Comparing the Effectiveness of Two Approaches to Preventing Severe Hypoglycemia

STUDY PROTOCOL

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Revision chronology:
04/29/2021 Original
06/04/2021 Version 2
10/29/2021 Version 3
07/01/2022 Version 4
11/29/2023 Version 5
11/27/2024 Version 6
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Trial Registration Data

Data Category	Information
Primary registry and trial identifying number	ClinicalTrials.gov, NCT0486387
Date of registration in primary registry	04-26-2021
Secondary identifying numbers	Not applicable
Source(s) of monetary or material support	Patient-Centered Outcomes Research Institute
Primary sponsor	Kaiser Permanente Washington Health Research Institute
Secondary sponsor(s)	Not applicable
Contact for public inquiries	James Ralston, MD, MPH; James.D.Ralston@kp.org
Contact for Scientific inquiries	James Ralston, MD, MPH; James.D.Ralston@kp.org
Public title	Comparing the Effectiveness of Two Approaches to Preventing Severe Hypoglycemia
Scientific title	Comparing the Effectiveness of Two Approaches to Preventing Severe Hypoglycemia
Countries of recruitment	United States of America
Health condition(s) or problem(s) studied	Severe hypoglycemia in persons with Type 2 diabetes
Intervention(s)	Usual care comparator: Proactive care management (nurse outreach with follow up as necessary)
	Active comparator: Proactive care management (nurse outreach with follow up as necessary) plus structured MyHC-T2D educational program, designed to improve hypoglycemia awareness and reduce severe hypoglycemia
Key inclusion and exclusion criteria	Ages eligible for study: ≥18 years; Sexes eligible for study: all
	Inclusion criteria: Age ≥18 years; diagnosed with type 2 diabetes; receiving primary care at Kaiser Permanente Washington (KPWA); enrolled at KPWAat baseline; planning to stay with a KPWA health plan for the next 6 months; at intermediate to high risk for severe hypoglycemia; and with history of severe hypoglycemia in the prior 12 months or impaired awareness of hypoglycemia.
	Exclusion criteria: Inability to give informed consent; unable to speak or read English; inability or unwillingness to attend online or telephone educational sessions, follow up calls, or to complete outcome assessments; prior diagnosis of dementia, severe psychiatric condition with psychosis, severe cognitive impairment; currently living in nursing home or hospice care, current use at baseline of Continuous Glucose Monitor, pregnant or planning to become pregnant.
Study type	Interventional
	Allocation: individually randomized; Interventional model: parallel assignment; Masking: single blind (outcome assessors will be blinded; participants will not be blinded)
	Primary purpose: Prevention
	Phase III
Date of first enrollment	01-26-2022
Target sample size	256
Recruitment status	Complete
Primary outcome(s)	Self-reported severe hypoglycemia in prior 12 months.
Secondary outcome(s) All secondary outcomes assessed 14 months after baseline. In MyHC-T2D intervention arm, 14 months post baseline corresponds to approximately 12 months after the main component of the MyHC-T2D intervention.	Measures using Continuous Glucose Monitoring (CGM)
	Hypoglycemia: % time glucose <54mg/dL, % time glucose <70 mg/dL, # of events ≥ 15 minutes glucose 54-69 mg/dL, # events ≥ 15 minutes glucose <54 mg/dL, # of events ≥ 15 minutes glucose <70 mg/dL between 12 AM and 6AM
	Hyperglycemia: % time glucose >180 mg/dL, % time glucose > 250 mg/dL
	Time in range: % time between 70 to 180 mg/dL
	Glucose Management Indicator
	Average glucose
	Glucose variation: coefficient of variation, standard deviation
	Self-reported measures: # of severe hypoglycemic events in prior 4 months: # of moderate hypoglycemia events in past 4 weeks; # of nocturnal hypoglycemic events in past 6 months; hypoglycemia unawareness; fear of hypoglycemia; diabetes knowledge; diabetes self-efficacy
	Hemoglobin A1c
	Hypoglycemia-related healthcare utilization: total number of urgent care, emergency department and inpatient visits for hypoglycemia as primary or principal diagnosis collected from the electronic health record (EHR)

Roles and Responsibilities

James Ralston, MD, MPH
Principal investigator and research physician

- Design and conduct of the study
- Preparation of protocol and revisions
- Overseeing and directing the study team and all implementation and data collection
- Leading Stakeholder Advisory Committee meetings
- Leading analyses and publication of study reports

Study Team:

Name, degree(s)	Role
Melissa Anderson, MS	Biostatistician
Ayat Bashir, MBBS, MRCP (UK)	Consultant
Kelly Ehrlich, MS	Project Manager
Laurel Hansell, MA, MPH	Qualitative Research Associate
Dena Burns-Hunt	Patient partner and Co-Investigator
Helen Hunt	Family member partner and Co-Investigator
Clarissa Hsu, PhD	Qualitative Lead and Co-Investigator
Andrew Karter, PhD	Co-Investigator
Evette Ludman, PhD	Co-Investigator
Lawrence Madziwa, MS	Programmer Analyst
Janet Ng, PhD	Implementation Lead and Co-Investigator
Emily Omura, MD	Endocrinologist
James Shaw, BSc (Hons Biochem), MB ChB, PhD, FRCP (Ed)	Consultant
Susan Shortreed, PhD	Biostatistician and Co-Investigator
Jane Speight, PhD CPsychol FBPsS	Consultant
Katherine Purwin-Tschernisch	Family member partner and Co-Investigator
Sergei Tschernisch, MFA	Patient partner and Co-Investigator

Study team responsibilities:

- Agreement of final Study Protocol *(All)*
- Adaptation of MyHC-T2D; development and oversight of interventions *(EL, JN)*
- Development of data collection instruments and protocols *(All)*
- Development and oversight of allocation procedures *(MA, SS)*
- Oversight of study recruitment, implementation of interventions and all data collection *(All)*
- Reviewing of study progress, as necessary agreeing changes to the protocol to facilitate the smooth running of the study *(All)*
- Data cleaning and analysis *(MA, SS, LM)*
- Presentation and publication of study results *(All)*
- Preparing reports for the Data and Safety Monitoring Board *(MA, SS, JR, KE)*
- Organization and conduct of Stakeholder Advisory Committee meetings *(JR, KE)*
- Developing and managing timeline, maintaining trial master files *(KE)*
- Preparing submissions to the Institutional Review Board, registering with ClinicalTrials.gov *(KE)*
- Budget administration and contractual management *(KE)*

Authors' contributions

JR and AK conceived of the study. *JR, AB, CH, DBH, HH, AK, EL, JN, JSh, JSp, KPT, and ST* led the design of the study and *KE, LH* and *LM* helped with implementation. *JR* is Lead Investigator on the contract. *MA* and *SS* provided statistical expertise in clinical trial design and *MA* is conducting the primary statistical analysis. All authors contributed to refinement of the study protocol.

Protocol Amendment History

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale.

