A Cognitive Behavioral Intervention to Reduce
Fear of Hypoglycemia in Young Adults with Type 1 Diabetes

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ABSTRACT

In persons with type 1 diabetes (T1DM), hypoglycemia is the major limiting factor in achieving optimal blood glycemic control. All persons with T1DM are at risk for hypoglycemia (blood glucose level < 70 mg/dl), which is life-threatening and accompanied by serious physical and psychological symptoms, resulting in a profound fear of hypoglycemia (FOH) and reduced quality of life. Young adults with T1DM are at greater risk for FOH and have worse glycemic control and self-management behavior than other age groups with T1DM. In our preliminary work, we found that 77% of young adults with T1DM reported FOH, and FOH resulted in increased glycemic variability. Glycemic variability (GV) is the minute-to-minute fluctuation in blood glucose that can be missed if looking only at A1C, a longer-term measure. Increased GV is dangerous because it is associated with cardiovascular events and diabetes complications. Cardiovascular disease remains the primary cause of mortality in T1DM; therefore, strategies to reduce it are necessary. A major gap exists in how to manage FOH as a component of diabetes self-management. Our overall objective is to reduce FOH and improve diabetes self-management, glycemic control, and GV in young adults with T1DM to reduce or delay diabetes complications and improve quality of life. We specifically aim to: (1) determine the feasibility and acceptability of a fear reduction program in young adults with T1DM, who experience FOH; and (2) determine the impact of an 8-week cognitive behavioral therapy (CBT)-based intervention on the outcomes: FOH, self-management behavior, glycemic control, and GV. To achieve these aims, we propose a randomized controlled trial in 50 young adults aged 18 to 35 years with T1DM. Participants will be screened for FOH levels. Eligible subjects will be randomized to the intervention program (Fear Reduction Efficacy Evaluation [FREE]) or attention control group. A one-week run-in phase is planned, with baseline measures of FOH, self-management behavior, A1C, and 24-hour real-time continuous glucose monitoring recordings (RT-CGM) to calculate GV for both groups. The intervention group will participate in eight weekly individual one-hour sessions using CBT and exposure treatment for specific fears. RT-CGM and a daily FOH diary will be used as feedback cues as part of the FREE program. The attention control group will participate in eight weekly individual one-hour diabetes self-management education (DSME) sessions and wear a 24-hour RT-CGM device (to measure GV only) during the same eight-week period. At completion, FOH will be measured, and RT-CGM recordings will be analyzed to determine differences between the FREE and control groups. Findings from this proposed pilot study will serve as the foundation for a larger clinical trial to reduce FOH and improve self-management, glycemic control, and GV. This program of research promises to reduce the development of diabetes complications and improve quality of life for young adults with T1DM.

Specific Aims

In persons with type 1 diabetes (T1DM), iatrogenic hypoglycemia is the major limiting factor in achieving optimal blood glucose control.[1] All persons with T1DM are at risk for hypoglycemia (blood glucose level < 70 mg/dl[2]), which is life-threatening[3] and has serious physical and psychological sequelae, resulting in fear of hypoglycemia (FOH).[4,5] FOH can be incapacitating, causing panic,[4] anxiety,[6] phobic disorders,[7] and greatly diminished quality of life.[8] FOH also results in greater glucose variability[9,10] (GV; the intra-day fluctuations in blood glucose) and poor glycemic control due to under- or overcompensation of food intake, insulin dosing, or physical activity.[11,12] Greater GV is associated with cardiovascular events,[13-15] a greater risk of hypoglycemia[16] and diabetes complications.[15] Despite improved insulin analogs, delivery systems, and glucose sensing technology, FOH persists.[4] The proposed study will pilot test a program to decrease FOH and examine its association with GV.

Our preliminary data using real-time measures demonstrated that 77% of young adults with T1DM reported FOH; FOH resulted in increased GV, with GV occurring after FOH.[10] Young adults are particularly at risk because they report greater FOH than adolescents[17] and have poorer glycemic control compared to middle-aged and older adults.[18] Self-reported hypoglycemia occurs on average twice weekly, but for some individuals it may occur nearly daily.[19] Fear management interventions using cognitive behavioral therapy (CBT) with exposure therapy and feedback have been effective in reducing anxiety in other populations,[20] but have not been tested for persons with diabetes[21] and are not a traditional part of diabetes self-management programs for T1DM. *We have developed and manualized a CBT-b*ased *program tailored to FOH in young T1DM adults, developed with input from the target population.*

Responding to PA-15-176: *Pilot and Feasibility Clinical Trials in Diabetes and Endocrine Metabolic Diseases,* the main objective of this R21 is a pilot and feasibility clinical trial to test a CBT program for FOH on the outcomes: FOH, self-management, glycemic control (A1C), and GV in young adults with T1DM who experience FOH. Fifty young adults with T1DM will be randomized to an intervention or attention control group. The intervention group will participate in eight weekly, individual one-hour sessions using principles of CBT and exposure therapy, using real-time continuous glucose monitoring (RT-CGM) and a daily FOH diary as feedback cues. The attention control group will participate in eight weekly, individual one-hour diabetes self-management education (DSME) sessions and use RT-CGM.

Specific aims for this pilot study are:

In 50 young adults with T1DM (18-35 years)[22] who experience FOH, we will:

1. Determine the feasibility and acceptability of an eight-week CBT-based Fear Reduction Efficacy Evaluation (FREE). Feasibility will be determined through analysis of recruitment (number recruited, screened, eligible, and consented) and retention (% session attendance, program completion rates). Acceptability will be determined through participant evaluation (written evaluation and interview at program completion, and a convened advisory group of previous participants).
2. Determine the impact of the FREE intervention, compared to an attention control group, on the outcomes: FOH (Hypoglycemia Fear Scale score), self-management (Self-Management Scale score), glycemic control (A1C), and glycemic variability (RT-CGM recordings).

   Primary hypothesis: Young adults with T1DM participating in the FREE program will demonstrate improvement in FOH compared to the attention control group.

   Secondary hypothesis: Young adults with T1DM participating in the FREE program will have improved self-management, glycemic control, and glycemic variability (GV) compared to the attention control group.

This study will generate information for a larger clinical trial to test the effectiveness of the FREE intervention to reduce FOH, improve self-management behavior, and improve glycemic control and GV. If effective, this intervention will serve as an important adjunct to diabetes care in young adults with T1DM, reduce the development of diabetes complications, and improve quality of life.

Research Strategy

1. Significance

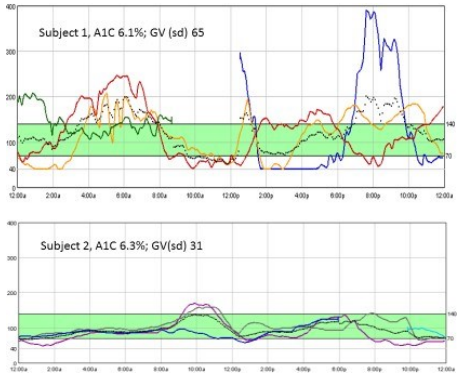
Why fear of hypoglycemia (FOH) in young adults? Young adulthood is the developmental period from age 18 to 35 years, when individuals transition to independent diabetes care as well as establish independence, careers, family, and parenthood.[22] This is before the onset of long-term diabetes complications, when healthy behavior changes can have a critical impact on future health.[23] Despite advances in insulin therapy and glucose-sensing technology, FOH remains a critical deterrent to type 1 diabetes (T1DM) self-management, psychological well-being, and quality of life (QOL).[17] Fear is conceptualized as an emotion arising from a cognitive appraisal of a specific threat or danger.[24] Normal fear is adaptive, stimulating more vigilance and improved performance; heightened fear leads to increased anxiety and may result in a delay to action or inappropriate action.[21,24,25] Fear may mimic the symptoms of hypoglycemia and impair its detection, exacerbating the problem.[5,26] At the extreme, fears can develop into anxiety disorders and phobias.[7,21,27]

