will be analyzed in the following hierarchical fashion:

1. Change from baseline to 6-month A1C in the q30 group
2. Change from baseline to 6-month A1C in the q90 group
3. Difference in change from baseline to 6-month A1C between q90 and q30 group tested for non-inferiority with a non-inferiority margin of 0.4%

Sample Size for Primary Outcome
The standard deviation (SD) of change in A1C was estimated from three published studies: COMMITTED, Wada et al. study, and MOBILE [18 31 32]. The change in A1C SD was 0.9% in the COMMITTED study, 0.5% in the Wada et al. study, and 1.5% in the MOBILE study for the CGM group and was 0.7%, 0.9%, and 1.2%, respectively, for the SMBG group (Table 1). The median estimated A1C SD was 0.9% for both treatment groups, and this estimate was used for the sample size derivation.

The sample size for testing change in A1C for each group was determined for various effect sizes (0.4%, 0.5%, or 0.6%) and power (80%, 85%, and 90%; Table 1).

Table 1. Sample size estimates for testing change in A1C (%) in each group.

Mean Change in A1C	Sample Size in Each Group [a]		
	80% Power	85% Power	90% Power
0.4%	42	48	56
0.5%	28	32	37
0.6%	20	23	26

[a] Sample size in each group assumes a change in A1C SD of 0.9% with a two-sided test at α=0.05. Sample sizes do not adjust for any dropouts.

Assuming a mean change in A1C of 0.5% with an SD of 0.9% and a two-sided test at α=0.05, a sample size of 37 participants in each group is required to have 90% power of detecting a significant change from baseline in each group.

The total sample size was increased to 168 participants (84 in each group) to account for dropouts and increase power for testing non-inferiority of the two groups.

Assuming 75 participants complete the study in each treatment group with the above assumptions (mean±SD change in A1C of 0.5% ± 0.9%), the study has >99% power for detecting a significant change in A1C in each treatment group.

The difference in mean A1C at 6 months will be tested for non-inferiority with a 0.4% non-inferiority margin adjusting for baseline A1c. The estimated 6-month A1C SD adjusted for baseline A1C was 0.9%. Assuming no treatment group difference and 150 completers (75 in each group) and a one-sided test at α=0.025, the power of detecting a non-inferior difference in mean A1C at 6-months is 77%.

Statistical Analysis – Aim 1: The primary outcome of change from baseline to 6-month A1C will be assessed using a mixed effect model adjusting for GLP-1 use and clinical practice (random effect) using an unstructured covariance structure to account for the repeated measurements. The comparison of change in A1C between q30 and q90 groups will also adjust for the baseline A1C. The primary outcome will be analyzed using a hierarchical method testing the change in A1C in the q30 group first, followed by testing the change in A1c in q90 group, and then testing non-inferiority of change in A1C between q30 and q90 groups. Testing will stop once a hypothesis fails to reach statistical significance. This gatekeeping strategy will control for the family-wise error rate at α=0.05. A subgroup analysis will be assessed for the primary outcome by adding baseline characteristics (demographics, medical conditions and medications) along with its interaction with the treatment group to the mixed model.

The secondary outcomes of TIR, TITR, mean glucose, and T>180 will be analyzed using a similar mixed effect model as the one for A1C, except the dependent variable of A1C will be replaced by the secondary outcome. The false discovery rate will be controlled using the Benjamini-Hochberg method.

Measures derived from device data (TIR, TITR, mean glucose, T>180) will be calculated by a biostatistician from the Jaeb Center for Health Research. Device data will be securely shared with only the Jaeb statistician working on this study using secure, encrypted University folders. Jaeb Center for Health Research will perform data cleaning and calculation of device metrics for statistical analysis by the CU study team.

Specific Aim 2: *Determine feasibility, acceptability, and reach of periodic use of OTC CGM among 1) primary care clinicians and 2) people with T2D not treated with insulin.*

2a: Measures of feasibility and acceptability will be higher for OTC CGM implementation than for prescription CGM implementation among primary care clinicians.

2b: Periodic OTC CGM use will have higher and more equitable reach and will be acceptable to participants (demographics, % recommended days worn, willingness to pay).