Version	Date	Description of Change	Brief Rationale
02	06/04/2021	New exclusion: use of CGM at baseline	Direct and real time feedback of glucose levels to participants could 1) impact the study's outcome of severe hypoglycemia and 2) interact in uncertain ways in the two comparison interventions.
03	10/29/2021	Revised inclusion: removed requirement for 24 months of continuous enrollment in the health plan at baseline, now only 1 month prior enrollment at baseline	Requirement for 24 months unnecessarily restricts sample pool.
03	10/29/2021	New exclusion: pregnant or planning to become pregnant	Per manufacturer's instructions, use of the CGM (required for study data collection) not recommended for women who are pregnant or planning to become pregnant.
03	10/29/2021	Collection of HbA1c test at 14 months, if the participant has not had one within the past 3 months. Addition of $25 incentive for those who have this test.	Added to ensure a 14-month measure to compare to baseline.
03	10/29/2021	Revised randomization method: covariate constrained randomization instead of matched pair	Allows balance on a greater number of cluster characteristics than matched pair, allows an odd number of clusters.
03	10/29/2021	Self-report data collection will use telephone surveys at all timepoints, not just baseline. There will be no web-based survey collection.	Changed to keep mode consistent, avoid potential mode differences
03	10/29/2021	Revised consent procedures: addition of signed e- or paper consent for participation in the trial	Signed consent required by our Institutional Review Board
04	07/01/2022	Change from cluster to individual randomization	Changes in health care delivery system now allow individual randomization. Individual randomization yields yields more assurance of comparable balance between study arms and higher likelihood of balanced sample size by arm
04	07/01/2022	Revised inclusion: expand age from ≥50 to ≥18	Expands sample to help meet enrollment targets
04	07/01/2022	Expanded recruitment pool to include individuals with type 2 diabetes with current prescription for insulin regardless of Karter risk stratification	Expands screening to help meet enrollment targets. No change to requirement for severe hypoglycemia in past 12 months or current impaired awareness of hypoglycemia.
04	07/01/2022	Update to Study Team: replacement Dr. Avantika Waring with Dr. Emily Omura	Administrative change: Dr. Waring has left Kaiser Permanente Washington
05	11/29/2023	Addition of new secondary outcomes of glycemic control	New outcomes consistent with International Consensus on Use of Continuous Glucose Monitoring. Will be Important to assess potential

		from Continuous Glucose Monitoring (CGM) data	intervention effects on frequency of high blood sugars and variability of blood glucose levels
05	11/29/2023	Revised plan for mediation analysis	Revised mediation analysis to reflect an updated approach using the causal mediation framework instead of the Baron and Kenney framework
05	11/29/2023	Revised analysis plan for handling missing data	Lowered the threshold for attrition that would trigger use of missing data methods to account for possible selection bias (from 15% to 10%). Other editorial changes to analysis plan were made for clarity, but were not substantive.
06	11/27/2024	Clarified clustering level for analysis	Revised analysis plan to account for patient clustering in the intervention arm within group training session cohorts rather than within clinic.
06	11/27/2024	Corrected Figure 4 to remove reference to randomization by clinic and add individual randomization	Figure 4 was incorrect, not updated per change in Protocol Version 04, see below. Now corrected in the Figure as well as the text.
06	11/27/2024	Changed references to "*my hypo compass"* intervention protocol to "MyHC-TD2"	Name changed per the now executed copyright license agreement with the original developers of *my hypo compass.* The study intervention is an adaptation of the original *my hypo compass,* which was developed and tested in persons with type 1 diabetes and was adapted in this study for use by persons with type 2 diabetes.
07	04/14/2025	Changed references to "MyHC-TD2*"* intervention protocol to "MyHC-T2D" (reverse order of last two characters)	The reference ending "…TD2" was incorrect. The name of the adapted intervention should have been MyHC-T2D.

Table of Contents

Contents

1. Introduction

1a. Background and rationale

Severe hypoglycemia is the most feared complication of glucose-lowering medications used to treat people with diabetes. Severe hypoglycemia, defined as a blood sugar low enough to require assistance, is associated with accidents,[1] falls,[2,3] motor vehicle accidents,[1] poor health-related quality of life,[4,5] emotional and interpersonal challenges,[6] chronic and acute cardiovascular disease,[7-12] dementia,[13-15] and death.[16-19] Older adults with type 2 diabetes on glucose-lowering medications are particularly vulnerable to the complications of severe hypoglycemia.[20] Severe hypoglycemia is also linked to hospitalization: of all emergency hospitalizations of older Americans for adverse drug events, an estimated 14% implicate insulin and 11% implicate oral hypoglycemic agents.[21] One in four diabetes-related hospital admissions is due to hypoglycemia.[22] Each year, about 11% of patients with type 2 diabetes self-report severe hypoglycemia.[23]

Preventing severe hypoglycemia requires patients to recognize when hypoglycemia is imminent and act to prevent it. Many patients who are at risk for severe hypoglycemia, though, have lost the hormonal response and associated symptoms that would usually alert them to low blood sugar. Impaired awareness of hypoglycemia is acquired over time through repeated exposure to hypoglycemia. Severe hypoglycemia is 17 times more common in individuals with impaired awareness of hypoglycemia.[24] Current type 2 diabetes self-management training does not address impaired awareness of hypoglycemia and provides limited coaching on when and how to avoid severe hypoglycemia. Recently developed interventions can restore hypoglycemia awareness, enabling immediate action to reverse hypoglycemia and reduce severe hypoglycemia in patients with type 1 diabetes.[25-29] We do not know if these interventions work in patients with type 2 diabetes.

The goal of this study is to compare the effectiveness of two evidence-based approaches for preventing severe hypoglycemia among patients with type 2 diabetes who are at high risk for severe hypoglycemia, defined as experiencing one or more severe hypoglycemic events in prior 12 months or having impaired awareness of hypoglycemia.

1b. Objectives:

1b.1 Primary objective

To determine if proactive care management plus MyHC-T2D is superior to proactive care management alone at preventing self-reported severe hypoglycemia in adults with type 2 diabetes at high risk for severe hypoglycemia. The primary outcome will be assessed through self-report via study survey at 14-months post baseline.

1b.2 Secondary objectives

1b.2.a Key secondary objectives

Key secondary outcomes will be assessed at 14-months post baseline through self-report in study survey (SR), continuous glucose monitors (CGMs; study participants will wear CGMs for 10 days), and electronic health records (EHRs).

1. To determine if proactive care management plus MyHC-T2D is superior to proactive care management alone in adults at high risk for severe hypoglycemia for the following:
    - Reducing percentage time with biochemical hypoglycemia (CGM assessed)
    - Reducing biochemical hypoglycemic events (CGM assessed)
    - Reducing the frequency of high blood sugars and reducing variability of blood glucose levels (CGM assessed)
    - Reducing number of severe hypoglycemic events in prior 4 months (SR assessed)
    - Reducing hypoglycemia unawareness (SR assessed)
    - Reducing number of self-reported moderate hypoglycemic events (SR assessed)

- Reducing fear of hypoglycemia (SR assessed)
- Reducing frequency of nocturnal hypoglycemia (SR assessed)
- Improving diabetes and hypoglycemia knowledge (SR assessed)
- Improving diabetes self-efficacy (SR assessed)
- Reducing hypoglycemia related healthcare utilization, including urgent care, Emergency Department and inpatient visits related to hypoglycemia (EHR assessed)

2. To assess differences in glycemic control, indicated by Hemoglobin A1c, between study participants in the proactive care management plus MyHC-T2D group and the proactive care management alone group.

1b.2.b Other secondary Objectives

Conduct a mixed methods process evaluation to evaluate the fidelity of implementation of intervention components, and clarify the causal pathway if intervention effects are found.

1c. Trial design

This study is an individually randomized controlled trial (RCT) comparing proactive care management[30,31] to proactive care management plus MyHC-T2D.[25,32]

2. Methods: Participants, interventions and outcomes

2a. Study setting

The study will be at Kaiser Permanente Washington (KPWA), an integrated care and coverage system with 34 owned-and-operated clinics for nearly 700,000 members. We will recruit and retain a representative population in the study in two steps from KPWA clinics.

2b. Eligibility criteria

Inclusion criteria

Participants eligible for the trial must meet all the following inclusion criteria at baseline

- Age ≥18 years;
- Diagnosed with type 2 diabetes;
- Receiving primary care at KPWA;
- Enrollment at KPWA at baseline;
- Planning to stay with a KPWA health plan for the next 6 months;
- Current prescription for insulin or at intermediate to high risk for a severe hypoglycemia episode using the hypoglycemia risk-stratification tool developed by Karter et al and validated in the KPWA patient population;[33,34] and
- Have history of a severe hypoglycemia episode in the prior 12 months or impaired awareness of hypoglycemia based on Gold score.[35,36]

Exclusion criteria

Any of the following criteria at baseline exclude participation in the study:

- Unable to give informed consent;
- Unable to speak or read English;
- Unable or unwilling to attend online or telephone educational sessions, follow up calls, or to complete outcome assessments;
- Prior diagnosis of dementia, severe psychiatric conditions with psychosis, severe cognitive impairment;
- Currently living in nursing home or under hospice care;
- Current use at baseline of Continuous Glucose Monitor;
- Pregnant or planning to become pregnant.