Previous negative experiences of hypoglycemia influence diabetes self-management behaviors.[11,17,28-32] Diabetes self-management is defined as the knowledge, skills, and behaviors needed for diabetes self-care.[33] Insulin doses may be inappropriately reduced and diet may be modified to avoid hypoglycemia. Dietary modifications may include excessive eating, particularly more carbohydrates[12,34] or snacking at night.[31,35] These modifications lead to increased GV and poor glycemic control. Registry data from the T1D Exchange Clinic Registry revealed that only 13% of young adults achieved glycemic targets,[36] and, in a survey of self-management practices, 45% of young adults reported they did not reach their glycemic goals due to FOH.[37] Over the past three decades, newer technologies have been designed to help patients with diabetes manage their treatment regimens, including continuous glucose monitoring (CGM) systems, insulin pumps, sensor-augmented pump therapy with insulin suspend features, and insulin bolus calculators. While these have improved glucose control (i.e., A1C), improved A1C has not consistently translated into reduced FOH.[38-44]

What has been used to address FOH? Diabetes education programs typically discuss FOH but have no strategies to manage it.[4] Glucose management and blood glucose awareness training have had variable effects on FOH.[4,45-53] Outcomes demonstrated that, as glucose levels lower, worry levels do not consistently decrease.[53] We hypothesize that the lack of consistent and sustainable reductions in FOH has occurred because the focus of these programs has been on glycemic control, not FOH. Any strategy that focuses on managing glucose to near-normal levels must include methods to cope with the fear that lower blood glucose levels could lead to hypoglycemia.[54] *A fear reduction program, informed by the proposed study, may provide a more comprehensive approach to diabetes care that reduces anxiety and improves glycemic control and GV.*

Why is glycemic variability (GV) important? GV has been associated with more frequent episodes of hypoglycemia[16] and fluctuations between glucose extremes (i.e., hypo- to hyperglycemic), which may occur with overtreatment of a hypoglycemic episode. Evidence supports the role that GV (daily fluctuation) plays in generation of oxidative stress,[14] endothelial dysfunction,[55] and diabetes complications in T1DM.[15] GV has also been associated with increased risk for cardiovascular events,[56] and cardiovascular disease remains the major cause of mortality in T1DM.[57] Though A1C provides a biomarker for average blood glucose over a 2- to 3-month period, it does not capture daily blood glucose fluctuations. As our previous research shows, individuals may have an optimal A1C yet high GV (Figure 1).[10] *GV is directly influenced by self-management behavior[58] and amenable to change with appropriate intervention.* This study will contribute new knowledge about the relationship of FOH and GV and its potential to impact diabetes self-management.

Figure 1. Glycemic Variability



Why a cognitive behavioral approach (FREE) to reduce FOH? Heightened fear develops from memories of previous negative hypoglycemic events that create a conditioned negative response to future fear triggers.[21,59] CBT has been used to reduce fear in other populations.[60] The FREE program will be based on the Beck Cognitive Behavioral Model.[61] The conditioned fear response is reframed through cognitive restructuring of negative thoughts, regulation of emotions (FOH), and changing maladaptive behaviors (self-

management behavior). Exposure therapy will be used to reduce FOH that is out-of-proportion to the threat through habituation to previously fearful situations (Figure 2).[61] RT-CGM readings and fear diary review will be feedback cues to reinforce learning. The goal is not to replace standard diabetes therapy, but improve diabetes self-management[62] through reducing fear. *Our program is designed to reduce FOH and improve diabetes self-management, leading to improved glycemic control and GV.*

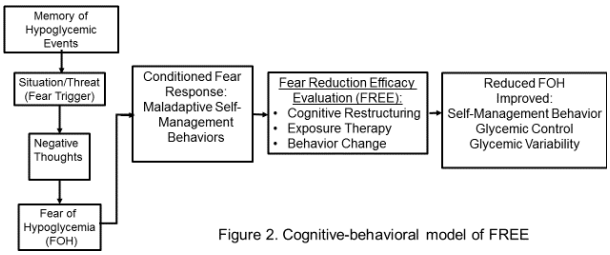


Figure 2. Cognitive-behavioral model of FREE

2. Innovation Most diabetes self-management research focuses on blood glucose management.[48,50,53] A FOH reduction intervention represents a novel approach to addressing the role of FOH in glycemic control and GV. Most individuals with T1DM struggle with hypo- and hyperglycemia and develop a profound fear from these experiences. *FOH does not resolve with education alone,[4] and the magnitude of the problem is poorly understood and under-appreciated*. As incidence of T1DM increases worldwide,[63] the scope of the problem will rise. We have reported temporal associations between FOH and increased GV[10] (**see 3.1b**), with strong justification for an intervention specifically targeting FOH. We will provide a CBT and exposure-based therapy intervention *unique to diabetes care* that has been effective in reducing fear and anxiety in other populations.[64] Along with state-of-the-art real-time CGM technology, this will provide feedback on FOH reduction through weekly diary and RT-CGM cues. The combination of real-time feedback and CBT is innovative. Because exposure-based CBT has been effective for fear reduction in other disorders, success is likely. This intervention differs from programs developed to improve glycemic control because the emphasis is on FOH. NIH emphasizes treatment of young adults with T1DM; this innovative CBT program could facilitate prevention or delay of diabetes complications if it is found that GV is less by reducing FOH. If effective, this could be developed into a web-based application and tailored to other groups.

3. Approach

3.1. Preliminary Studies

3.1a. Research Team Expertise. This application brings together an interdisciplinary team with shared (T1DM, FOH, CGM technology for GV measurement, chronic illness, and clinical practice) and complementary (CBT, feedback, intervention studies, and Certified Diabetes Educator [CDE®]) expertise. Collectively, the team's research strengths span conceptual, methodological, clinical, statistical, and research abilities in the areas of self-management and chronic disease.

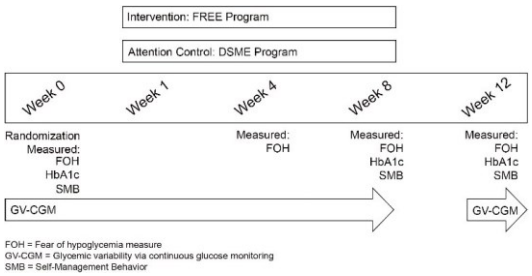
3.1 b. Preliminary Work and Findings. This grant application builds on our previous studies. **(1)** First, we reported the association of GV with daily fear (using a prospective repeated-measures design) in 35 young adults with T1DM.[10] The presence of FOH was not an inclusionary criterion; however, findings revealed: (a) FOH was highly prevalent, reported by 77% of the sample. (To our knowledge, there are no documented reports of FOH prevalence.) Daily diary comments related to FOH included: "I worry every day," "It is a chronic fear," "I live with it constantly, and it is never gone." (b) FOH was linked to GV. Significant temporal relationships emerged: same-day fear levels were associated with same-day GV (r = .263, p < .001), and previous-day fear levels were associated with *next-day GV* (r = .218, p = .005). (3) A1C levels were not consistently associated with lower GV; *53% of those with optimal A1C levels (< 7% recommended target) had high GV* (> 50 dL glucose standard deviation). (d) No significant sex differences were observed in the association of FOH and GV.[10] **(2)** To examine the challenges of hypoglycemia and FOH further, focus groups were conducted. FOH emerged as a major stressor (unpublished data). As part of the study, participants provided suggestions on strategies to address FOH. They were very interested in a fear reduction program and favored individual, face-to-face meetings. (**3)** Lastly, based on this feedback, we developed, manualized, and carried out the FREE program in five young adults. All subjects completed the program. They provided feedback on program length, content, and approach, evaluating the program very positively. Stigma of participation in CBT therapy was not an issue. Participant suggestions have been incorporated.

3.2. Design and Methods

3.2 a. Overview. Young adults aged 18 to 35 years with T1DM (≥ 1 year) who experience FOH will be randomized to an intervention or attention control group. Following a one-week run-in phase, in which baseline RT-CGM recordings will be obtained and subjects adjust to wearing a RT-CGM, subjects will be randomized to

the intervention or attention control group. Both groups will be blinded to the study hypothesis. The intervention group will participate in eight weekly individual one-hour sessions using a CBT-based approach (FREE), wear a RT-CGM device, and keep a daily fear diary. The attention control group will participate in eight weekly individual one-hour sessions on diabetes self-management education (DSME)[62] and wear a RT-CGM device for eight weeks (for GV measurement only, **no diary**). Data is collected: (1) at the beginning of a one-week run-in period (Week 0); (2) at Week 4; (3) completion of the intervention (Week 8); and (4) post-program at (Week 12). FOH, self-management, and A1C will be measured, and RT-CGM recordings will be analyzed to determine within-group and between-group differences (Figure 3).