Statistical Analysis – Aim 2: Measures of feasibility, acceptability, reach of periodic use of OTC CGM, and other outcomes are obtained from a clinician survey, practice survey, and patient survey respectively. These measures will be defined as numerical variables or binary variables. All the numerical variables will be summarized using mean ± standard deviation and median (min, max) for clinicians and patients respectively. Binary variables will be summarized using frequency (in %). For 2a, paired t tests, Wilcoxon signed rank tests, and/or linear mixed models will be used to compare means of numerical measures of feasibility and acceptability for OTC CGM than prescription CGM. One sample t tests or 95% confidence intervals will be used to infer the population means of the numerical measures. When a binary measure is used, the frequencies for OTC and prescription CGM will be compared using a McNemar's test. The population mean of the binary measure will be inferred using a one sample exact test or a 95% confidence interval under the binomial distribution. The same statistical plans in 2a will be applied to the measures used in 2b.

Power and Sample Size – Aim 2: HT2a will be tested based upon a minimum sample size of 30 clinicians who complete the survey (though we anticipate 40, which will increase power). An effect size (difference of means / standard deviation of difference) of 0.53 can be detected with 80% power using a paired t test. For HT2b, the same power can detect a targeted acceptance rate of 80% against a null rate of 70% using a normal test.

Qualitative Analysis Plan. Interviews will be professionally transcribed and loaded into ATLAS.ti software (ATLAS.ti Scientific Software Development, GmbH). We will use a grounded hermeneutic editing approach incorporating inductive and deductive strategies to qualitatively analyze interviews.[33] This involves coding text to organize it into categories based on topics of discussion using pre-determined codes (e.g., facilitators, barriers, acceptability, practice context) based on research questions while allowing for emergent codes based on other relevant topics discussed by participants. This will help us understand specifically how clinician and patient characteristics and preferences and other contextual factors support or hinder use of intermittent CGM for management of T2D not requiring insulin use.

12. Informed Consent Process

Informed consent – Patients

Before completing any procedures or collecting any data, informed consent will be obtained.

The potential participant will be provided the IRB-approved Informed Consent Form to read and study staff will review the consent form with the potential participant, including review of study procedures and risks. Participants will have the opportunity to carefully review the consent and ask questions prior to signing. Potential study participants will be encouraged to discuss the study with family members prior to deciding to participate in the study. Participants will have the opportunity to ask questions prior to signing. The participant will sign the informed consent document electronically or in ink. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. 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. The consent form will also include contact information for the study PI and COMIRB. A copy of the consent form will be provided to the participant. This process will be documented in the study records (e.g. Documentation of Consent Process).

A participant is considered enrolled when the informed consent form has been signed.

Informed consent – Clinicians & Staff

We are requesting a waiver of documentation of consent for surveys and interviews conducted with clinicians and staff in participating practices. This portion of the study (data collected from practice members) is minimal risk, as it only collects information related to activities conducted in the normal course of work duties (offering standard-of-care, FDA-cleared device). We propose using postcard consent for surveys and interviews with practice clinicians and staff. Postcard consent will be provided prior to completion of surveys and interviews and subjects' signatures will not be obtained on consent documents. We have included a postcard consent document that follows the COMIRB postcard consent template (9/10/25).

13. Confidentiality and Privacy

The greatest potential risk of this study is the inadvertent loss of confidentiality. All reasonable efforts will be made to protect the confidentiality of participant identities and study data. Survey and laboratory data will be collected and stored in REDCap and will be accessible only to the study team. However, the A1c values will be provided to the participants' primary care provider with patient participant permission. CGM data will be accessed via Dexcom Clarity, which is HIPAA compliant. Survey, device, and laboratory data used for analysis will not contain personally identifiable information and will be reported in aggregate. Downloaded surveys, clinical data, and interview data (audio files and transcripts) will be stored on secure, password-protected servers with access limited to study personnel. All paper consent forms and data will be stored in locked filing cabinets accessible only to a limited subset of relevant study personnel. We will de-identify interview transcripts for analysis and will use password-protected analytical files using ATLAS.ti qualitative data analysis software. Should participants withdraw from the study, no further study data about those subjects will be gathered from CGM devices or surveys.

14. References

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