2c. Interventions

Randomization will be at the individual level. Participants will be assigned to one of the two following interventions.

2c.1. Proactive care management

Population care management nurses trained in diabetes care will deliver evidence-based care to prevent hypoglycemia based on ADA guidelines.[30,31] They will use existing standard training, tools and workflows already in use at KPWA. The study will provide a continuing nurse education training covering these materials for nurses delivering proactive care management in both study arms prior to enrolling the first study participant. Care for this group will be similar to care usually received from KPWA nurses after a recent severe hypoglycemic event. Current practices include the following: for participants with overly aggressive glucose targets or impaired awareness of hypoglycemia, nurses work with the participant's primary care provider to personalize a care plan that may include adjusting glucose targets, de-intensifying hypoglycemic medications, enhancing self-monitoring of blood glucose, providing glucagon kits and training, or referring for consideration of Continuous Glucose Monitoring (CGM).[37,38] For participants on glucose-lowering agents who need help with self-monitoring, nurses provide basic coaching on hypoglycemia signs, symptoms, and actions such as how to safely raise blood sugar and refer to dieticians as needed.[31,39] Nurses also ensure standard primary care at KPWA including regular assessment and follow-up for mental health and social needs that may contribute severe hypoglycemia risk.[40] Outreach for care will include one standardized outreach call followed by additional calls or other follow up as indicated to meet current standard of care.

2c.2 Proactive care management plus MyHC-TD2 education

Participants in this group will receive the same proactive care management as described above, plus MyHC-T2D, an adapted version of the *my hypo compass* protocol which was developed and tested in patients with type 1 diabetes. The MyHC-T2D curriculum uses standardized Facilitator and Participant handbooks and behavioral intervention techniques to facilitate discussions on strict avoidance of hypoglycemia using four key principles around compass points: 1) *Never* delay appropriate treatment of hypoglycemia; 2) *Establish* times of *Extra* risk; recognize hypoglycemia by 3) *Subtle* symptoms; and 4) being *Watchful* to detect and prevent hypoglycemia, particularly asymptomatic nocturnal hypoglycemia. The MyHC-T2D protocol for this study will consist of the following activities:

- *Baseline outreach and engagement in structured educational sessions*: KPWA nurses specializing in diabetes will call participants and coordinate care for severe hypoglycemia risk factors as in the proactive care group. Nurses will elicit and address barriers for attending MyHC-T2D training.[41-43] Participants will be mailed the MyHC-T2D Glucose/Hypo diary and Participant Handbook in preparation for structured educational sessions. They will have the same nurse care manager throughout the intervention.
- *Structured Educational Session 1*: Two diabetes nurse educators trained on the MyHC-T2D protocol will lead online virtual group sessions (**Figure 1**). The sessions will include 8 participants and will be conducted based on the Facilitator Guide and Participant Handbooks (**Appendix B**). Educational session #1 will be approximately 3 hours. Nurse educators will encourage participants to reflect on personal hypoglycemia events using the Glucose/Hypo diary. The

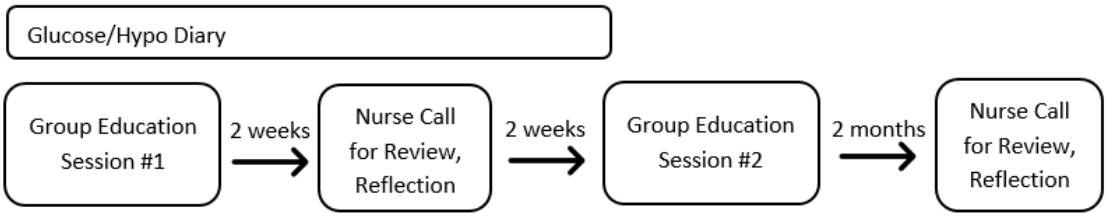

Figure 1: MyHC-T2D Education Activities

session will promote patient understanding and self-management strategies by group discussion of the MyHC-T2D compass points. Diaries will be completed over the first 4 weeks of the study. Daily 4-point and weekly 8-point blood glucose profiles will be done to determine times of increased hypoglycemia risk including at night and allow reflection on possible prevention strategies.

- *Telephone Review:* Approximately 2 weeks after the first educational session, nurse care managers will call participants for a 10- to 15-minute review. Nurses will discuss progress and review the Glucose/Hypo diary. They will encourage reflection on any hypoglycemia events and self-management strategies.
- *Structured Educational Session 2*: A diabetes nurse educator will lead an online virtual follow-up session with participants in their original groups. This 60-minute session, led by the same diabetes nurse educator as the first session, will facilitate discussion on progress with reference to the 4 points of hypo compass. Participants will be encouraged to reflect on hypoglycemia symptoms experienced during each event including subtle symptoms with review and discussion of the treatments implemented.
- *Telephone Booster*: Approximately 3 months after intervention start or 2 months after the second educational session, nurse care managers will call participants for a 10- to 15-minute review and booster call. Nurses and participants will reflect on any hypoglycemia events and review self-management strategies.

2c.3. Training and monitoring intervention fidelity.

We will ensure maximum generalizability and relevance to providers and healthcare systems by applying the Treatment Fidelity Workgroup of the NIH Behavioral Change Consortium framework to ensure interventions are delivered as intended.[44]

Training

- Proactive care management: All intervention nurses will use existing standard training, tools and workflows which are already in use at KPWA to provide the proactive care management part of both interventions. All KPWA nurses are trained in these protocols. The study will provide a continuing nurse education training to refresh nurses in these standard protocols for all nurses prior to enrolling the first study participant
- MyHC-T2D protocol: Study intervention leads will train the diabetes nurse educators in delivery of the MyHC-T2D protocol with input and assistance from the program originators. The diabetes nurse educators will conduct all online virtual educational sessions. These will be recorded for fidelity monitoring, and for qualitative assessment per Aim 2. The study intervention leads and the diabetes nurse educators will train the MyHC-T2D intervention nurses for telephone review and booster follow up calls.

Fidelity

We will maintain and assess fidelity through four proactive strategies:

- Use of standardized written nurse and participant materials. Study intervention leads and diabetes nurse educators and population care nurses will meet regularly to ensure protocol clarity and treatment integrity and fidelity.
- Observation of nurses delivering the proactive care management and MyHC-T2D activities by a supervising RN for the first two intervention months.
- Use of fidelity assurance checklists for protocol integrity and skills to be covered in each educational session. After each session, the nurse will check each point that was covered. If a point was not covered, the nurse will plan for follow-up. This checklist will also permit calculation of the percentage of points covered. An independent Fidelity Monitoring Research Associate will review completed checklists using a standard protocol to document adherence and give formative feedback.

- Monitoring for potential drift through audio recording sessions. After 2 months of observation, the Fidelity Monitoring Research Associate will randomly review 10% of sessions, coding for intervention adherence and returning results to be reviewed in weekly supervision meetings. If nurses "drift" from protocols, we will add training and supervision and monitor until fidelity is established.