Figure 3. Study Design



3.2b. Setting and Sample. The study will take place remotely at the University of Illinois at Chicago (UIC) Medical Center and College of Nursing (CON) and in the participant's living environment. Inclusion criteria: (1) 18- 35 years old, (2) diagnosis of T1DM ≥ 1 year confirmed by self-report and insulin dependence since diagnosis, (3) receive medical care from an endocrinologist, (4) use insulin pump or multiple daily injection (MDI) therapy, (5) have FOH (screening questionnaire)[65], and (6) attended a basic diabetes educational program to control for baseline knowledge, (6) has a mobile device, computer or phone to use to connect for weekly sessions, (7) has a private area for weekly sessions. Exclusion criteria: (1) pregnant or breastfeeding; (2) receiving psychotherapy for depression or anxiety disorders, (e.g., panic, obsessive compulsive disorder), or have received therapy specifically for FOH; (3) have a co-existing chronic illness or receiving medications (excluding insulin) that may influence diabetes self-management or GV. We anticipate few comorbidities that will influence diabetes management and GV, due to the age of the target population. Our preliminary data revealed no co-existing cardiovascular, pulmonary, or other major organ diseases.

3.2c. Recruitment. Subjects will be recruited through the UIC medical center and diabetes websites and organizations, and Research Match using flyers, e-announcements, and recruitment letters and emails. We will identify potentially eligible subjects through the electronic medical record system and send recruitment letters and emails. The total number of annual clinic visits for young adult patients with T1DM was 832. The number of patients using insulin pumps is not available through the EMR classification system; however, we estimate 56%-73% will use pumps, based on our preliminary data and data from the T1D Exchange Clinic Registry for this age group.[18] There is a sufficient pool from which to recruit. We have been successful in recruiting using these methods for our previous studies.

3.2d. Sample Size Determination. The sample size estimate will allow examination of within-group and between-group differences from beginning to end of the intervention and to calculate effect sizes to power a future larger study. To determine the sample size to meet these goals, the mean, SD, and mean/SD of FOH levels from our first study were used to re-estimate the expected effect size. The expected estimated effect size was 0.72. Twenty-five subjects will be required in each group (treatment and control; n = 50 total). A 20% attrition rate is expected, based on previous psychoeducational interventions in T1DM,[49,51,53] Thus, we will accrue 30 subjects per group, to achieve a final sample size of 25 subjects per group (***n* = 50 total**).

3.2e. Procedures. 1.) Study staff will screen subjects for inclusion/exclusion criteria by phone. Worry item scores of 3 or 4 (4-point Likert), indicating that worry occurs *often* or *very often,* on any item on the worry scale of the Hypoglycemia Fear Scale-II (HFS-II)[65] will be used to determine the presence of FOH. This method has been validated for this scale.[66] 2.) Those who meet study criteria will be invited to participate in the study. All study procedures will be explained and questions answered. If in agreement to participate, a link to complete the consent form in REDCap will be sent by email. 3.) Once the consent is completed, an appointment for a video-or telephone meeting will be scheduled and supplies and materials will be mailed to the participant's home. At the first video- or telephone meeting study procedures will be reviewed and the study participant will be instructed on how to complete the baseline data collection tasks: one-time urine pregnancy (women to confirm eligibility), one-time waist circumference measure, questionnaires in REDCap through a URL link,

perform the fingerstick test for A1C (average blood glucose), and how to place and care for the continuous glucose monitor. This will be the start of the one-week run-in period to obtain baseline measures (Week 0) and allow subjects to become familiar with wearing the RT-CGM sensor. Following the one-week run-in period, subjects will be randomly assigned to the FREE intervention or attention control group. Randomization will be computer-generated with permuted blocks in multiples of two. The use of permuted blocks preserves balance in the randomization over the course of the study (i.e., at any point in time, there will be approximately equal numbers of patients randomized to the FREE group or the attention control group). Randomization allocation will be concealed from the investigators by through REDCap as set up by the study statistician (Chang Park) who is not involved in performing the study protocol. During the study period, subjects will continue to receive their usual diabetes care with their health care provider and be encouraged to ask questions regarding blood glucose management of their diabetes health care provider. Subjects will continue to care for their diabetes as they normally would.

Table 1. Elements of the FREE Program

	Time
Hypoglycemia and Its Causes Fear as a Normal Human Emotion Effect of Fear on Health and Health Behaviors Safety and Avoidance Behaviors	Week 1
Blood Glucose Cues Introduction to CBT	Week 2
Cognitive Restructuring, Safety Behaviors Introduction to Progressive Relaxation	Week 3
Exposure Therapy: Develop Fear Hierarchy Coping Strategies	Week 4
Exposure Practice, Coping, Relaxation and Cognitive Restructuring	Weeks 5-7
Review Techniques Learned, Develop a Plan to Maintain Gains	Week 8

3.2e1. FREE Intervention. Subjects randomized to the FREE intervention group will: (1) attend eight individual weekly remotely-delivered one-hour sessions based on principles of CBT and exposure treatment (Table 1). Program length was based on similar successful CBT programs.[67] FREE sessions will be conducted by one consistent licensed clinical psychologist (Dr. Duffecy) who is a study co-investigator. The program curriculum is adapted from existing programs used for health-related anxiety using traditional CBT techniques. Treatment will target incorrect beliefs about hypoglycemia, hypervigilance to symptoms, fear of symptoms, and maladaptive behavioral responses in response to glucose levels. Participants will create a fear and avoidance hierarchy and be taught to begin approaching previously feared situations (e.g., spending time alone, reducing snacking, allowing glucose readings to reach lower safe levels, etc.) to experience habituation and the resulting decrease in anxiety (Appendix P1). Weekly homework will be assigned to reinforce the content. (2) FREE intervention subjects will continue to wear a RT-CGM for the eight weeks, and (3) complete a daily FOH diary (Appendix P3). RT-CGM readings and daily diaries will serve as feedback cues for glucose and FOH levels as part of the FREE program. (4) Participants will change their RT-CGM site as instructed by study staff member who is a registered nurse who will monitor remotely to assure proper placement and care.

Table 2. Elements of the Attention Control (DSME) Program

	Time
Living with Diabetes	Week 1
Using Medications Safely for Therapeutic Effectiveness; Blood Glucose Monitoring	Week 2
Healthy Eating; Incorporating Nutritional Management into Lifestyle Self-Assessment: What is your Eating Style?	Week 3
Being Active: Incorporating Physical Activity into Lifestyle; Barriers and Strategies Self-Assessment: Activity Patterns/Preferences	Week 4
Healthy Sleep; Sleep Patterns; Challenges and Strategies for Success Self-Assessment: Sleep Quality	Week 5
Self-Management in the Workplace Balancing Work Stress	Week 6
Psychosocial Concerns Caring for Self	Week 7
Preventing Complications Review and Wrap-Up	Week 8

3.2e2. Attention Control Group. Subjects randomized to attention control: (1) attend eight weekly remotely-delivered individual one-hour sessions on diabetes self-management. Topics follow the American Diabetes Association DSME standards (Table 2; Appendix P2)[68] and are led by a Certified Diabetes Educator (CDE®) and study co-investigator (Dr. Quinn). Weekly homework will be assigned. (2) Attention control subjects will continue to wear a RT-CGM for the eight-week session (for GV measurement **only**) and will **not**

keep a diary); and (3) will change their RT-CGM site as instructed by study staff (registered nurse) who will monitor remotely to assure proper placement and care of the glucose sensor.

At the end of the data collection period, participants in both groups will return the supplies in a pre-paid envelope provided with the study maerials.

3.2e3. Subject Retention Strategy. Both FREE intervention and attention control groups will (1) have weekly sessions scheduled at a time convenient for the participants; (2) wear a RT-CGM; (3) receive appointment reminders; (4) be compensated at Weeks 4, 8, and 12; and (5) receive a personalized folder with copies of their CGM recordings at study's end. Weekly sessions for both the FREE and attention control groups will include topics of interest and value to the study population. Use of RT-CGM technology is highly desirable for many young adults with T1DM and served as both an incentive and retention factor in our previous study.

3.2e4. Treatment Fidelity Strategy. To maintain treatment fidelity, both FREE and attention control DSME sessions will follow a manualized protocol.

3.2f. Measures.

