Study Title: Pilot Feasibility Study for HypoPals, a Mobile Health Program for Improving Hypoglycemia Management

PI: Yu Kuei Lin, MD

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Project Title: Feasibility trial of HypoPals, a mobile health intervention for improving hypoglycemia self-management in T1D adults using advanced diabetes technologies

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List of personnel:

Name	Title	Department	Role
Yu Kuei Lin, MD	Clinical Assistant Professor	Internal Medicine/MEND	Principal investigator
John Piette, PhD	Professor	Health Behavior and Health Education	Co-investigator
Nicolle Marinec	Senior Project Manager	Health Behavior and Health Education	Other (external collaborator)
Jenny Chen	Research Area Specialist Senior	Health Behavior and Health Education	Research Staff
Sean Newman	App Programmer	Health Behavior and Health Education	Research Staff
Patrick Neggie	App Programmer	Health Behavior and Health Education	Research Staff
Adam Martin-Schwarze	Biostatistician	SABER/Biostatistics	Biostatician
Diana Hall	Clinical research project manager	Internal Medicine/MEND	Study coordinator
Emily Hepworth	Clinical research study coordinator	Internal Medicine/MEND	Study coordinator
Annika Agni	Research Staff	Family Medicine	Research Staff

Protocol Summary

Background: Hypoglycemia is a major complication of diabetes, which continues to occur in people living with type 1 diabetes (T1D) despite the current standard of care including advanced diabetes technologies. Survey and qualitative studies inform that reduced ability to detect hypoglycemia symptoms and unhelpful beliefs around hypoglycemia are related to increased risks for developing hypoglycemia in T1D advanced diabetes technologies. We have devised a mobile health (mHealth) text messaging behavioral intervention program ("HypoPals") for improving hypoglycemia symptom detection and tailoring unhelpful hypoglycemia beliefs. A pilot study is needed to inform the integrity of the mHealth technology, preliminary intervention fidelity and acceptability, and effectiveness trial conduct.

Objective: Conduct a pilot study of an mHealth hypoglycemia behavioral intervention program to evaluate the mHealth technology integrity, preliminary intervention fidelity and acceptability, and the feasibility of the effectiveness trial conduct.

Study design: This is a pilot feasibility 2x2 factorial design randomized clinical trial at the University of Michigan. The study duration will be three years.

Study population and participants: Registrees of the T1D Exchange, a national T1D patient registry, will be approached for recruitment. Adults with T1D, using continuous glucose monitor (CGM) ≥1 year and continue to experience ≥1 severe hypoglycemic episode (SHE) OR spending ≥1% of time in level 2 hypoglycemia will be recruited.

Intervention: All eligible participants will undergo a 2-week basic hypoglycemia education. Four possible experimental conditions (10 weeks) will be randomly assigned to participants in 1:1:1:1 ratio: (1) Hypoglycemia symptom detection training+psychoeducation; (2) hypoglycemia symptom detection training only; (3) psychoeducation only; (4) usual care. The entire intervention phase will last 12 weeks.

Endpoints: Outcomes of mHealth technology integrity (e.g., connectivity to CGM data, message delivery), intervention fidelity and acceptability (message reading and acceptability) and trial conduct (e.g., recruitment, retention, outcome assessment) will be collected. The primary outcome is the number of people to recruit to reach to n=20 completing the intervention.

Scheduled activities:

	Pre-screening (Pre-consent)	Recruitment	Week 0 (baseline)	Week 2	Week 6	Week 12	Week 26	Week 52
Demographics	X							
Clinical and diabetes history	X							
Severe hypoglycemia history	X		X			X	X	X
CGM data collection	X		X			X	X	X
Eligibility criteria confirmation		X						
Informed consent		X						
Hypoglycemia symptom detection; confirmation; beliefs; management intention setting; decision and action to manage hypoglycemia			X			X	X	X
Interoceptive awareness			X					
Advanced diabetes technology changes			X	X	X	X	X	X
Randomization/Intervention initiation			X					
Feasibility Outcome Evaluation								
mHealth technology integrity outcomes			X	X	X	X		
Intervention fidelity and acceptability outcomes								
Intervention fidelity			X	X	X	X	X	X
Intervention acceptability						X		
Trial conduct outcomes								
Feasibility of protocol and recruitment conduct	X	X	X	X	X	X	X	X
Feasibility of outcome measurements			X			X		
Participation compensation feedback						X		
Safety Evaluation								
Pregnancy Reporting			X	X	X	X	X	X
Adverse events reporting			X	X	X	X	X	X
Diabetic ketoacidosis reporting and CGM hyperglycemia assessment			X	X	X	X	X	X
Estimated coordinator time commitment (min)	20	60	20	10	10	10	20	20