2d. Outcomes

2d.1 Primary outcome measure

We will measure number of self-reported severe hypoglycemia episodes in the past 12 months at baseline and 14 months after the baseline. We assess the primary outcome 14-months after baseline, to allow 2 months for baseline collection of CGM and intervention activities prior to the 12-month outcome window (**Figure 2**). This timing is consistent with prior studies showing that symptoms of hypoglycemia return after 3 to 4 weeks of avoiding hypoglycemia[45] and early impacts of the MyHC-T2D intervention on the percent time with glucose less < 54 mg/dL in patients with type 1 diabetes. [25]

- Planned primary outcome: Self-report of any severe hypoglycemia episode (yes/no) in the prior 12 months assessed 14 months after baseline using a validated question from the Diabetes Care Profile: "In the past year, how many times have you had a severe low blood sugar reaction such as passing out or needing help to treat the reaction?"[46,47].
- Alternative primary outcome: Count of the number of self-report severe hypoglycemia episodes in the prior 12 months assessed 14 months after baseline using the validated question from the Diabetes Care Profile. We will evaluate the distribution of number of severe hypoglycemia events in the prior 12 months assessed on all participants at the baseline survey. If more than 60% of respondents report having had 2 or more severe hypoglycemia events in the prior 12 months, we will change our primary outcome to be a count of the number of severe hypoglycemia events in the prior 12 months.

2d.2 Secondary outcome measures

- Outcomes measured by Continuous Glucose Monitor, over 10 days, at baseline and 14-month assessment:
  - Percent time with biochemical hypoglycemia (<54 mg/dL);
  - Number of Level 2 biochemical hypoglycemic events (15 or more minutes <54 mg/dL).
  - Percent time biochemical hypoglycemia (< 70 mg/dL)
  - Number of level 1 hypoglycemic eventss (≥ 15 minutes at 54 - 69 mg/dL)
  - Number of nocturnal hypoglycemic events (≥ 15 minutes < 70 mg/dL between midnight and 6 am)
  - Percent time 70 to 180 mg/dL
  - Percent time above 180 mg/dL
  - Percent time above 250 mg/dL
  - Average blood glucoses, mg/dL
  - Standard deviation of glucose
  - Coefficient of variation for glucose (%CV)
  - Glucose management indicator
- Outcomes measured by self-report survey at baseline, 6, 10, and 14 months:
  - Number of severe hypoglycemic events in prior 4 months;
  - Hypoglycemia unawareness measured by the single item Gold survey;[35,36]
  - Number of symptomatic[48] hypoglycemic events in the prior 4 weeks;[46]
  - Fear of hypoglycemia using the Hypoglycemia Fear Survey-II;[49]
  - Numberof nocturnal hypoglycemia events (defined as "during sleep") during past 6 months;[50]
  - Diabetes and hypoglycemia knowledge with the revised Diabetes Knowledge Test;[51]
  - Diabetes self-efficacy using the 8-item Diabetes Self-Efficacy scale.[52]

- Outcomes defined based on data collected from the EHR:
  - Hemoglobin A1c (HbA1c). The most recent HbA1c measures in the 12 months before baseline will be used for the baseline measure. Most recent measures within the past 3 months will be collected at 14 months. If the participant has not had an HbA1c within the past 3 months at 14 months, they will be asked to have one for the study.
  - Hypoglycemia-related healthcare utilization: total number urgent care, emergency department and inpatient visits for hypoglycemia as primary or principal diagnosis.

Figure 2 shows the relationship between outcome measures and study activities. Due to cost and participant burden, we will collect CGM measures only at baseline and at 14 months. We will measure all secondary outcomes including potential mediators of the intervention, at 6, 10 and 14 months after baseline assessment to identify potential early vs. later effects of the intervention.[32]

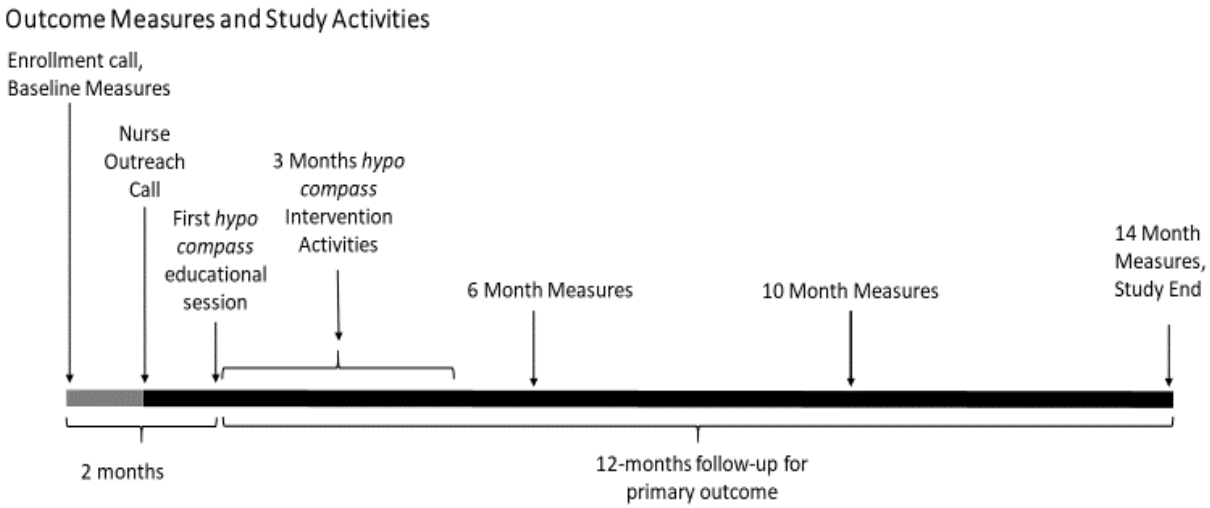

Figure 2: Outcome measures and study activities

2e. Participant timeline

Figure 3 shows the study flow diagram and **Figure 4** the schedule of enrollment, interventions and assessments. Participants in the proactive care management group will receive one standardized proactive outreach call from KPWA nursing staff, with follow up as indicated by the participant's needs. Participants in the proactive care management + MyHC-T2D group will receive the same standardized proactive outreach call in addition the standardized MyHC-T2D educational intervention, delivered over approximately three months. As described above, self-report data will be collected at baseline, 6- ,10- and 14 months, and CGM and EHR data at baseline and 14 months. Duration of participation for an individual participant will be 14 months from baseline data collection.

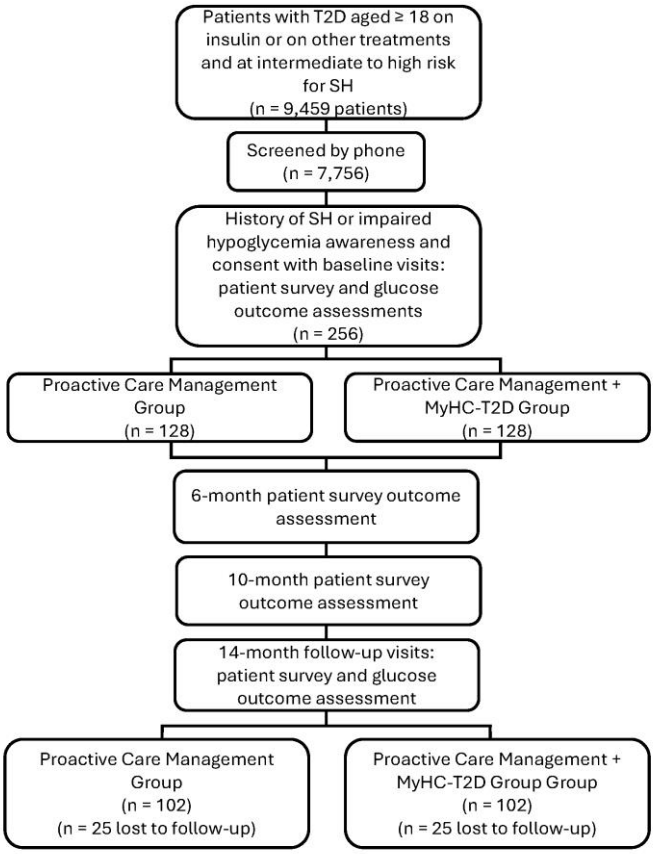

Figure 3: Study Flow

Figure 4. Schedule of enrollment, interventions, and assessments

		STUDY PERIOD				
	Allocation	**Enrollment**		**Post-Enrollment**		**Close-out**
TIMEPOINT	***Pre-enrollment***	***Pre-enrollment***	***Baseline***	***6 month***	***10 months***	***14 months***
ENROLLMENT:						
Identification		X				
Telephone screen			X			
Informed Consent			X			
Individual randomization			X			
INTERVENTIONS:						
Proactive care management			←	→		
Proactive care management + MyHC-T2D			←	—	— →	
ASSESSMENTS:						
Primary Outcome: Self-report severe hypoglycemia events			X	X	X	X
Secondary outcomes:						X
Self report measures			X	X	X	X
CGM Measures			X			X
EHR measures			X			X
Process Measures						X
Qualitative Assessments		X	X	X	X	X