3.2f1. Baseline and Post-Intervention Measures. *Self-report instruments* will be used to obtain demographic, literacy and health information, previous history of hypoglycemia, diabetes self-management, (see Table 3 for a complete list of measures). The scales chosen have strong psychometric properties and have been validated in diabetes populations. The primary outcome, FOH, will be measured using the Worry Subscale of the Hypoglycemia Fear Scale. This 18-item, 5-point Likert scale measures situation-specific worries about hypoglycemia and provides one overall score for hypoglycemic worry. The scale has strong psychometric properties (Cronbach's alpha 0.95).[65] Self-management will be measured with the Diabetes Self-Management Scale (Cronbach's alpha 0.84).[69] Convergent and construct validity are demonstrated for both scales.[65,69] *Glycemic control* will be measured with a fingerstick for A1C using previously published methods (A1C Now®, Chek Diagnostics, Indianapolis, IN).[70]

3.2f2. Glycemic Variability. Subcutaneous interstitial glucose levels will be monitored using a Dexcom G series (San Diego, CA) or Medtronic sensor (Annaheim, CA) Participants will be instructed on the placement of the glucose sensor and transmitter and how to change weekly. When CGM supplies are returned, glucose data will be downloaded for later analysis. To analyze GV, the raw data will be downloaded to an EXCEL spreadsheet. Research staff will be trained on cleaning data, confirming regular calibration, identifying errors, and reviewing missing data or time-points. The frequency and time spent in hypo- and hyperglycemia will be calculated (% and minutes; < 70 and > 180 mg/dL). GV will be determined by calculating the daily glucose standard deviation (GlucSD), continuous net glycemic action (CONGA), coefficient of variation (CV%), and interquartile range (IQR). These intra-day measures are recommended for comprehensive evaluation of GV.[71,72]

Table 3. Measures		
Variables	Measure	Frequency
Demographic, health, and literacy information	Demographic, health questionnaire, self-reported height, weight, waist circumference, Hypoglycemia Patient Questionnaire[2] Health Literacy Screener (Newest Vital Sign)[73]	Week 0
Aim 1		
Recruitment Retention Acceptability	Number recruited, screened, eligible, consented Attendance rate; Completion rate Participant evaluation survey and interview (Appendix P4) Advisory panel	Weekly Weekly Week 8 End of study
Aim 2		
FOH	Hypoglycemia Fear Scale-II (HFS-II[65])	Weeks 0, 4, 8,12
Glycemic measures Glycemic control Glycemic variability	 A1C (A1C Now®) RT-CGM (Dexcom® or Medtronic®): daily glucose standard deviation (GlucSD), continuous net glycemic action (CONGA), coefficient of variation (CV%), interquartile range (IQR), time spent in hypo- and hyperglycemia (**see 3.2f3**)	 Weeks 0, 8, 12 Weeks 0-8, and 12
Diabetes self-management	Diabetes Self-Management Questionnaire[69]	Weeks 0, 8, 12

3.2f3 Related Variables. Self-efficacy, anxiety, diabetes distress, depressive mood, and quality of life will be measured with validated instruments (Self-Efficacy for Diabetes Scale,[74] General Anxiety Disorder-7 Item [GAD-7],[75] Diabetes Distress Scale,[76] Center for Epidemiological Studies Depression Scale [CES-D], and Diabetes Quality of Life Scale[77] respectively, at Weeks 0, 8, and 12). Subjects who score 16 or greater on the CES-D will be offered a list of mental health resources (See Mood Score Script, Ver 1, 11-28-18 and Health Resource, Ver 1, 11-28-18). Subjects who withdraw from the study prior to weeks 8 and 12 will be asked to complete week 8 and/or week 12 data collection at the appropriate time. All questionnaire data will be collected remotely through REDCap by sending a link to the study participant for the appropriate week of data collection.

3.2g. Data Analysis

The statistical estimation method for this study is a mixed-effects model with repeated measures (SPSS 24). This is superior to repeated-measures ANOVA because it avoids the limitations of strong assumptions such as sphericity and constant variance, and operates in a more general missing-at-random framework.[78] Participants who have a missing data point are not excluded, thus producing unbiased estimation of intent-to-treat (ITT) and reducing type 1 error.[79] We have built-in procedures to minimize missing data, but missing data cannot be completely eliminated; thus, patterns will be examined, and longitudinal multiple imputation will be applied to compare any differences using Multiple Imputation for Chained Estimation (MICE).[80]

Aim 1. Feasibility will be evaluated by assessing recruitment, retention, and participant evaluation. Records will be kept of the number of recruited, screened, eligible, and consented subjects. Retention will be evaluated by weekly attendance (% session attendance, program completion rates). Acceptability will be determined through participant evaluation (written evaluation and interview at program completion [Appendix P4]) and a convened advisory group of previous participants (Table 4). As part of feasibility, we will also track the number of RT-CGM sensor failures, placement sites, time to failure, and adverse sensor site problems.

Aim 2. We will evaluate the effects of within-group and between-group differences from baseline (Week 0) to program completion (Week 8) and post program (Week 12) on the outcomes: FOH, self-management, glycemic control, and GV, using an intent-to-treat approach. To address sex as a biologic variable, sex differences in primary and secondary outcomes will be explored. Diabetes duration and depressive mood will also be statistically controlled.

H1: FOH will be reduced. Within-group and between-group differences in HFS worry score from baseline to study completion and post program will be compared using a mixed-effects model.

H2a: Diabetes self-management will be improved. Within- and between-group differences in the Diabetes Self-Management Scale score from baseline to study completion and post program will be compared using a mixed-effects model.

H2b: Glycemic control. Within- and between-group differences in A1C from baseline to study completion and post program will be compared using a mixed-effects model.

H2c: GV will decrease. GV will be determined through GlucSD, CONGA, CV%, and IQR, as well as daily time spent in hypo- or hyperglycemia. Within- and between-group differences will be calculated from daily RT-CGM recordings using a mixed-effects model.

3.2 h. Table 4. Study Timeline

Year 1	July	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	June
Study set-up	X	X	X									
FREE subjects				4			4			4		
Control subjects				4			4			4		
Total subjects				**8**			**16**			**24**		
Year 2	July	Aug	Sept	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	---
FREE subjects	6			6			6					
Control subjects	6			6			6					
Total subjects	**36**			**48**			**60**					
Convened advisory panel											X	
Data analysis/report findings											X	X

3.3 Strengths, Limitations, and Potential Problems with Alternative Solutions

Strengths. (1) This study directly focuses on FOH reduction, lacking in previous interventions. (2)The RCT study design is a strength, as is use of RT-CGM monitoring to measure GV. (3) subjects using both insulin

pump and MDI will be eligible to evaluate FOH in this population, differences in GV from different insulin delivery methods will be controlled statistically using propensity score analysis. (4) We chose to conduct FREE sessions as individual sessions. Individual sessions will allow provision of a higher intervention dose by addressing each subject's specific fears and was preferred by our population. (5) The eight-week time frame allows adequate time to measure FREE program effects. It is similar in length to other successful CBT programs.[53,67] (6) The attention control group will receive a program equal in time and attention to the intervention group's. The content is distinct from the FREE program. (7) The post-program evaluation at Week 12 allows evaluation of treatment sustainability. (8) The study team is a strength, bringing together expertise in T1DM management, intervention science, CBT strategies, and GV measurement.

Limitations Potential Problems and Alternative Solutions. (1) We address recruitment concerns with strategies successful in previous studies. We established relationships with clinical sites (University of Illinois Health System, Loyola) that reports high volumes of accessible patients contactable for studies. (2) Our FREE pilot study had no attrition. We plan retention strategies outlined in 3.2e3. (3) To address fidelity concerns, a treatment manual and fidelity checklist will be used for both FREE and attention control sessions. All future videoconference sessions will be recorded and reviewed (telephone sessions will not be recorded). Participation for both groups will be reinforced at weekly meetings, weekly RT-CGM site changes by study staff, and follow-up reminders at mid-week (via text message). (4) Potential RT-CGM sensor failure is addressed by using a RT-CGM device that continuously displays glucose levels. This alerts subjects if the device stops recording to contact study staff. To further reduce the chance of missing data, sensors will be replaced weekly by the study participant. This process will be monitored by a trained registered nurse. (5) Because RT-CGM may affect GV, both groups will wear a RT-CGM during the eight-week intervention and able to view their real-time glucose levels. Changes in glycemic control from RT-CGM use are very small.[81]

3.4 Future Directions. FREE's effectiveness could be studied in a larger, adequately powered clinical trial. FREE has potential for tailoring to other age groups and deploying as a web-based or smartphone app, allowing greater dissemination than traditional face-to-face. The long-term goal is the integration of fear-reducing strategies in mainstream diabetes education and care.