Events can occur ±1 week of the dates.
CGM, continuous glucose monitor; EMR, electronic medical records

1. Introduction

Background & objectives

Level 2 hypoglycemia (blood glucose <54 mg/dL) is a dangerous complication of diabetes. Despite using advanced diabetes technologies such as continuous glucose monitoring systems (CGMs) and automated insulin delivery systems (AIDs), level 2 hypoglycemia continues to impact people living with type 1 diabetes (T1D).[1-4] Reduced abilities to detect hypoglycemia symptoms[5] and unhelpful hypoglycemia beliefs[1] are key risk behavioral factors leading to developments of level 2 hypoglycemia in this population. However, it remains unknown whether hypoglycemia symptom detection training, which helps improving hypoglycemia symptom awareness, and psychoeducation, focusing on tailoring unhelpful hypoglycemia beliefs, conducted via mobile health technologies for expanding access to these interventions, can effectively improve hypoglycemia self-management and reduce level 2 hypoglycemia in advanced diabetes technology users. Our ***long-term goal*** is to develop scalable, personalized interventions for addressing unhelpful patient behaviors that limit the optimal use of advanced diabetes technologies for minimizing dangerous hypoglycemia. We plan to, under the Multiphase Optimization Strategy (MOST) framework,[6] evaluate the impact of mobile health hypoglycemia symptom detection training for improving hypoglycemia symptom awareness, and psychoeducation for tailoring unhelpful beliefs, for reducing severe and level 2 hypoglycemia, and identify predictors of hypoglycemia reduction with each intervention component for intervention personalization with a 2x2 factorial design randomized trial (hypoglycemia symptom detection training, on vs. off; psychoeducation, on vs. off). A pilot study is needed to inform the integrity of the mHealth technology, preliminary intervention fidelity and acceptability, and effectiveness trial conduct.

Objective: To conduct a pilot study of an mHealth hypoglycemia behavioral intervention program to evaluate the integrity of the mHealth technology, preliminary intervention fidelity and acceptability, and the feasibility of effectiveness trial conduct such as protocol conduct (e.g., screening, recruitment and retention) and outcome measurements.

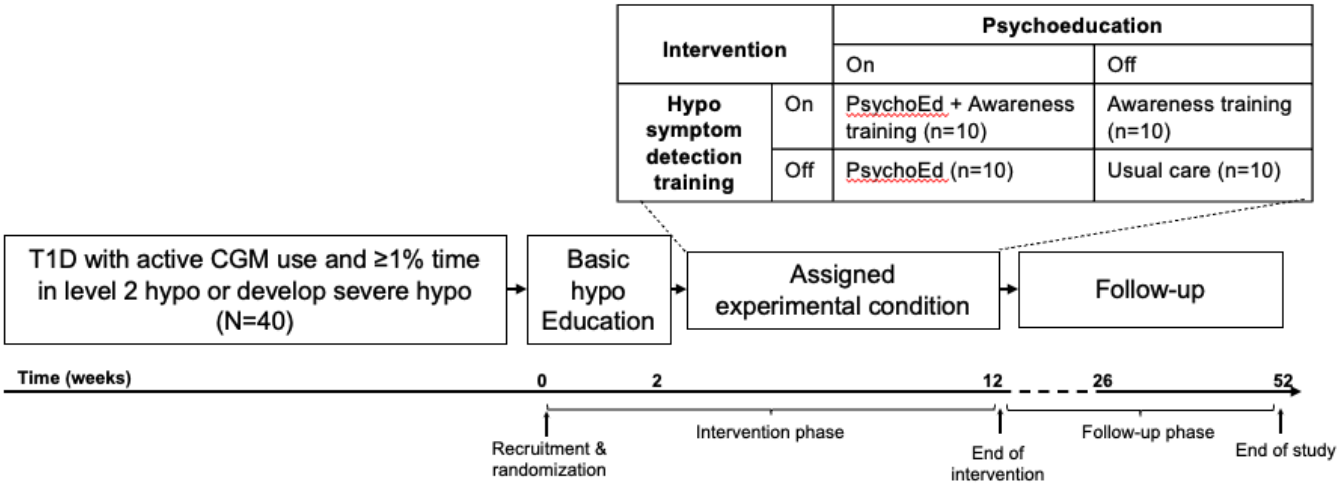
Risk/benefits assessment for justifying the study:

- ***Potential risks:*** The most likely risk to participants is the time burden associated with participation in the study. We do not expect study-related text messages and collections of patient demographics, CGM data and patient reported outcomes through self-reporting instruments to significantly increase participants' health risks to higher than they would otherwise experience in their ordinary daily life. Other potential risks include the breach of confidentiality or data security ("rare"). Some participants may experience distress from the content of text messages about hypoglycemia. Patients will be informed that they can stop from participating in the trial if they do not want to continue with the study.
- ***Potential benefits:*** An impactful and widely accessible hypoglycemia behavioral intervention program can improve hypoglycemia self-management and reduce hypoglycemia and related complications and burdens. If this mHealth program is effective, participants may also experience reduction in hypoglycemia.
- ***Assessment:*** Participants will be exposed to no more than minimal risk while the information gained could help develop an impactful program to reduce life-threatening hypoglycemic events.

2. Study design

Trial design overview, setting, and schema

This is a pilot 2x2 factorial design randomized clinical trial at the University of Michigan. All candidates will undergo pre-screening and consent procedures prior to recruitment. After recruitment and baseline assessment, all participants will undergo randomization and a 2-week basic hypoglycemia education. Subsequently, based on randomization results, four possible experimental conditions will be implemented in participants in 1:1:1:1 ratio: (1) Hypoglycemia symptom detection training+psychoeducation; (2) hypoglycemia symptom detection training only; (3) psychoeducation only; (4) usual care. Each experimental condition will last 10 weeks. After the end of the intervention, all participants will undergo the 40-week follow-up phase with conduct at 26th week and 52nd week to complete the 52-week study.



Randomization, allocation, and blinding

Adaptive randomization with minimization method will be conducted to ensure equal number of participants (n=10) will be randomized into the same number of the 4 experimental conditions (i.e., in 1:1:1:1 ratio). The randomization will be stratified based on whether the participant have severe hypoglycemia within the year OR spending ≥1% of time in level 2 hypoglycemia on CGM, and the status of closed-loop pump use. The procedure of randomization will be determined by the study statistician.

The experimental condition allocation mechanism will be generated by the study statistician and held by the PI. When a participant is recruited, the study coordinator will collect the allocation information from the PI and assign the allocation to the participant.

Even randomization errors are not expected, when they occur, we will apply the intention-to-treat principle and include the affected participant into the analysis. When needed, we may also work with the Data and Safety monitor, who will provide independent, objective assessment, and under the previously published guidance,[7] and consider removing affected participants.

This study will not use blinding given complete blinding participants and study investigators from the intervention (i.e., education content) participants receives will not be possible.

End-of-study definition

The end of the study is defined as completion of the 52-week follow-up assessment.

3. Study population

Eligibility criteria

- Inclusion criteria:
    1. Provision of signed and dated informed consent form
    2. Age 18-70
    3. Self-reported diagnosis of type 1 diabetes for at least 5 years
    4. Previous attendance of structured diabetes education program
    5. Using CGM ≥1 year
    6. Ongoing Dexcom CGM use time ≥70% based on CGM report at screening
    7. Have had experienced ≥1 episode of SH in the past year while using CGMs OR spending ≥1% of time in level 2 hypoglycemia at the time of pre-screening
    8. Using cellphone with functionality for sharing real-time data to Dexcom Clarity and receiving text messages
    9. Be able to communicate in English (spoken and written)
    10. Willing to comply with all study procedures including sharing CGM glucose information, receiving and reading intervention text messages, and completing study questionnaires
- Exclusion criteria:

1. Active participation in clinical trials on diabetes/hypoglycemia interventions
2. Pregnancy or planning for pregnancy within a year
3. Untreated adrenal insufficiency or hypothyroidism
4. Uncontrolled mental disorder or chronic cognitive dysfunctions (include but not limited to uncontrolled schizophrenia, depression and bipolar disorders; learning disability; active alcohol and substance dependence; dementia or cognitive impairment independent of hypoglycemia

Pre-screening, recruitment, and study initiation processes

We are conducting a REDCap survey (HUM00232351) with the T1D Exchange, a national type 1 diabetes patient registry. At the end of the survey, participants will be asked whether they are interested in participating additional research including mHealth studies, and if they are interested in participating in other studies, to leave their contact information (email or phone number). Survey participants will be pre-screened based on their age, diabetes history and CGM use status and history. A candidate list will be created with only survey participants who answered 'yes' to the question. The candidates will then be directly contacted either through email or phone number by our team for recruitment (and T1D Exchange will not be involved in the recruitment process or any other study procedures). We will contact the candidate either through email and telephone for up to three times. The candidate list will be kept for records about the number of times a candidate is being contacted. The study team will check eligibility and discuss with the candidate about the project and answer questions before proceeding to consenting.

For remote consenting, the research team will send REDCap consent form to the candidates and go over the consent with the candidates (either through phone or a virtual meeting). The candidate can download a copy of the consent form from the REDCap page. Study information including mobile health text messages and the need of CGM glucose information sharing will be informed during the consenting process. We will give candidate as much time as needed to consider whether to participate in the study. The participant will also be encouraged to discuss with others as a part of the consenting process. If the candidate is willing to provide informed consent, they will be asked to type down the full legal name on the REDCap page to complete the consenting process. Any questions the patient may have will be answered.

After study enrollment, the randomization will then be completed and the intervention will then be initiated based on the experimental condition allocated.

Pre-screen failure: Pre-screen failures are defined as participants who completed the pre-screening process but are not meeting the eligibility criteria. Individuals who do not meet the criteria for participation in this trial because of meeting one or more exclusion criteria that are likely to change over time may be rescreened. Examples include not using Dexcom CGMs ≥1 year and use of cellphone not compatible with Dexcom CGM software.

Participation compensation

Participants can receive up to $270 gift card as participation compensation and the compensation will be split throughout the study: $30 after completing enrollment, $180 at the end of intervention, $30 after 26-week follow-up and $30 after 52-week follow-up. We estimated the appropriate level of compensation to avoid the compensation being viewed as coercive.

4. Intervention

Intervention components

All interventions will be delivered via mHealth text messages. All participants will receive 2-week text messages of basic education about hypoglycemia. Participants may then receive the hypoglycemia symptom detection training and/or psychoeducation intervention components or usual care based on the intervention assignment.

- ***Basic hypoglycemia education intervention component.*** Daily text messages providing education about definitions, risks, and causes of hypoglycemia and hypoglycemia prevention and management skills will be provided. The rationale for including this intervention component is to ensure participants have at least a basic level understanding of hypoglycemia to control the heterogeneity of diabetes education they have received from local diabetes education programs. This component will also define

the language used to communicate hypoglycemia-related concepts in the remaining program for those who receive other intervention component(s).