2f. Sample size

We estimate 256 patients (128 randomized to proactive care management, and 128 randomized to MyHC-T2D) will consent and complete the baseline survey. To account for loss to follow-up, we assume an 80% response rate for the primary outcome measured at 14-months, for an analytic sample size of 204 (102 per group). Power calculations for comparing two independent proportions and assumed a 0.05 type I error rate. Assuming 60% of patients in the proactive care management group will self-report having had a severe hypoglycemia event in 12-month look back (yes/no), we have 90% power to detect a 22.6% absolute difference between groups (i.e. 37.4% severe hypoglycemia rate in MyHC-T2D arm) for the primary outcome. We have 80% power to detect an absolute difference of 19.7% between groups. Our study has power to detect a meaningful difference (30% or more reduction in frequency of self-reported severe hypoglycemia events).[54] Other studies including for the original *my hypo compass* have similar or larger effects on severe hypoglycemia reductions.[25-29] We also have 80% power to detect a 1.4% difference and 90% power to detect a 1.6% difference between groups in the secondary outcome of the percent time with biochemical hypoglycemia (<54 mg/dL); this difference is consistent with the effect seen with the original *my hypo compass*.[25,32]

2g. Recruitment

We will recruit the study population in two steps.
Step 1, Automated risk stratification: We will identify a cohort of adults (≥18 years) with T2D receiving primary care at KPWA. We will identify all individuals with either a current prescription for insulin or who have intermediate-to-high risk for a SH event based on our hypoglycemia risk-stratification tool.

Step 2, Phone screening for verbal consent and to identify patients at highest SH risk: We will mail eligible participants an invitation with study brochure and notification that staff will call them about the study. KPWHRI Survey Research Program (SRP) members will then call the potential participant to explain the study, assess eligibility and interest, and conduct informed verbal consent with those who are eligible and interested. We expect 1001 eligible. Based on a similar recruitment[55] and participation in other diabetes education trials, we anticipate at least 25% will consent and complete baseline data collection.[56]

To retain participants and minimize data loss, we will provide $100 incentive for completing data collection at baseline and 14 months ($30 for the survey and $70 for CGM at each time point) and $30 for self-report-only measures at 6 and 10 months. Participants who agree to have an HbA1c test for the study at months will receive an additional $25.

3. Methods: Assignment of interventions

3a. Allocation

After identifying potentially eligible patients based on EHR data, and verify eligibility, documenting verbal consent, collecting baseline data by phone, and receiving written consent, we will randomize study participants to one of our two intervention arms using a 1:1 allocation ratio. Randomization will occur by selecting sequential assignments from randomization sequences generated by the study biostatistician, and stored on a computer inaccessible to study staff. The randomization list will use permuted blocks of randomized size 4 or 8. Randomization will be stratified by age (18-74 versus 75+ years) and risk score for severe hypoglycemia (moderate versus high risk), to ensure balance of these important risk factors of SH events across intervention arms. Individuals with low risk but using insulin will be randomized in the moderate risk strata. Randomization assignment will be concealed from the study staff verifying eligibility and will only be revealed after baseline data has been collected, and the next sequential randomization assignment has been requested. Outcomes will be measured and analyzed at the participant level.

3b. Blinding (masking)

Blinding or masking will be maintained for research staff collecting outcomes, including those collecting self-report and CGM data. However, participants, nurses, and providers engaged in the interventions cannot reasonably be masked to the study groups, nor can study staff conducting fidelity monitoring or those collecting qualitative data.

The study programmer and biostatisticians will have access to unblinded data to conduct data summaries by intervention group as necessary for reporting to the Data and Safety Monitoring Board (DSMB). The Principal Investigator and other study investigators will remain blinded until all study data for the relevant analyses is collected.

4. Methods: Data collection, management, and analysis

4a. Data collection methods

Study data will be collected using self-report surveys at baseline, 6, 10- and 14-months; biochemical measures of percent time with hypoglycemia and number of biochemical hypoglycemic events using CGM at baseline and 14 months; and data extracted from the EHR for Hemoglobin A1c and hypoglycemia-related healthcare utilization at baseline and 14 months. The outcomes are described in section 2d, above.

4a.1 Self-report measures:

All self-report instruments are included in **Appendix C**. Survey questions will be administered at baseline and all follow up time points (6, 10 and 14 months) by telephone by trained KPWHRI survey research program (SRP) staff. Telephone data collection will be performed using Sawtooth Ci3 and WinCATI computer-assisted telephone interviewing (CATI) software. SRP Interviewers are trained in standardized survey interviewing techniques, use of the CATI system, and will be trained in project-specific procedures including item-by-item specifications for each questionnaire. Interviewers' phone performance, productivity, and response rates are routinely monitored; corrective or remedial training is provided if necessary. Interview quality is continuously assessed using silent monitors installed on all telephones; completed interviews are edited and coded within 48 hours, and interviewer feedback occurs on a regular basis. SRP Interviewers are certified in NIH Human Subjects Protections.

4a.2. CGM data:

CGM data will be collected at baseline and 14 months using the Dexcom 6G Pro CGM integrated sensors and transmitters in blinded mode. We chose Dexcom sensors because of validity, reliability, ability to record glucose measurements blinded to the participant; and the ability to store up to 10 days of data. At both timepoints we will collect 10 days of CGM readings. The readings will be blinded at the time of data collection but shared with the participant at the end of the study.

Baseline CGM data will be collected after collection of baseline self-report data but before beginning any intervention activities. CGM data at 14-months will be collected at the same time as outreach for 14-month follow up self-report. In both cases the process will be the same:

The study nurse or medical assistant (MA) will telephone the participant and schedule a CGM virtual visit. S/he will then mail the sensor-transmitter unit (programmed to keep glucose readings blinded from the participant) and instructions to the participant, along with postage-paid packaging to return at the end of the 10-day recording period. At the virtual visit, the nurse or MA will walk the participant through placing the device, will answer any questions and will provide a telephone number that the participant can call for questions or issues that may come up. The participant will then wear the device for 10 days with readings stored on the unit. The study nurse or MA will make one follow up call near the end of the 10 days, to check in, answer questions and confirm that the participant will remove and mail back the single use sensor-transmitter on the planned date. At the end of the recording period the participant will remove and mail back the device using the provided mailing materials. The data will then be read or downloaded from the sensor-transmitter using the DexCom 6G Pro reader/receiver.

4a.3 EHR data:

The study programmer will extract data from the EHR to assess study eligibility for recruitment and collect outcome measures including HbA1c and hypoglycemia related health care utilization, including emergency department and urgent care visits and hospitalizations. If participants are asked to have an HbA1c at 14 months, the results will be collected from the medical record in the same way as other HbA1cs.

4a.4 Data collection incentives:

Participants will be mailed $100 for completion of baseline and 14-month follow up study measures ($30 for the survey and $70 for CGM at each time point). They will be mailed $30 for completion of self-report-only measures at 6- and 10-month follow up. Participants who agree to have an HbA1c test for the study at months will be mailed an additional $25.