3.5. Focus Group Meeting

After the completion of the research, we will invite enrolled participants those who were in the FREE Intervention group and checked the box and provided their initials of the informed consent document indicating they are willing to be contacted for future research, to a one-hour Zoom meeting to get their feedback on the study protocol.

3.5.a. Recruitment. Subjects will be recruited through a recruitment email.

3.5.b. Procedures. 1.) Subjects who consented to be contacted for future research as above will be recruited for the focus group meeting. 2.) If agreeable to participate, electronic consent will be obtained through a REDCap URL link, the focus group meeting informed consent (version 11, addendum, 5.12.21) will be obtained. 3.) There will be 2 focus group meetings; One focus group meeting is for the subjects who enrolled before COVID pandemic and participated in the FREE Intervention face-to-face. A second focus group meeting is for the subjects who enrolled during the COVID pandemic and participated in the FREE Intervention remotely. 4.) The size for each focus group on zoom is 5-6. Subjects and the principle investigator will meet through the Zoom link for approximately 1 hour. During the one-hour Zoom meeting the principle investigator will ask some questions (focus group script, version 1, 5.12.21). 5) The focus groups will be audio-recorded and a note-taker will be present.6.) After the focus group meeting, compensation ($50) will be provided in cash.

4.1 Protection of Human Subjects

4.1.1 Risks to Human Subjects

a. Human Subjects Involvement, Characteristics, and Design

Human subjects will be involved in all aspects of this research because the purpose of the study is to test a fear reduction intervention in young adults with type 1 diabetes (T1DM). Fear of hypoglycemia (FOH) is a critical problem associated with poor glycemic control, greater glucose variability, and diminished quality of life (QOL). It affects most people with T1DM and is greater among young adults than adolescents. To our knowledge, there have been no programs developed to alleviate this problem in the exact way that we do.

Study population. We plan to recruit 60 subjects for an expected attrition rate of 20%. **This will result in a final sample of 50 subjects.** Inclusion criteria include: 18 to 35 years of age, diagnosed with T1DM ≥ 1 year, receive medical care from an endocrinologist, use insulin pump or multiple daily injection (MDI) therapy, experience FOH, and attended a basic diabetes education program (to control for baseline knowledge). Exclusion criteria include: pregnancy or breastfeeding; receiving psychotherapy for depression or anxiety disorders (e.g. panic, obsessive compulsive disorder); received therapy specifically for FOH; or have a coexisting chronic illness or receiving medications (excluding insulin) that may influence diabetes self-management or glycemic variability(GV).

Sampling plan. Convenience sampling will be used to recruit subjects. Remote delivery will allow us to include study participants beyond the Chicago metropolitan area.

Procedures. Subjects will be randomized to the intervention group or an attention control group to minimize bias. Randomization will be computer-generated with permuted blocks in multiples of two. All subjects in the intervention group will: (1) receive eight weekly individual remotely-delivered one-hour sessions based on principles of cognitive behavioral therapy (CBT) with exposure therapy, (2) complete a daily fear diary, (3) wear a real-time continuous glucose monitor (RT-CGM), (4) complete a post-program assessment of study outcomes at 8 weeks, and (5) be instructed on changing and caring for their RT-CGM site by a study staff member who is a registered nurse who will monitor placement and care. All subjects in the attention control group will: (1) receive eight weekly remotely-delivered one-hour individual diabetes self-management education (DSME) sessions, (2) wear a RT-CGM, (3) complete a post-program assessment of study outcomes at 8 weeks, and (4) be instructed on changing and caring for their RT-CGM site by study personnel (registered nurse) to assure proper placement and care of the device. Methods to maintain intervention fidelity in the intervention and attention control groups include: (1) treatment manual; (2) fidelity checklist; (3) having all FREE intervention sessions conducted by one licensed, trained clinical psychologist who is a member of the research team; (4) having all attention control group sessions conducted by one registered nurse who is a Certified Diabetes Educator® and a member of the research team; (5) videotaped sessions with review by study staff for consistency of treatment that will be reviewed by a member of the research team, who is not involved in carrying out the study protocol, for intervention fidelity; (6) weekly RT-CGM site changes; and (7) weekly reminders of next appointments. All study procedures will take place remotely (by phone, vidoconference, REDCap and by mail) by study personnel who are based out of the University of Illinois (UIC Medical Center. During the study period, subjects will continue to receive their usual diabetes care with their health care provider. Subjects will be encouraged to discuss any questions regarding blood glucose management with their diabetes health care provider.

b. Sources of Materials

Data will be collected from study subjects only for research purposes as follows: (1) self-reported data from questionnaires and daily diary (FREE intervention group only); (2) drop of blood from a finger prick for A1C; and (3) RT-CGM from a glucose sensor placed under the skin.

1. Self-reported data will include information collected: (a) during recruitment to establish study eligibility; (b) demographic (sex, race, ethnicity, health literacy), health (diabetes duration, hypoglycemic experiences, comorbidities), and key study variables (fear of hypoglycemia, diabetes self-management; and related study variables (anxiety, depressive mood, diabetes distress, quality of life) collected from questionnaires; and (c) daily FOH diary (FREE intervention group only).
2. A1C will be determined from a drop of blood from a finger prick. Study participants will be trained using standardized procedures by a member of the study personnel (registered nurse). The A1C result will be reported by the participant and entered into REDCap.
3. Continuous interstitial glucose levels to calculate glycemic variability will be obtained from a RT-CGM sensor placed under the skin using standard procedures by trained study personnel (registered nurse). The sensor transmits the glucose levels to a receiver (the size of a quarter) that the subject wears.
4. Program evaluation obtained from questionnaires and interview. At the end of the study, subjects will be invited to a convened advisory group (via videoconference) to provide additional suggestions and feedback.
5. Data to evaluate program feasibility will include (1) recruitment (number recruited, screened, eligible, consented); (2) retention (attendance and completion rate records) maintained by study personnel.

c. Potential Risks

The potential risks to subjects include:

1. Bleeding, irritation, discomfort, or infection at the finger prick site (for A1C) and insertion site (for RT-CGM). The risk for these problems is very minor and is minimized by following standardized procedures using trained study personnel. Fingerstick procedures are familiar to all persons with type 1 diabetes as it is the standard of care is to test capillary glucose a minimum of four times per day. CGM is also becoming a standard of care with approximately 60% of patients with T1D having used a CGM.
2. Loss of confidentiality. Standard procedures will be used to avoid breaches in confidentiality. We expect this risk to be low. We will require that participants have a private area for weekly intervention sessions.
3. Individuals in the FREE group may feel emotional discomfort in discussing fears and memories of potentially sensitive thoughts and experiences related to hypoglycemia. We expect this risk to be low based on our experience in previous studies that examined experiences with hypoglycemia.
4. It is possible that, in discussing fears and reframing thoughts about FOH, blood glucose levels may change (either increase or decrease). For example, if fear levels are reduced, it is possible that blood glucose may be lower at times, and the subject may experience hypoglycemia.
5. Completing self-report measures on FOH, depressive mood, and diabetes distress may cause subjects some emotional distress.