- ***Hypoglycemia symptom detection training.*** Text messages providing training for improving hypoglycemia symptom detection will be delivered after episodes of CGM-determined hypoglycemia (glucose level <70 mg/dL consecutively for ≥15 minutes). The training messages will provide (1) knowledge about the type of symptoms of hypoglycemia can present with, including body, sense, mental and mood changes, and quick self-tests that patients can perform to actively detect mental changes during hypoglycemia; (2) the time of the recent hypoglycemia episode and an invitation for patient self-recalling of hypoglycemic symptoms during the episode, and; (3) training on developing a list of one's own hypoglycemia symptoms and the habit of self-checking hypoglycemia symptoms when receiving CGM hypoglycemia data. These messages were developed based on the concept of the Blood Glucose Awareness Training (BGAT) program, which demonstrated that self-evaluating of hypoglycemia symptoms can help improve hypoglycemia symptom detection[8] and reduce hypoglycemia.[9]
- ***Psychoeducation.*** Daily text messages for tailoring unhelpful hypoglycemia beliefs that were identified in our prior survey[1] and interview study (manuscript submitted) will be provided. The psychoeducation will focus on (1) helping patients identify their own internal motivations for reducing hypoglycemia, and; controlling hyperglycemia and social risk perception related to hypoglycemia self-management (for directing outcome expectancy towards favoring managing hypoglycemia); (2) calibrating hypoglycemia risk perception; and; (3) helping patients develop their own hypoglycemia management coping strategies (for improving hypoglycemia management coping self-efficacy). These messages incorporate the structure and content of a prior hypoglycemia psychoeducation program demonstrated to successfully tailor hypoglycemia beliefs and reduce hypoglycemia.[10] Behavioral changing techniques from motivational interviewing (including decision matrix) and cognitive behavioral therapy (including belief challenging with Socratic-style questions, problem-solving, and exposure therapy) were also incorporated. Weekly hypoglycemia outcome feedback messages, guided by summarized weekly CGM hypoglycemia data, will also be delivered for improving hypoglycemia management self-efficacy. We adopted two-way interactive messages for improving engagement with and efficacy of the intervention messages.[11] Patient-shared hypoglycemia self-management experiences were also incorporated to help patients feel understood and more accompanied while acquiring field-tested techniques of hypoglycemia self-management.
  (All text messages were developed to deliver intervention contents with positive framed advocacies in an autonomy-respected, empowering, and non-oppressive manner.[12])
- *mHealth technology.* We have developed and feasibility-tested[13] the mHealth technology with the Twilio platform,[14] including an application programming interface (API) to receive patient's glucose levels shared via Dexcom Developer[15] for sending hypoglycemia symptom detection training messages after CGM-determined hypoglycemic episodes and guiding weekly hypoglycemia outcome feedback messages to be delivered. This program can also deliver two-way interactive test messages.

Fidelity measures: ***Text message delivery, reception and reading*** will be checked for fidelity. For text message ***delivery***, a log of the text messages (with content and time stamps) delivered to each participant will be available on the HypoPals mHealth program website and will be monitored weekly to ensure correctness of the content and time delivered during the intervention period. We will contact participants at, 2, 6 and 12 weeks, either through telephone calls or text messages, to confirm timely ***reception*** of these text messages. When contacting participants, we will also evaluate self-reported text message ***reading*** based on regularity (e.g., from right away to ignoring it completely) and completeness (from the whole message to not at all), with an adapted mSustain survey.[16] A log of participants' responses to the two-way interactive text messages will also be available on the mHealth program website and the rate of responding will also be used for fidelity assessment. During the telephone visits at weeks 0, 2, 6, 12, 26 and 52, we will also verbally assess whether the participant has changes in diabetes care including receiving additional diabetes and hypoglycemia-related interventions.

Rescue therapy

Rescue therapy will not be applied to this study as there currently exists no widely available program for reducing hypoglycemia. All study subjects will continue receiving their current care from their diabetes healthcare providers for hypoglycemia management.

5. Intervention and participant discontinuation

Discontinuation of study intervention

The study intervention will be discontinued if:

- The researcher believes that it is not in the participant's best interest to stay in the study.
- Participant becomes ineligible to participate.
- Participant's condition changes and needs treatment that is not allowed while taking part in the study.
- Participant deviates from or do not follow instructions from the researchers.
- The study is suspended or canceled.

The reason(s) for discontinuing the participant from the intervention will be documented.

When a participant discontinues from study intervention but not from the study, remaining study procedures will be completed as indicated by the study protocol.

Discontinuation from the study

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

- Significant study intervention non-compliance, unless varying compliance is an aspect of the study objectives
- Lost-to-follow up (defined as unable to contact subject and unable to obtain CGM data)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- 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. Participants who discontinue before the completion of the intervention phase will be replaced. No replacement will occur if the participants withdraw or lose follow-up during the follow-up phase.