4a.5 Procedures for participants not completing study activities, or withdrawing consent

Participation in this study is voluntary. Even after consent, participants may choose to not do specific study components such as CGM data collection. They may decline survey questions or choose not to participate in intervention activities. Participants will not be considered withdrawn from the study unless they state clearly that they wish to withdraw. For participants who do not complete specific activities but do not withdraw consent, we will continue to use what information they have provided and will extract and use EHR data as described in the consent process. If participants withdraw their consent, we may still use information collected before withdrawal, but will not collect any additional information and will destroy any record of their name or other information that may identify them. This will be clearly stated in the consent materials and reviewed as part of the informed consent process.

4a.6. Process evaluation

In addition to collection of data for primary and secondary outcomes described above, we will conduct a process evaluation to assess whether the interventions were implemented as planned and to test and refine the hypothesized causal pathways (**Figure 5)**. These results will be essential to ensure future implementations of severe hypoglycemia prevention are centered on patient needs and are feasible and acceptable for healthcare providers and systems.

We will use qualitative and quantitative methods for assessing the *fidelity, dose and mechanism* of the intervention.

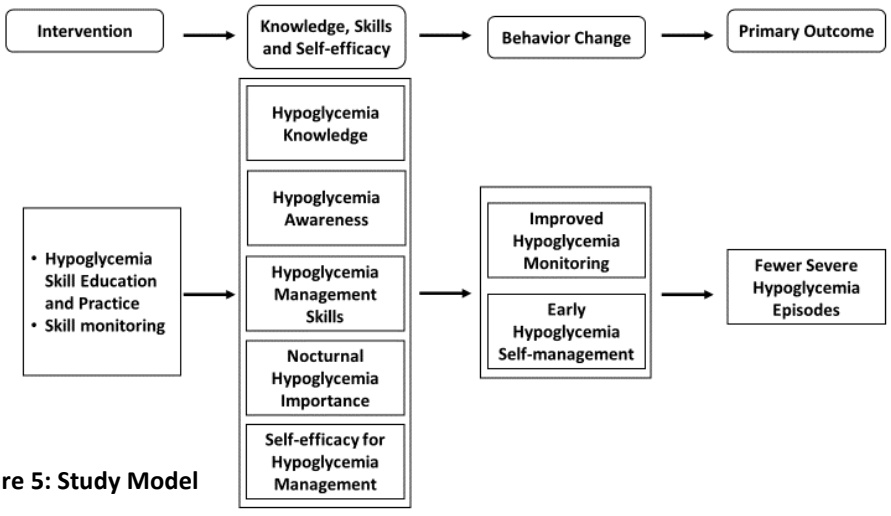

Figure 5: Study Model

*Qualitative assessments***:** To assess delivery *fidelity* and *dose* to clusters and individuals, we will observe nurse care managers and diabetes nurse educators working with participants and interview them after interventions.[57] For observations of nurse care managers, we will develop a tool to capture information on protocol integrity for outreach calls to patients in both comparator groups. We will do observations in the last 2 months of intervention implementation to separate evaluation from earlier fidelity monitoring and feedback training to nurses conducted by the intervention team. We will observe nurses on initial proactive care management outreach calls in each comparator group. We will observe nurses on the two follow-up educational calls in the MyHC-T2D group. We will also observe selected MyHC-T2D group educational sessions facilitated by the diabetes nurse educators.

After the intervention and collection of outcomes, we will conduct interviews with participants, diabetes nurse educators and clinic nurse care managers. We will ask participants to reflect on their experiences with the

intervention and the impact of the intervention on care including unintended consequences. We will interview participants in each comparator group, diabetes nurse educators delivering the in-person education sessions and nurse care managers in each comparator group. We will purposively sample participants to ensure robust representation based on race/ethnicity, gender, and educational attainment. For evaluating intervention *context*, we will also interview the healthcare system's stakeholders, examples of which may include directors of nursing, endocrinology, primary care, quality and health plan representatives. We will analyze interview and observational data using a template analysis approach based on a code manual from our conceptual model and emergent themes. Atlas.ti will be used to organize and manage the data. model and the intervention.[58] [59]

Quantitative data for process evaluation will include process data such as number and type of participant contacts, data collected for fidelity monitoring, and outcome data such as number of self-reported severe hypoglycemia episodes. **Table 1** describes how these data will be used, with results from the qualitative assessments. We will collect quantitative data as follows:

- Fidelity checklists filled out by study nurses
- Participant contacts collected from EHR data and
- Variables for mediation analysis collected from combination of self-report and EHR data.

Integrating results: We will do a concurrent triangulation mixed methods design, where qualitative and quantitative data will be collected at the same time and used to validate and/or add detail and depth to the data from two data collection approaches.[57]

Table 1: Process Assessment: Domains, Question, Methods [60]

Evaluation Domain	Research Questions	Research Methods
Fidelity	Is the intended intervention delivered at the cluster level? individual level?	Qualitative analysis of nurse and patient interviews, nurse observations -Quantitative analysis of fidelity checklists and participant contacts
Dose	Is the intended amount of the intervention delivered at the cluster level? Individual level?	-Qualitative analysis of nurse and patient interviews, nurse observations -Quantitative analysis of fidelity - checklists and participant contacts
Mechanism	Why and how did the intervention work?	-Quantitative mediation analysis of causal pathway -Qualitative analysis of patient and nurse interviews
Reach	Did the intended populations receive the intervention?	Quantitative descriptive analysis of clusters and individuals using administrative and EHR data
Context	What clinic, institutional, state and national factors may moderate intervention?	-Qualitative analysis of interviews with stakeholders

4b. Data management

Data for this study will be captured from telephone surveys, capture by CGM monitoring devices (baseline and 14 months) and extraction from EHR databases. If a participant is asked to have an HbA1c test at 14 months for the study, this will be done by the healthcare system, paid for by the study, and results collected from the medical record.

- **Telephone surveys** will be administered by the KPWHRI SRP. Staff will be trained and quality monitored as described in Section 2.c.1, Data Collection Methods, Self-Report data, above. Instruments will be programmed with skip patterns and range checks. KPWHRI, and specifically SRP, maintain a HIPAA-compliant environment. Data in DatStat Illume, which will be used for survey data, is encrypted at all times. Other protections include real-time scanning for viruses and malware, and scanning and blacklisting of suspicious incoming email and web traffic. Multiple real-time systems monitor internal activity including movement of data between internal systems. Data collected through DatStat Illume are stored on Microsoft SQL Server systems located behind the Kaiser Permanente firewall. Access to both the DatStat web server and the database servers is restricted to IT Operations staff. Access to data collected through DatStat is limited to Kaiser Permanente Washington employees with a need for access.
- **Data collected via CGM:** Study staff will download data from each participant's CGM sensor transmitter unit using the Dexcom receiver. The receiver will transmit this data to the Dexcom CLARITY server from which data and reports will be retrieved. Data for individuals will be identified only by a device ID, which will be linked to study ID using crosswalks kept only at KPWHRI.

- **EHR data** will be extracted by the study programmer from automated administrative and EHR data sources, including the KPWHRI Data Warehouse, a research-centric repository of datasets maintained by the Research Institute. Data are stored in Teradata, SQL Server, and SAS format and cover enrollment, demographics, diagnoses and procedures, vital signs, pharmacy, lab tests, costs. A rich collection of powerful SAS macros can be used in conjunction with the KPWHRI data. KPWHRI data warehouse content and usage are documented by a wiki-based system authored by the data warehouse's architects, managers, and users. Access and security for electronic data sources are described below in Section 3. Ethics and Dissemination, Confidentiality.

