Overcoming Barriers and Obstacles to Adopting Diabetes Devices (ONBOARD) Trial

Study Protocol and Statistical Analysis Plan

NCT04672655

November 11, 2020

ONBOARD: Overcoming Barriers and Obstacles to Adopting Diabetes Devices
Version 1
November 2020

CHAPTER 1: INTRODUCTION

1.1. Purpose

The primary objective of this randomized controlled trial is to examine the impact of a behavioral support intervention for adults with type 1 diabetes (T1D) who are starting on continuous glucose monitoring (CGM). This trial compares adults with T1D who are starting on CGM with behavioral supports (the intervention group) versus those who are starting on CGM without behavioral supports (the control group). We will examine group differences over a 3-month period on two sets of outcomes. The first set of outcomes includes glycemic variables (e.g. hemoglobin A1c, time in range). In this set of outcomes, A1c is the identified primary endpoint. The second set of outcomes includes psychosocial variables (e.g. diabetes distress, worry about hypoglycemia, technology attitudes), with diabetes distress as the primary endpoint. After the initial comparison of intervention to control across the first 3 months after starting CGM, we will conduct a longitudinal follow-up of glycemic and psychosocial outcomes at 6 and 12 months.

1.2. Background

1.2.1. Type 1 Diabetes (T1D) is a burdensome chronic disease; many adults with T1D do not meet treatment targets. The Centers for Disease Control and JDRF data estimate that there are over 1 million adults in the US with T1D (1, 2); 15,000 adults are newly diagnosed with T1D annually and by 2050 4.4 million adults in the US are expected to have T1D (1). T1D requires constant attention to glucose levels, food intake and physical activity, and insulin dosing decisions. Giving too much or too little insulin could result in hypo- or hyperglycemia, both of which carry risks of developing long-term complications. *National data show that the majority of adults do not meet ADA's recommended glycemic target* of A1c<7.0% (86% of adults 18-25; 70% of adults over 25) (5). Adults with T1D are well-positioned to benefit from behavioral interventions that are tailored for their unique needs and integrated into clinical care.

1.2.2. Existing and emerging diabetes technologies can dramatically improve health and reduce burden, but adoption rates are low. Diabetes technology offers major advances in diabetes management that reduce self-management burden and improve health outcomes and quality of life for individuals with T1D (6-8). These devices include continuous glucose monitoring (CGM) systems and insulin pumps. CGM technology provides in-the-moment information about glucose levels, including direction and speed of change. CGM reduces management burden by reducing the need for frequent finger sticks. CGM has been shown to be cost-effective (9) and to help adults improve both glycemic control and time spent in target glucose range without increasing risk of hypoglycemic episodes or diabetic ketoacidosis (10-12). Furthermore, improvements in CGM accuracy have enabled the crucial next step toward automating diabetes management with closed loop systems. Closed loop systems have shown the ability to reduce hypoglycemia and glucose variability and increase time in range (16-20). In addition, these systems decrease the mental burden of living with T1D (21-23). *To experience the benefits of current and future diabetes technologies adults with T1D must be willing to wear and maintain a CGM and insulin pump over time.* We know that currently, more than half (~62%) of individuals with T1D use insulin pumps in the US (5), while only 14% of adults with T1D currently use CGM. Further, a concerning proportion of adults (27%) quit CGM within the first year due to the daily burden of using the device (24). *Providing adults with T1D with the resources and tools to work through modifiable barriers could lead to continued CGM use and increased readiness for closed loop.*

Table 1. ADA 2018 Recommendations for CGM

Current recommendation	State of the science
(**CGM)…is a useful tool to lower A1C in adults with T1D**.	**A - Strong evidence**
Robust diabetes education, training, support are required for optimal implementation and ongoing use.	**E- Expert consensus or clinical experience** (clinical trials needed) (ADA, 2018)

1.2.3. There is no official standard of care for CGM initiation. Table 1 presents CGM recommendations from ADA's 2018 Standards of Medical Care in Diabetes (42). ADA recommends that adults receive robust education, training, and support for CGM use (42); this recommendation comes from expert consensus and clinical experience. There is a need to develop high-quality, evidence-based behavioral interventions to provide recommended training and support. *If adults with T1D receive comprehensive education and support alongside CGM initiation, they may be more likely to use the devices and to experience short- and long-term health and quality of life benefits.* Given that CGM is becoming part of "usual care" for

people with T1D and is a component of closed loop systems, the next key step is to test interventions that provide additional resources and support for CGM uptake versus CGM alone.

1.2.4. The need for guided diabetes device 'onboarding'. To address the need for increased support for initiating diabetes devices, the overall objective of the proposed study is to provide adults with T1D with a tailored behavioral intervention using evidence-based strategies and tools to enable them to maximize benefit from CGM and increase readiness for closed-loop technology. According to the widely used Technology Acceptance Model (44), factors such as the technology's perceived usefulness and ease of use influence likelihood of using and benefitting from the technology. Therefore, our ONBOARD (*Overcoming Barriers & Obstacles to Adopting Diabetes Devices*) intervention package will prepare adults with T1D to use and benefit from CGM by 1) setting realistic expectations for the technology; 2) providing resources and problem-solving skills to work through barriers; 3) helping to highlight benefits of the technology; and 4) planning for potential issues that may arise in the future to prevent CGM discontinuation. This study addresses a major gap in the literature on what guidance and support adults with T1D need, beyond education, to benefit from advances in diabetes devices and to increase their readiness to adopt new diabetes technologies.