Loss of follow-up

A participant will be considered lost to follow-up if s/he fails to be contacted at week 12, week 26 or week 52 and study staff are unable to contact the participant after at least 3 attempts AND follow-up CGM data were not able to be collected. The following actions must be taken if a participant fails to return to be contacted:

- The site will attempt to reschedule the missed evaluations and contact the participant, obtain information for better contact time and ways, and ascertain if the participant wishes to and/or should continue in the study.
- The site will attempt to collect CGM data through Dexcom Clarity or Developer.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, up to 3 telephone calls, text messages, and emails and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods. These contact attempts will be documented in the participant's study file.
- Should the participant continue to be unreachable and her/his CGM data can no longer be collected, s/he will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6. Endpoints and Safety Assessments

To evaluate the feasibility of the study evaluating an mHealth behavioral intervention program for improving hypoglycemia self-management, including mHealth technology integrity, intervention acceptability, and trial conduct.

The primary outcome is the number of people to recruit to reach to n=20 completing the intervention.

mHealth technology integrity outcomes

- Percentage of participants completing the intervention without experiencing major mHealth technology glitches (defined as needing to hold the intervention before the glitches are resolved)

    - For technology team/delivery window
        - Retrieving CGM glucose information to mHealth server (including after transmitter changes)
        - Texting research team when missing CGM data for 3 days
        - The ability to switching on/off message delivery
        - Sending messages at right time (including time zone)
        - Sending messages in the right sequence (including the introduction messages comes together)
        - Notifying study team when participants text 'Stop' on receiving messages
    - Specifically for hypoglycemia symptom detection training program
        - Messages triggering by CGM hypoglycemia (CGM glucose <70 mg/dL x 15 consecutive minutes)
        - Messages indicating the correct time when hypoglycemia develops
        - Sending messages at selected time points (e.g., 10am, 3pm, 10pm, etc)
    - Specifically for psychoeducation program
        - Sending correct responding messages and timely sending responding messages (i.e., two-way messaging)
        - Retrieving and calculating current hypoglycemia outcome in the past two weeks
    - For participants
        - The messages were received at correct times
        - The messages delivered correct content
        - Recording responses from patients

<u>Intervention fidelity and acceptability outcomes</u>

- Intervention fidelity
    - Percentage of times participants will need to hold intervention due to CGM or cellphone technology change
        - Dexcom CGM discontinuation
        - Change to cellphone type that has no access to Dexcom Clarity
    - Percentage of CGM usage time
    - Percentage of participants reporting reading message content at the end of the intervention (a secondary outcome)
    - Percentage of two-way message responded
    - Time to finish the hypoglycemia symptom detection training and/or psychoeducation intervention
- Intervention acceptability
    - Percentage of participants finding message content helpful (a secondary outcome)
    - Number of message received per day

<u>Trial conduct outcomes</u>

- Feasibility of protocol and recruitment conduct
    - Pre-screening:
        - Percentage of patients undergoing prescreening
        - Percentage of pre-screened patients eligible
    - Recruitment:
        - Number of patients contacted (a secondary outcome)
        - Number of people to recruit to reach to n=20 completing the intervention (primary outcome)
        - Percentage of contacted patient being eligible and consented (a secondary outcome)
        - Reasons eligible participant for not consenting
        - Average time delay from prescreening to enrollment
        - Average time delay from enrollment to intervention initiation
    - Retention:
        - Rate of participant retention (at 12 weeks) (a secondary outcome)
        - Rate of participant retention (at 26 weeks) (a secondary outcome)
        - Rate of participant retention (at 52 weeks) (a secondary outcome)