4c. Statistical methods

Comparative effectiveness analyses will apply intent-to-treat principles, with study participants analyzed based on randomization group, regardless of intervention received. To assess comparability across study groups, we will summarize demographic characteristics and responses to baseline surveys in the two comparison groups. The preliminary analysis plan defines the primary outcome as a binary indicator for whether or not (yes/no) the participant self-reported having had a severe hypoglycemia event in the prior 12-months, assessed 14 months after baseline. We will estimate relative risk of severe hypoglycemia in the MyHC-T2D group vs. proactive care management group by fitting a modified Poisson regression model with the binary self-report measure as the dependent variable and randomization group as the independent variable. Models will adjust for age, sex, risk score, and the number of self-reported severe hypoglycemic events in the 12 months prior to baseline. Modelswill be fit using generalized estimating equations (GEE) and robust variance estimation to account for correlation due to patient clustering in the intervention arm within group training session cohorts, and the misspecified mean-variance relationship in using Poisson regression for a binary outcome.

Prior to conducting analysis of 14-month outcomes, we will look at the baseline distribution of the self-reported number of severe hypoglycemic events in the prior 12-months collected at baseline. If more than 60% of enrolled patients report 2 or more events, we will revise the primary outcome to be defined as the self-reported *number* of severe hypoglycemic events in the past 12-months, measured at 14-months post baseline (a count rather than a binary outcome and fit a Poisson regression model to estimate the rate ratio for severe hypoglycemia events for the MyHC-T2D group relative to the care management group. We will assess model fit, and consider zero-inflated models as an alternative, if the number of participants reporting zero events violates distributional assumptions of the Poisson model. If primary analyses use the binary outcome measure (i.e. fewer than 60% of patients report 2 or more events in the 12-months prior to baseline), but 40% or more of respondents report 2 or more events at 14-months, we will do a secondary analysis with the count variable as the outcome.

Generalized linear regression models estimated with GEE and robust sandwich errors will also be used to estimate intervention effects on secondary outcomes, with link function and error distribution appropriate for each outcome. For secondary outcomes measured at multiple follow-up time points (6-, 10- and 14-months post-baseline), we will fit a single regression model that includes outcome measures from all follow-up time points. Models will include indicator variables for time, intervention group, and interaction terms between these variables, to estimate intervention effects at each time point. Models will adjust for age, sex, risk score and the baseline measure of the outcome. For hypoglycemia-related health care utilization (urgent care and emergency department visits, hospital admits), we will follow a similar analytic plan as the primary outcome, including the process to determine whether to model these outcomes as binary or count variables.

Standards for Preventing and Handling Missing Data. Outreach with repeated calls will maximize response rates of follow-up phone surveys. Response rates and data collection will be monitored and if attrition is greater than 10%, statistical methods will account for potential selection bias. We will compare baseline characteristics of responders and non-responders and consider multiple imputation or inverse probability weighting (IPW) to account for potential bias due to missing data.

Addressing HTE standards.
Exploratory analyses will assess whether treatment effects vary by patient characteristics including age (under 75 years vs. 75 years and older), sex, race/ethnicity, comorbidities, insulin use and/or sulfonylurea use, baseline IAH presence, and baseline SH history. We will include interaction terms between randomization group and these characteristics in the primary and secondary outcome models to estimate comparative effectiveness by subgroup.

We provide a brief description of the power we estimate we will have for some subgroup analyses. For those with minority racial and ethnic backgrounds (approximately 30% of participants), we will have 90% power to detect a 39% difference and 80% power to detect a 35% difference in the rate of severe hypoglycemia between comparators for this subgroup. For females (approximately 50% of participants) and those the 65 years of age or older (approximately 50% of participants), we will have 90% power to detect a 31% difference in the rate of severe hypoglycemia and 80% power to detect 27% difference. All of these effect sizes are smaller than those in the MyHC-T2D study in patients with type 1 diabetes.[34]

Process Evaluation: We will use descriptive analysis to assess intervention recruitment, reach and delivery. If significant differences ($p<0.05$) between intervention groups are found for the primary outcome, we will perform mediation analysis to test the hypothesis that the possible causal pathway for reducing the occurrence of severe hypoglycemia is through improvements in hypoglycemia knowledge, hypoglycemia awareness, self-efficacy of hypoglycemia management, blood glucose testing, and hypoglycemic medication adjustment and other factors in causal pathway in **Figure 2**. Mediation analysis will use a regression-based approach within the causal mediation framework,[53] separating the total intervention effect into a natural indirect effect (effect occurring through the mediator), and a natural direct effect (effect through all other pathways). To estimate these effects, we will use either a log-linear or Poisson model for the outcome model (depending on whether the primary outcome is defined as a binary or count variable), and linear regression for the mediator model. The effect of each mediator will be estimated in separate models.

4d. Trial monitoring

4d.1 Data monitoring

This study will have a Data Safety Monitoring Board (DSMB) to ensure safety of research participants. The DSMB will include an external researcher with prior DSMB experience (the chair), and two clinicians with expertise in type 2 diabetes and in the treatment and care for patients with severe hypoglycemia and impaired hypoglycemia awareness. The DSMB will meet once in the first 6 months after study funding and prior to patient enrollment to review study protocols and plans for study reports (enrollment, completion, and adverse event-reporting tables by study group) and recommend changes. The study team will track participant-reported serious adverse events whether related or not to study participation. The team will provide ongoing reports to the DSMB and the Institutional Review Board. The DSMB will meet twice per year, in person or by phone, as directed by the committee. The study Principal Investigator, biostatisticians, and project manager will attend all open portions of DSMB meetings.

The DSMB will receive ongoing reports to ensure data validity and integrity, including recruitment reports, participant characteristics by study arm to ensure adequacy of randomization and balanced enrollment, participant completion of study visits, and completeness of study data collection. The DSMB may also choose to see outcome data, with this data blinded except to the study biostatisticians. If the DSMB deems it necessary to unblind themselves to interim trial reporting this may occur, similarity the DSMB may decide to unblind the study Principal Investigator if patient safety is a concern.

We do not propose interim analyses or stopping guidelines. The assessment of the primary outcome requires 14 months of follow-up from baseline; the study enrollment period is only 8 months long, therefore enrollment (and likely study interventions) will be complete for all participants before primary outcome data is available on

any participants. We cannot feasibly stop the trial for futility or harms seen on the primary outcome before the end of enrollment.

4d.2 Harms

Adverse events: For this study an adverse event will be defined using the definition from 21 CFR 312.32 (a) as any *untoward medical occurrence in a participant without regard to the possibility of a causal relationship.* Adverse events will be collected after the participant has provided consent and enrolled in the study and through 14-month follow up.

Adverse events will be collected using self-report open-ended survey questions at all follow up data collection timepoints, including 6-month, 10-month and 14-month follow ups. Adverse events will be classified as to whether they are:

1. Expected or unexpected in nature, severity, or frequency for the population under study (i.e. not mentioned in study documents or consent);
2. Related or possibly related to the study procedures or participation in the research; and
3. Serious adverse events (SAE) or not.

Expected adverse events are those which could be anticipated for the population under study. These will be listed and discussed as part of informed consent. For this study, severe hypoglycemic events are a risk for this population and indeed a planned outcome measure, thus an expected adverse event. However, we do not anticipate that the study intervention will provide additional risk. The intervention is an adjunct to usual care aimed at preventing severe hypoglycemia for this high-risk population. Other expected adverse events could include complications of CGM data collection. It is uncommon, but inserting the CGM monitoring sensor could cause infection, bleeding, or pain, and wearing the adhesive patch could irritate the skin. Only a few patients in the CGM G6 clinical studies got slight redness and swelling. No sensor wires broke in the clinical studies; however, there is a remote chance a sensor wire could break or detach and remain under the skin. Such sterile broken sensor wires do not usually pose a significant medical risk. Participants will be fully informed of these risks before consenting to the study. If they experience any adverse events with the CGM monitor, participants will be instructed to contact the KPWA Endocrinology service which provides support for all KPWA patients who use continuous glucose monitors and who will provide medically appropriate advice and care as necessary. If the participant has blood drawn for an HbA1c test, having blood drawn can be uncomfortable and can cause a bruise. Some people may feel nervous or get dizzy. In rare cases, it can cause people to faint. Participants can choose not to have this test and still participate in the study. The informed consent process will include a discussion of risks and the release of information to their medical team and coordination of care as needed.