4.1.2 Adequacy of Protection Against Risks

a. Recruitment and Informed Consent

Subjects (18-35 years) will be recruited from Chicago metropolitan area university medical centers, diabetes websites, and organizations and Research Match, using flyers, e-announcements, and recruitment letters. At the University of Illinois at Chicago (UIC), we will identify subjects through the electronic medical record systems and send recruitment letters. Potentially eligible interested subjects will be screened by study personnel for inclusion and exclusion criteria. Informed consent will be obtained prior to performing any research procedures. The informed consent process will begin when potential subjects are contacted. The researcher will explain the study purpose, procedures, benefits, risks, confidentiality, and research subject's rights. After all questions have been answered and the subject verbally agrees to participate, e-consent will be obtained using REDCap. Study participants will be able to download a copy of the consent from REDCap and/or a copy will be mailed to them.

b. Protections Against Risk

Methods to minimize risk include:

1. Minimization of bleeding, irritation, discomfort, or infection at the finger prick site (for A1C) and insertion site (for RT-CGM). The risk of for these problems is very minor and is minimized by following standardized procedures. RT-CGM placement and finger pricks will be done using sterile technique and standardized procedures. Participants will be trained on these procedures by a trained registered nurse. In addition, subjects will be instructed to observe their RT-CGM insertion site daily and contact the research personnel if there are signs of bleeding, irritation, redness, or pain.
2. Loss of confidentiality. Strict procedures will be put into place to minimize the risk of breach of confidentiality. All study staff will be trained on methods of maintaining subject confidentiality. Subjects will be assigned a unique code number. A master list that links the subject identity to the data will be kept by the principal investigator (PI) and stored in a locked office separately from the data. **Data storage**: All data will be stored and analyzed by code number. This consists of coded questionnaires and A1C results in REDCap, diary, and RT-CGM recordings. The coded data will be entered into a password-protected computer with a secure server for analysis. Hard copy (paper copy) data (diary) will be stored in a locked office. No identifiers (except subject ID) will be included. Only members of the research team will be able to access these data. **Procedures during data collection:** Privacy will be provided during recruitment by screening potential subjects in a private setting. The screening data that contain personal identifiers will be kept separate from the coded study data and stored in REDCap or HIPAA-protected UIC Box folder. All data collection and study procedures will take place in a private location. To insure intervention fidelity, a fidelity checklist will be instituted. The first 25 FREE intervention and attention control program sessions will be audiotaped for review (this has been completed). These audiotapes will be stored by subject code number. Only the research staff will have access to the audiotapes. The tapes will be stored in a HIPAA-protected UIC Box folder and destroyed three years following data analysis.
3. Individuals in the FREE group may feel emotional discomfort in discussing fears and memories of potentially sensitive thoughts and experiences related to hypoglycemia. CBT has not been shown to cause harm. The material discussed during the intervention will be thoughts, feelings, and experiences initiated by the subject for discussion. Subjects will not be probed to discuss anything that they are not comfortable discussing. The FREE sessions will be conducted by a licensed clinical psychologist with extensive experience using CBT and exposure interventions. If a subject has questions or concerns about his or her diabetes management, he or she will be encouraged to discuss these concerns with his or her diabetes health care provider. Should a subject identify that she or he would like to seek psychological counseling unrelated to their FOH, a list of counseling agencies will be provided. If the psychologist interventionist determines that continuation in the FREE program would not be appropriate due to confounding psychological issues that become evident during the study, continuation in the study may be stopped and a list of counseling agencies provided.
4. It is possible that, in discussing fears and reframing thoughts about FOH, blood glucose levels may change (either higher or lower). For example, if fear levels are reduced, it is possible that blood glucose may be lower at times, and the subject may experience hypoglycemia. To reduce this risk, subjects will be reminded

to measure their capillary blood glucose at the usual times, as recommended by their diabetes care team, and at any time they feel they that their blood glucose is outside of their target range (high or low). Subjects will also be reminded to carry their glucose testing supplies and fast-acting carbohydrate (glucose) at all times to respond to low blood sugar. During the FREE sessions, subjects will be asked to check their capillary blood glucose at the beginning and end of each session.

5. Because people with T1DM are always at risk for hypoglycemia, study staff will remind participants to have fast-acting carbohydrate available should a subject develop hypoglycemia during a meeting session (either FREE or attention control group). During the course of this study, subjects will have an additional measure of glucose through the RT-CGM; however, they will be instructed not to rely on the RT-CGM for blood glucose levels for treatment and to verify glucose readings with a capillary measure. Additionally, subjects will be under the care of an endocrinologist. This is an inclusionary criterion for study participation, which will ensure that subjects have resources to assist them with their diabetes care.

6. Completing self-report measures on FOH, self-management, anxiety, depressive mood, diabetes distress and quality of life may cause subjects some emotional distress. The risk is minimal. In our previous studies with the same population, no subjects reported emotional distress with these measures. However, study staff will be aware of the possibility and address any concerns that are voiced.

7. Should a subject require medical or other professional intervention due to an adverse event or illness, treatment may be obtained through the UIC Medical Center, the subject's regular doctor, or the treatment center or clinic of their choice. Subjects will be provided contact information for the PI should they want to talk to her about their illness or injury.

4.1.3. Potential Benefits of the Proposed Research to Human Subjects and Others

There may be no direct benefits to participating in the study. However, subjects in the FREE intervention group may benefit from discussing their concerns about hypoglycemia and may experience a reduction in fear of hypoglycemia and improved glycemic control. The possible risks are no greater than those experienced in normal day-to-day life. Most persons with T1DM experience FOH and voice concerns of how it negatively influences their daily lives.

4.1.4 Importance of Knowledge to be Gained.

The risks to the study participants are minimal and no more than those encountered in daily life. Knowledge gained from this study may provide an important intervention for reducing fear of hypoglycemia and improving diabetes self-management and glycemic control in the future in young adults with T1DM. If effective, this intervention has important clinical implications for reducing diabetes complications and improve quality of life in this population.

4.1.5 Data Safety Monitoring Plan for: A Cognitive Behavioral Intervention to Reduce Fear of Hypoglycemia in Young Adults with Type 1 Diabetes
PI: Pamela Martyn-Nemeth

This study will involve young adults (aged 18 to 35 years) with T1DM who experience fear of hypoglycemia (FOH). We plan to recruit 60 subjects for an expected attrition rate of 20%. **This will result in a final sample of 50 subjects.** Subjects will be enrolled and will complete a one-week run-in period to collect baseline data, including real-time continuous glucose monitoring (RT-CGM) to calculate baseline glycemic variability. Following the run-in period, subjects will be assigned to one of two groups. The attention control group = 8 weeks of diabetes self-management education sessions and 8 weeks of RT-CGM. The FREE intervention group = 8 weeks of a fear reduction intervention using CBT and exposure therapy and 8 weeks of RT-CGM and a diary used as a feedback cue. Both groups will have their RT-CGM sites changed weekly (study participants will be trained and monitored by study staff). The risk associated with this study is minimal for the interventions and data collection methods employed by the study. The potential for a serious adverse event is very low. Pamela Martyn-Nemeth, PhD, RN, will be the primary monitor, and a Safety Monitoring Committee will share the responsibility of monitoring the data.

Monitoring entity or who will monitor the study

The individuals responsible for data safety and monitoring will be the PI, Dr. Pamela Martyn-Nemeth, and a Study Monitoring Committee (SMC). A SMC will be appointed to provide oversight and monitoring of our data on an annual basis by individuals not directly associated with the study. The SMC will consist of: (1) Eileen Collins, PhD, RN, Professor, Department of Biobehavioral Health Science, College of Nursing; (2) Terry Unterman, MD, Professor of Medicine, Department of Medicine, Endocrinology, Diabetes and Metabolism; and (3) Lisa Sharp, PhD, Psychologist and Associate Professor, Pharmacy Systems, Outcomes and Policy, College of Pharmacy, and (4) Chang Park, PhD, study statistician—all at UIC. Drs. Collins, Unterman, and Sharp have expertise in reviewing the scientific design, conduct of study, intervention fidelity, evaluation of safety and risks to subjects, interpretation of data, and making recommendations concerning continuation, modification, suspension, or termination of the study.

Dr. Martyn-Nemeth will meet with the SMC annually and provide a written and verbal progress report. The report will include a summary of cumulative recruitment, randomization, cumulative retention and attrition rate, study group demographics, adverse events, and data completeness and quality. The SMC will provide oversight of the study, as well as consider factors external to the study that may impact the safety of the participants or the ethics of the study. A written report of the meeting will be compiled that summarizes the review of data and outcomes, as well as any recommendations with respect to modification of the protocol. The report will be submitted to the UIC IRB and to the NIH.

Procedures for monitoring study safety, minimizing research-associated risk, and protecting the confidentiality of subject data.

Study Safety. Study procedures will take place remotely at private locations of research personnel and participants. All study personnel involved in conducting the research, including recruitment and screening for eligibility, data management, and provision of interventions, will receive training that will address: (1) overview of the study objectives and procedures, (2) background and training on collecting data free from bias, (3) protection of human subjects and confidentiality, (4) training and monitoring study participants in performing finger pricks for A1C and placing RT-CGM sensors using infection control procedures as well as procedures specific to measuring A1C and placing RT-CGM sensors (with verbal, written and video instruction with videoconference presence for the first time these procedures are performed and any time thereafter if needed. and (5) data and intervention monitoring.