        - Percentage of participants discontinuing study intervention
        - Reasons for participants to be discontinuing study intervention
        - Percentage of participants discontinued from the study (including the loss of follow-up)
        - Reasons for participants to be discontinued from the study (intervention duration, assessment burdensome, treatment condition, etc)
    - Compensation fairness
        - Percentage of participants found the compensation fair
- Feasibility of outcome measurements:
    - Percentage of participant changing advanced diabetes technologies during the study
    - Percentage of participants with CGM data collected (at 12 weeks) (a secondary outcome)
    - Percentage of participants with CGM data collected (at 26 weeks) (a secondary outcome)
    - Percentage of participants with CGM data collected (at 52 weeks) (a secondary outcome)
    - Percentage of participants with questionnaires completed at 12 weeks
    - Percentage of participants with questionnaires completed at 26 weeks
    - Percentage of participants with questionnaires completed at 52 weeks
    - Percentage of people finding self-reported instrument having too many questions to answer
    - Percentage of people finding self-reported instrument taking too much time
    - Percentage of people finding self-reported instrument too tiring to complete
    - Other feedback from study coordinators including training protocol

Safety and adverse events

- This protocol uses the definition of adverse event and classification of adverse event, the relationship between the adverse events with the study procedures, and the expectedness of the adverse event from 21 CFR 312.32 (a), which could be found on website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32
- The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during scheduled study contacts with participants or upon review by a study monitor. All AEs, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.
- Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.
- Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.
- Diabetes-related complications including diabetic ketoacidosis are unexpected adverse events that may not be related to the study intervention. These adverse events will be monitored but will not be reported. If the rate of these adverse events appears to be higher than expected, the study team will discuss with study monitor about whether to put the study on hold to decide the next steps.
- Study coordinators will record events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.
- All SAEs (defined as death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, and other important medical events) will be reported to the Data and Safety Monitor. A trained member of the study team will be responsible for conducting an evaluation of a serious adverse event and shall report the results of such evaluation to the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the event. The NIH will be notified if there are IRB actions (such as regulatory hold) taken on the study.

Pregnancy

Pregnancy is an exclusion criterion of the study. During the study period, inquiries about whether the participant found herself pregnant at the times indiated as the Scheduled Activities table will be conducted

through telephone or emails. If a participant reports being pregnant, we will manage as participation discontinuation as above.

Data and Safety Monitoring Plan (DSMP)

We do not expect the intervention (i.e., behavior-tailoring text messages for improving hypoglycemia self-management) to significantly increase participants' health risks to higher than they would otherwise experience in their ordinary daily life. Thus, this project may qualify as a "minimal risk" study.

All research team members will complete and maintain up-to-date human subject training certifications including the Collaborative IRB Training Initiative (CITI) and Good Clinical Practice (GCP) certifications. The entire study protocol, including the DSMP, procedures to protect study participants and their privacy and confidentiality, and the patient consenting process, will be approved by the relevant institutional review board (IRB) and other regulatory and oversight entities prior to the initiation of any study procedure.

The study team will meet weekly to review study issues. We will maintain a record of protocol deviation and review it every 3 months for any unusual patterns. An official review of study data, protocol adherence, and safety, including severe adverse events, will be conducted by the PI, the study coordinator and the Data and Safety Monitor(s) after every 5 participants have completed the study. If the Data and Safety Monitor(s) have serious concerns with participant data or safety integrity, study activities will be halted and plans for addressing these issues will be developed to continue the study, or the decision to terminate the study will be made in consultation with the IRB. Additional meetings/conferences with the study team/mentors will be made as needed to discuss problems and make recommendations as an ongoing process throughout the study. No interim analysis will be conducted for this pilot/feasibility study.

Stop rule: The study will be terminated if the risk-to-benefit ratio is higher than expected.

Data Integrity: Data integrity of the study will be monitored through an electronic data system (REDCap). This electronic data system will prompt data entry or show visual signals if there are data missing and to be filled. Additional measures (e.g., number range or selection box) will be implemented to minimize data entry errors. The database will be tested before its actual use in research. Documentation integrity will also be reviewed after every 5 participants have completed the study procedure as discussed above.

Privacy and Confidentiality: Procedures to protect privacy and confidentiality, such as using unique numeric identifiers for subject identification, collecting information limited to the amount necessary for the study, and storing data in a HIPPA-compliant database (REDCap), will be implemented. The electronic data will be accessible only to investigators and study team members. The data will be available for review by the FDA or any other authorized governmental agencies.

Safety Monitoring: The occurrence of adverse events (AEs) will be sought by non-directive questioning of the patients at recruitment and study end. At the time of enrollment, participants will be provided contact information for questions or AE reporting. A review of AEs or severe adverse events (SAEs) will take place after every 5 participants have completed the study.