Relation to the study intervention or data collection will be assessed by an independent physician reviewer as:

- **Definitely related** – There is clear evidence to suggest a causal relationship. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures and cannot be explained by concurrent disease or other factors.
- **Probably related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- **Possibly related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an adverse event may rate only as "possibly 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 procedures or administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which

other factors or underlying disease provides more plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- **Not related** – The adverse event is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology.

A **serious adverse event (SAE)** will be defined as harm experienced by the study participant that resulted in any of the following:

- Death;
- A life-threatening situation (from the event as it occurred) that placed the participant at risk of death;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability, incapacity, or condition requiring treatment or impairing subject ability to carry out normal daily activities;
- A congenital anomaly/birth defect; or
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health or wellbeing and may require medical or surgical intervention or procedural modifications (that are not minor) to prevent one of the other outcomes listed in the bullets above.

All adverse events will be reported to our Institutional Review Board (IRB) on at least an annual basis following the standard practice of our institution, and to the DSMB at all DSMB meetings and at additional timepoints if requested.

In addition, adverse events will be reported on an expedited basis that are: (1) unexpected; and (2) related or possibly related to study procedures or participation in the research; and (3) suggests that the research places subjects or others at a greater risk of harm than was previously known or resulted in a serious adverse event (SAE). Per institutional reporting requirements these events will be reported within 1 business day of discovery if a death or within 15 days for other serious adverse events.

If a participant experiences an adverse event after informed consent is completed but before the participant has started to receive the study intervention, the event will be reported as not related to the study intervention.

5. Ethics and dissemination

5a. Research ethics approval

This protocol and all informed consent scripting and documentation (sample text included in **Appendix A**) will be reviewed and approved by the KPWRHI IRB with respect to compliance with applicable research and human subjects regulations. The KPWHRI IRB will also review participant recruitment, intervention and data collection materials and plans, any other requested documents and any subsequent modifications. No activities involving human subjects will take place unless they have been reviewed and approved. Subsequent to initial review and approval, the KPWHRI IRB will review a continuation and progress report at least annually. These reports will include the total number of participants enrolled, a report on study progress, summaries of adverse events and summaries DSMB meetings and recommendations.

5b. Protocol amendments

Any modifications to the protocol which may impact on the conduct of the study, potential benefit for the participant or may affect participant safety, including changes of study objectives, study design, participant population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendments will be agreed upon by the study investigators and will be submitted for review and approval by the KPWHRI IRB prior to implementation.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be agreed upon by the study investigators and will be

documented in a memorandum but do not require a formal protocol amendment. The KPWHRI IRB may be notified of administrative changes as appropriate for review and approval before implementation.

5c. Consent

We will request a waiver of consent to identify and approach potential participants. We will request a waiver of documentation of consent for collection of baseline survey data in advance of signed consent.

The study programmer will identify potential study participants using the risk stratification tool and data from the EHR. Staff from the KPWHRI SRP will then mail an invitation letter and a hard copy of the Consent form to potential participants. The invitation letter will introduce the study, let potential participants know that research staff will be calling them to see if they are eligible and interested and will give a toll-free telephone number to call if the potential participant does not want to be contacted. The Study Consent form will contain a description of the study, study contact information and all required consent elements (Approved Consent Form in **Appendix A**).

After mailing the invitation letter and Consent form, staff from the KPWHRI SRP will call potential participants to assess interest, complete telephone screening, and if the respondent is eligible and interested,collect verbal consent to collect baseline self-report data. When the baseline survey is completed, the interviewer will collect the participant's email address for e-Consent, and enter the participant into the study's REDCap e-Consent database. The study REDCap e-Consent database will send an email to the participant with link to the e-Consent form. Both the email and e-Consent form will have a telephone number to call if the participant has questions or wants to discuss the consent before signing. The participant will review, sign and submit the e-Consent form. They will be able to print a copy for their own records or can request a copy from the study. The e-Consent instructions will clearly state this. If the participant does not return e-Consent, the study will send up to two email reminders and finally follow up by telephone, to answer any questions and, if the participant is willing, walk through consent and completion of the e-Consent by phone.

If the participant does not want to use e-Consent, the study will mail two hard copies of the Consent form with a business reply envelope and instructions to sign and return one copy and keep the other for the participant's records. If the paper consent is not received, the study will make up to two follow up reminder calls, and finally do a second mailing with business reply envelope.

If after follow up, any participants do not return either e- or paper consent, the study will destroy their baseline survey data and will not contact them again.

Consent for process measures and observations will be included in the signed written e- or paper consent. For nurse and participant interview we will request a waiver of documentation of consent conduct informed verbal consent using scripts and materials that have been reviewed and approved prior to each activity and will document consent in study records. We will conduct no activities without prior review and approval by the KPWHRI Institutional Review Board.

5d. Confidentiality

All Kaiser Permanente staff must annually complete confidentiality training and sign a confidentiality agreement. All investigators, key personnel, and all those responsible for the design and conduct of research are required to receive training in the protection of human subjects. Access to areas where identifiable or protected health information is used is restricted and requires use of individualized key cards. Data handling procedures are clearly documented. All KPWHRI staff with access to identifiers or protected health information is required to review these procedures. New employees are trained regarding data handling procedures, confidentiality and security.

Access to all information stored on Kaiser Permanente computers is limited to staff who have been specifically granted rights by the Information Security Division. All Kaiser Permanente data are protected from unauthorized access by anyone outside the organization by firewall and virus-blocking software. Limiting access to only authorized individuals who are within the Kaiser Permanente firewall protects servers within KPWHRI. Servers are located in a locked room, accessible only to Kaiser Permanente computer support staff. Patient identifiers and demographic data are kept in separate files from protected health information.

All research data collected from participants will be labeled with a unique study identification number and not the participant's name or any other information that could identify the participant. Only the code number will appear on data records and computer files. The participant's contact information will be kept in restricted folders accessible only to relevant study staff.

5e. Declaration of interests

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, or publication of this trial will be disclosed and managed. Further, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

KPWHRI and its sub-contract, the Division of Research, Kaiser Foundation Hospitals have established policies and procedures for all study team members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

5f. Access to data

All study data will be collected and retained by KPWHRI. No data with identifying information will be shared outside the institution. Aggregate data and de-identified data sets may be shared as allowed by the Informed Consent and if approved by the Institutional Review Board.

5g. Ancillary and post-trial care

This study does not have provisions for ancillary or post-trial care. However, all participants enrolled in the study will be current members of Kaiser Foundation Health Plan of Washington and receiving care at KPWA. The proposed study interventions will be delivered by KPWA nurses and overseen by participants' primary care health providers and their teams. Ancillary and post-trial care will thus be provided by the participants' primary care provider and KPWA as covered by their own insurance. The study will not provide compensation for those who may suffer harm from the trial.

5h. Dissemination policy

We will share study results with all participants in this study. We will send a mailed study results letter or summary to all patient participants at the end of the study after analyses for our primary outcomes are complete. We will share results with nurses and providers in the KPWA healthcare delivery system by making presentations at staff meetings and sharing results at seminars and in internal newsletters. For patient participants we will also share their blinded baseline and 12-month CGM results with each participant after they have completed the protocol. If a participant has an HbA1c test these results will also be shared.

For the larger scientific and health care communities, we will disseminate results, methods and tools using presentations at scientific conferences, publications in peer-reviewed journals. We will post materials on publicly available websites as feasible and sharing tools and methods (e.g. manuals and guides, interview instruments, participant materials) as appropriate upon request.

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