Dr. Martyn-Nemeth will assure that informed consent is obtained prior to performing any research activities, all subjects meet eligibility criteria, and the study is conducted according to the IRB-approved research plan.

Compliance of regulatory documents and study data accuracy and completeness will be maintained through an internal quality assurance process. Quality control will include annual data verification and protocol compliance checks, as well as checks for missing data by Dr. Pamela Martyn-Nemeth and study personnel. Protocol adherence will be monitored by Dr. Martyn-Nemeth by auditing 50% of the cases for compliance with IRB requirements, informed consent requirements, verification of source documents, and compliance with the study protocol. To ensure reliability of data entry, a random sample of data entries will be reviewed and compared with the raw data by Dr. Martyn-Nemeth, and the results will be recorded. An acceptable error rate will be < 0.3%. Results of the audit will be documented. Monthly research meetings will be scheduled to assure quality of the conduct of the research and promote communication among study team members and good data management activities.

Minimizing research-associated risk

Potential subjects will be screened to ensure that they meet study inclusion criteria.

Sources of materials: Data will be collected from study subjects only for research purposes as follows: (1) self-reported data from questionnaires; (2) daily diary (FREE intervention group only); (2) drop of blood from a finger prick for A1C; and (3) RT-CGM from a glucose sensor placed under the skin.

Potential risks

The potential risks to subjects include:

1. Bleeding, irritation, discomfort, or infection at the finger prick site (for A1C) or insertion site (for RT-CGM). The risk for these problems is very minor and is minimized by following standardized procedures and using trained study personnel.
2. Loss of confidentiality. Standard procedures will be used to avoid breaches in confidentiality. We expect this risk to be low.
3. Individuals in the FREE group may feel emotional discomfort in discussing fears and memories of potentially sensitive thoughts and experiences related to hypoglycemia. We expect this risk to be low based on our experience in previous studies that have examined experiences with hypoglycemia.
4. It is possible that, in discussing fears and reframing thoughts about FOH, blood glucose levels may change (either increased or decreased). For example, if fear levels are reduced, it is possible that blood glucose may be lower at times, and the subject may experience hypoglycemia.
5. Completing self-report measures on FOH, depressive mood, and diabetes distress may cause subjects some emotional distress.

Protection against risk

1. Minimization of bleeding, irritation, discomfort, or infection at the finger prick site (for A1C) and insertion site (for RT-CGM). The risk of for these problems is very minor and is minimized by following standardized procedures. Participants will be trained on RT-CGM placement and finger pricks using sterile technique and standardized procedures. Training and monitoring will be performed by a trained registered nurse. In addition, subjects will be instructed to observe their RT-CGM site daily and contact the research personnel if there are signs of bleeding, irritation, redness, or pain.
2. Loss of confidentiality. Strict procedures will be put into place to minimize the risk of breach of confidentiality. All study staff will be trained on methods of maintaining subject confidentiality. Subjects will be assigned a unique code number. A master list that links the subject identity to the data will be kept by the principal investigator (PI) and stored separately from the data in a locked office. **Data storage**: All data will be stored and analyzed by code number. This consists of coded questionnaires and diaries, A1C finger prick results, and RT-CGM recordings. [RT-CGM data may be downloaded from a secure server over the internet (encrypted using AES-256 Encryption) using Dexcom Clarity data management software. The RT-CGM data is de-identified at all times and only associated with the study code number from point of access through storage on the College of Nursing secure server.] The coded data will be entered into REDCap and a password-protected computer with a secure server for analysis. A1C results will be stored in REDCap. Hard copy (paper copy) data (diaries) will be stored in a locked office. No identifiers (except subject ID) will be included in the download. Only members of the research team will be able to access these data. **Procedures during data collection:** Privacy will be provided during recruitment by screening potential subjects in a private setting. The screening data that contain personal identifiers will be kept separate from the coded study data and stored in a locked office, REDCap or HIPAA-protected UIC Box folder. All data collection and study procedures will take place in a private location. To insure intervention fidelity, a fidelity checklist will be developed. The first 25 FREE intervention and attention control program sessions will be audiotaped for review (already completed). These audiotapes will be stored by subject code number. Only the research staff will have access to the audiotapes. The tapes will be stored in HIPAA-protected UIC Box folder and destroyed three years following data analysis.
3. Individuals in the FREE group may feel emotional discomfort in discussing fears and memories of potentially sensitive thoughts and experiences related to hypoglycemia. CBT has not been shown to cause harm. The material discussed during the intervention will be thoughts, feelings, and experiences initiated by the subject for discussion. Subjects will not be probed to discuss anything that they are not comfortable discussing. The FREE sessions will be conducted by a licensed clinical psychologist who has extensive experience using CBT and exposure interventions. If a subject has questions or concerns about his or her diabetes management, he or she will be encouraged to discuss these concerns with his or her diabetes health care provider. Should a subject identify that she or he would like to seek psychological counseling unrelated to their FOH, a list of counseling agencies will be provided. If the psychologist interventionist determines that continuation in the FREE program would not be appropriate due to confounding psychological issues that

become evident during the study, continuation in the study may be stopped and a list of counseling agencies provided.

4. It is possible that, in discussing fears and reframing thoughts about FOH, blood glucose levels may change (either higher or lower). For example, if fear levels are reduced, it is possible that blood glucose may be lower at times, and the subject may experience hypoglycemia. To reduce this risk, subjects will be reminded to measure their capillary blood glucose at the usual times, as recommended by their diabetes care team, and at any time they feel they that their blood glucose is outside of their target range (high or low). Subjects will also be reminded to carry their glucose testing supplies and fast-acting carbohydrate (glucose) at all times to respond to low blood sugar. During the FREE sessions, subjects will be asked to check their capillary blood glucose at the beginning and end of each session.

5. Because people with T1DM are always at risk for hypoglycemia, study staff will remind participants to have fast-acting carbohydrate available should they develop hypoglycemia during a meeting session (either FREE or attention control group). During the course of this study, subjects will have an additional measure of glucose through the RT-CGM; however, they will be instructed not to rely on the RT-CGM for blood glucose levels for treatment and to verify glucose readings with a capillary measure. Additionally, subjects will be under the care of an endocrinologist. This is an inclusionary criterion for study participation, which will ensure that subjects have resources to assist them with their diabetes care.

6. Completing self-report measures on FOH, self-management, anxiety, depressive mood, diabetes distress, and quality of life may cause subjects some emotional distress. The risk is minimal. In our previous studies with the same population, no subjects reported emotional distress with these measures. However, study staff will be aware of the possibility and address any concerns that are voiced.

7. Should a subject require medical or other professional intervention due to an adverse event or illness, treatment may be obtained through the UIC Medical Center, the subject's regular doctor, or the treatment center or clinic of their choice. Subjects will be provided contact information for the PI should they want to talk to her about their illness or injury.

Procedures for identifying, reviewing, and reporting adverse events and unanticipated problems to the IRB and NIH.

Throughout the study, Dr. Martyn-Nemeth will monitor the participants for adverse events (AEs). Dr. Martyn-Nemeth and study staff will review AEs individually in real time and in aggregate on a monthly basis and consult with co-investigators as needed. Dr. Martyn-Nemeth will review serious adverse events (SAEs) in real time. Dr. Martyn-Nemeth will ensure that all protocol deviations, AEs, and SAEs are reported to the UIC IRB according to applicable IRB requirements, and corrective actions will be taken as deemed necessary by the IRB. Events determined by the PI to be unanticipated problems that are SAEs involving risks to subjects or others will be reported by the PI to the UIC IRB per IRB policy or within 1 week. Unanticipated problems that are determined by the PI to be not serious will be reported per IRB policy or within 2 weeks.

Unanticipated problems will be reported to appropriate UIC institutional officials and NIH as required by the reporting procedures of each institution. Dr. Martyn-Nemeth will provide a report to the NIH of (1) unanticipated problems or unexpected SAEs that may be related to the study protocol, (2) IRB-approved revisions to the study protocol that indicate a change in risk for participants, (3) a summary of recommendations made by the DSMB or other monitoring entity, (4) the action plan for response, and (5) notice of any actions taken by the IRB or regulatory bodies regarding the research and any responses to those actions.