Adverse Event (AE) and Serious Adverse Event (SAE) Reporting: As mentioned in the Safety and Adverse Event section.

7. Statistical design

Statistical hypothesis

This pilot/feasibility study was not designed to test any hypothesis. Descriptive analysis will be conducted to summarize the participant baseline characteristics, preliminary intervention acceptability and fidelity, and trial conduct feasibility.

Sample size determination

N=20 participants completing the study was determined to demonstrate the feasibility. To ensure we meet this goal, we plan to enroll up to N=40 with n=10 into each experimental condition. However, if we reach N=20 completing the study, we may stop further recruitment.

Interim and sub-group analysis

No interim and sub-group analyses will be conducted.

8. Qualification

Yu Kuei Lin, MD (PI) is an Assistant Professor of Internal Medicine and diabetes/hypoglycemia researcher. He has successful experience in evaluating diabetes patients' hypoglycemia status with CGM glucose information through survey studies. Dr. Lin will be responsible for the oversight, design, conduct and data collection and analysis of this project.

John Piette, PhD (Co-I) is a Professor of Health Behavior and Health Education and the Director of the Michigan Center for Diabetes and Translational Research Intervention and Technology Research Core and an internationally renowned mHealth interventionist. He and his mHealth team has supported to develop and will assist to maintain the mHealth-CGM program. Dr. Piette will support the trial for feasibility testing the mHealth-CGM program.

Nicolle Marinec, MPH (Externa Collaborator) is the Associate Managing Director of the Program for Quality Improvement for Complex Chronic Conditions (QUICCC) which is led by Dr. Piette, a Co-Investigator of the study. Ms. Marinec manages the University of Michigan mHealth system staff that are part of the study team. In her role, she will provide overall management of mHealth system staff as well as support for day-to-day mHealth system research activities. Ms. Marinec is employed by the VA Ann Arbor Healthcare System.

Jenny Chen (Research Staff) is a senor program manager and a part of the University of Michigan mHealth system team. She will work with Nicolle to provide management of mHealth system staff as well as support for day-to-day mHealth system research activities.

Sean Newman and Patrick Neggie (Research staff) is an mHealth programmer and has supported to develop the current mHealth-CGM program; he will support the maintenance and refinement of the mHealth-CGM system.

Adam Martin-Schwarze (Statistician) is a biostatician of the Statistical Analysis of Biomedical and Educational Research Group unit of the U-M School of Public Health Department of Biostatistics; he will support the participant randomization and statistical analysis.

Diana Hall, MPH (Clinical research project manager) has experience in conducting qualitative studies, recruiting participants and supporting the conduct of clinical trials as study coordinator; she will serve as a study coordinator and support the administrative tasks, coordination, patient contact/recruitment and outcome measures collections in this study.

Emily Hepworth (Study coordinator) has experiences in conducting clinical studies including recruiting participants and collecting study outcomes; she will serve as a study coordinator and support the administrative tasks, coordination, patient contact/recruitment and outcome measures collection in this study.

Annika Agni (Research staff) has experience in interacting with study participants including conducting focus group interviews and qualitative data analysis, CGM data collection. Under our supervision, she will serve as a study coordinator and support the administrative tasks, coordination, patient contact/recruitment and outcome measures collections in this study.

9. Ethics and Dissemination

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers up to 5 years after the completion of the primary endpoint by contacting the PI. Data user agreement and IRB approval are needed prior to sharing the collected data.

10. Study timeline

Project timeline	Year 1				Year 2				Year 3	
	0-3	4-6	7-9	10-12	0-3	4-6	7-9	10-12	0-3	4-6
Enrollment										
Intervention										
Follow-up										
Data analysis										

11. Protocol History

Version	Date	Description of Change	Brief Rationale
V1.0	05/04/2023	- (initial version)	
V1.1	06/10/2023	Clarifying loss of follow-up definitions, study outcomes and adverse events and reporting; update study coordinator information	
V1.2	07/28/2023	Clarify randomization time, check other additional intervention for fidelity evaluation.	

12. References

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