All study staff will be informed by Dr. Martyn-Nemeth about AEs. If any protocol changes are needed, the PI will submit a modification request to the UIC IRB. Protocol changes will not be implemented prior to IRB approval unless necessary to eliminate apparent immediate hazards to the research subjects. In such a case, the IRB will be promptly informed of the change following implementation, according to IRB policy.

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APPENDIX: Trial Protocol

P1. Outline of FREE Intervention

The FREE intervention will consist of eight weekly individual one-hour sessions with a licensed clinical psychologist and will target incorrect beliefs about hypoglycemia, hypervigilance to symptoms, fear of symptoms, and maladaptive behavioral responses in response to glucose levels. As is typical in CBT interventions, each session will include a "homework assignment" for the participant to practice skills outside of the session. The RT-CGM site will be changed weekly. An outline of the session content is provided below.

Week 1: Review of program goals, which are to reduce fear of hypoglycemia while improving awareness of blood glucose cues. Discuss hypoglycemia and its causes, including diet, exercise, stress, and insulin. Discuss fear as a normal human emotion to the perception of a threat. Identify how fear of hypoglycemia affects glucose control. Discuss safety and avoidance behaviors. Review the RT-CGM and fear diary instructions for use.

Homework: Record fear levels and hypoglycemia events for the week. Get comfortable using RT-CGM for feedback.

Week 2: Identify blood glucose cues. Present the cognitive behavioral model, including the role of thoughts, behaviors, and emotions. Discuss how memories of past hypoglycemic events influence diabetes care.

Homework: Record daily emotions and emotions associated with hypoglycemia events. Monitor RT-CGM glucose levels. Remember to verify any RT-CGM sugars that are out-of-range with a capillary blood glucose. Also check capillary blood glucose anytime you think/feel your blood glucose may be out-of-range regardless of the RT-CGM reading.

Week 3: Teach cognitive restructuring, including exploring realistic probabilities of hypoglycemic events, and identifying catastrophic thought patterns. Identify fear reduction strategies employed (safety behaviors) and examine behavioral responses to probable hypoglycemia. Introduce progressive relaxation.

Homework: Describe safety behaviors employed over the week. Use RT-CGM readings as a cue to blood glucose awareness. Practice relaxation and cognitive restructuring.

Week 4: Introduce exposure and the purpose of exposure. Discuss own safe ranges for blood glucose. Develop fear hierarchy. Begin graded exposure to items on hierarchy by starting with items low on the list and working up the list. Review RT-CGM data.

Homework: Practice exposure. Practice relaxation.

Week 5: Review previous week's exposure practice. Troubleshoot any difficulties. Continue graded exposure to items on hierarchy. Review coping mechanisms, including relaxation and cognitive restructuring.

Homework: Practice exposure. Practice relaxation.

Week 6: Review previous week's exposure practice. Troubleshoot any difficulties. Continue graded exposure to items on hierarchy while reinforcing appropriate use of coping. Review RT-CGM data.

Homework: Practice exposure. Practice relaxation.

Week 7: Review previous week's exposure practice. Troubleshoot any difficulties. Continue graded exposure to items on hierarchy.

Homework: Practice exposure. Practice relaxation.

Week 8: Review previous week's exposure practice. Review techniques learned and develop a plan to maintain gains.

P2. Outline of Attention Control: Diabetes Self-Management Program

The attention control condition will consist of eight weekly one-hour sessions. Sessions will be individual diabetes self-management education (DSME) sessions led by a CDE®, based on the National Standards for Diabetes Self-Management Education. To be similar in structure and time as the FREE intervention group, each session will include a homework assignment for the participant to complete outside of the session, which will be reviewed the following week. The RT-CGM site will be changed weekly. An outline of the session content is provided below.

Week 1: Introduction to diabetes self-management education program. Living with T1DM, current self-management challenges, and understanding the disease process.

Homework: Complete diabetes care self-assessments.

Week 2: Using medications safely for therapeutic effectiveness. Insulin management and care. Challenges with pump and MDI use. Blood glucose awareness and monitoring. Assessment and treatment of hypo- and hyperglycemia.

Homework: Blood glucose monitoring and glucose awareness self-assessments.

Week 3: Healthy eating: Incorporating principles of a healthy diet into lifestyle. Review of major nutrients. Discuss how eating patterns and styles affect health and diabetes self-management. Diabetes and alcohol.

Homework: Self-assessment of eating style.

Week 4: Being active: Incorporating physical activity into lifestyle. Barriers encountered and strategies to meet activity goals. Blood glucose management with activity. Principles of healthy activity.

Homework: Self-assessment of activity patterns and preferences.

Week 5: Healthy sleep: Sleep patterns, challenges, and strategies for success. Sleep hygiene principles.

Homework: Self-assessment of sleep quality.

Week 6: Self-management in the workplace. Balancing work stress; leisure/work balance. Stress management strategies. Workplace disclosure.

Homework: Self-assessment of workplace stressors.

Week 7: Psychosocial concerns: Emotions and diabetes. Navigating relationships. Disclosure/non-disclosure. Setting limits. Developing personal success strategies.

Homework: Self-assessment of stressors and coping style.

Week 8: Preventing, detecting, and treating complications.

Summary and Review: Plans to maintain behavior change.

P3. FREE Diary

Fear of Hypoglycemia Level

Hypoglycemia Events

Morning

Time _____

Low Fear High Fear
1 2 3 4 5 6 7 8 9

Notes: _____

_____

Time _____ Capillary blood glucose _____

Treatment:

_____

Time _____ Capillary blood glucose _____

Mid-day

Time _____

Low Fear High Fear
1 2 3 4 5 6 7 8 9

Notes: _____

_____

Treatment:

_____

Time_____ Capillary blood glucose: _____

Treatment:

_____

Evening

Time _____

Low Fear High Fear
1 2 3 4 5 6 7 8 9

Notes:_____

Time: Capillary blood glucose: _____

Treatment:

Directions: On the left side, circle one number your fear of hypoglycemia at the beginning of your day. Repeat at mid-day and evening but at these times, circle your fear level since the last report. Try to use the range, not just 1, 5, or 9. There is no right answer. Only you know how you feel each

time. On the right side, enter the time and capillary blood glucose level for any hypoglycemic events that occur each time and the treatment. If no hypoglycemic events occur, enter zero for that day.

P4. FREE PROGRAM EVALUATION

We value your feedback! Circle one number for each item listed below with *1* being most helpful and *7* least helpful. There is a space for comments at the end. Thank you!

	Not Helpful						Very Helpful
CONTENT							
Learning signs of anxiety & how it affects diabetes	1	2	3	4	5	6	7
Learning to recognize how memories influence thoughts	1	2	3	4	5	6	7
Learning to recognize emotions linked to hypoglycemia events	1	2	3	4	5	6	7
Learning fear reduction strategies	1	2	3	4	5	6	7
Using safety behaviors	1	2	3	4	5	6	7
Using healthy coping behaviors	1	2	3	4	5	6	7
EXERCISES							
Relaxation exercises	1	2	3	4	5	6	7
Identifying most unhelpful thoughts	1	2	3	4	5	6	7
Developing a fear hierarchy	1	2	3	4	5	6	7
Setting personal goals	1	2	3	4	5	6	7
Homework assignments	1	2	3	4	5	6	7
Wearing a RT-CGM	1	2	3	4	5	6	7
Keeping a daily log	1	2	3	4	5	6	7

Go on to the next page . . . .

FREE PROGRAM EVALUATION

	Not Helpful						Very Helpful
ENVIRONMENT							
Meeting location	1	2	3	4	5	6	7
Meeting time	1	2	3	4	5	6	7
Meeting room	1	2	3	4	5	6	7
FORMAT							
Initial orientation meeting	1	2	3	4	5	6	7
Individual meeting sessions	1	2	3	4	5	6	7
Length of each weekly session	1	2	3	4	5	6	7
Length of program	1	2	3	4	5	6	7

ADDITIONAL COMMENTS (use back side of paper if necessary):

Thank you for your feedback!

OPEN-ENDED INTERVIEW QUESTIONS:

1. Did you feel that the program was helpful to you?

   If so, in what way?

2. What were the program strengths?

3. What suggestions do you have for program improvement?