1.3. Preliminary Studies

The preliminary work described here focused on identifying modifiable barriers to diabetes device use, pinpointing targets for intervention, and highlighting links between intervention targets and important diabetes outcomes.

1.3.1. We found that non-users of CGM are younger, have higher A1c values, and more negative attitudes toward diabetes technology compared to CGM-users. Through an online survey of participants in the T1D Exchange Clinic Network, we collected data from 1,503 adults with T1D regarding their current device use and major barriers to using diabetes devices (54.7% women; mean age=35.3±14.8 years; mean diabetes duration=20.4±12.5 years; 70% using insulin pumps; 37% using CGM). On average, non-users of CGM were 5 years younger; had higher A1c values (.37% higher mean A1c); and reported more barriers to device use compared to CGM users (22).

Table 1. Top Barriers to Device Use (*n*=1503)

Barrier	% Yes
Hassle of wearing devices all of the time	47.3
Do not like having diabetes devices on my body	34.8
Do not like how diabetes devices look on my body	26
Nervous that the device might not work	20
Do not want to take more time from my day to manage diabetes	17.5
Nervous to rely on technology	17
Worries about what others will think about you	10.5
I do not like diabetes devices because people notice them and ask questions about them	10.4

1.3.2. Physical, data, social, and trust barriers interfere with CGM use. In the same survey, barriers to using diabetes devices (CGM and insulin pump) fell into several categories: 1) hassle/ burden of wearing devices on the body; 2) nervous to rely on the technology; 3) time burden of managing diabetes; and 4) devices drawing unwanted attention from others (Table 1). We conducted a follow-up survey of adults who had discontinued using diabetes devices to learn their reasons for discontinuation (Table 2). Rates of CGM discontinuation are considerably higher than pump discontinuation (5). After cost, issues with alarms, accuracy, discomfort and pain led to CGM discontinuation. *Our preliminary data highlight why many adults with T1D feel the negatives outweigh positives of CGM and stop using this beneficial technology. Survey data strongly support the ADA recommendation for robust support tailored to the commonly endorsed barriers to using CGM to promote increased uptake and sustained use of CGM and, eventually, closed loop systems.*

Table 2. "Why did you stop using your CGM?" (n=249)

	% Yes
Cost of supplies	35.3
There were too many alarms	32.1
It wasn't accurate	30.1
Don't like diabetes devices on my body	29.7
Wearing a CGM took too much time and effort	28.9
It was uncomfortable or painful	28.1
Too hard to get it to work right	22.1
Cost of device	21.7
Made it hard for me to sleep	20.1
Didn't trust it	18.1

1.3.3. Closed loop systems depend on CGM accuracy to gain user trust. Closed loop systems require wearing a CGM and an insulin pump and partially automate insulin delivery. Given the novelty of closed loop systems, we aimed to understand major factors that could influence willingness to trust and accept the potential risks of closed loop. I applied my expertise in qualitative research methods to analyze focus groups with participants in a closed loop system trial (n=32). Results showed that user expectations and trust shaped overall satisfaction with the system and likelihood of continued use. Specifically, overly high/unrealistic expectations contributed to increased negative evaluations of the system (3). Issues with CGM accuracy and intrusiveness of alerts hurt

user trust and decreased the likelihood that someone would opt to continue using the system (24). Relatedly, our extensive interviews with adults with T1D (n=113) highlighted that CGM accuracy was a major priority when considering closed loop system adoption (45), since accuracy of CGM determines the system's ability to improve glycemic control. *Our results highlight additional potential barriers and intervention targets to promote adoption and sustained use of CGM, and to increase readiness for using closed loop systems. Results demonstrate the investigator's strong ability to conduct qualitative research related to T1D experience.*

1.3.4. Interventions with problem-solving, motivational interviewing, and social learning components can improve psychosocial and health outcomes in adolescents and adults with diabetes. Multicomponent interventions are advantageous because they capitalize on effective pieces of existing, evidence-based interventions (46, 47). Multicomponent interventions that include motivational interviewing, problem-solving, and cognitive behavioral therapy have demonstrated ability to improve A1c in T1D (48-50). Extensive evidence supports the benefit of problem-solving interventions for diabetes management (51-57). Motivational interviewing has also proven to be effective in promoting positive behavior change in diabetes management (58-60). Finally, successful programs to improve psychosocial and health outcomes often incorporate a social component, whether through group delivery (61), an online forum (63), or involvement of a peer coach (64-68). While these strategies can be beneficial, another powerful tool, informed by social learning theory (69), is to incorporate videos of first-person stories that model how individuals worked through relevant problems (70, 71). For example, YourWay, an Internet-based, social learning and problem-solving program, helped adolescents with T1D work through psychosocial barriers to diabetes self-management (63). Through digital storytelling, YourWay presented participants with first-person "stories" of diabetes problem-solving, which can help individuals develop problem-solving skills and self-efficacy through "vicarious learning" (72, 73).

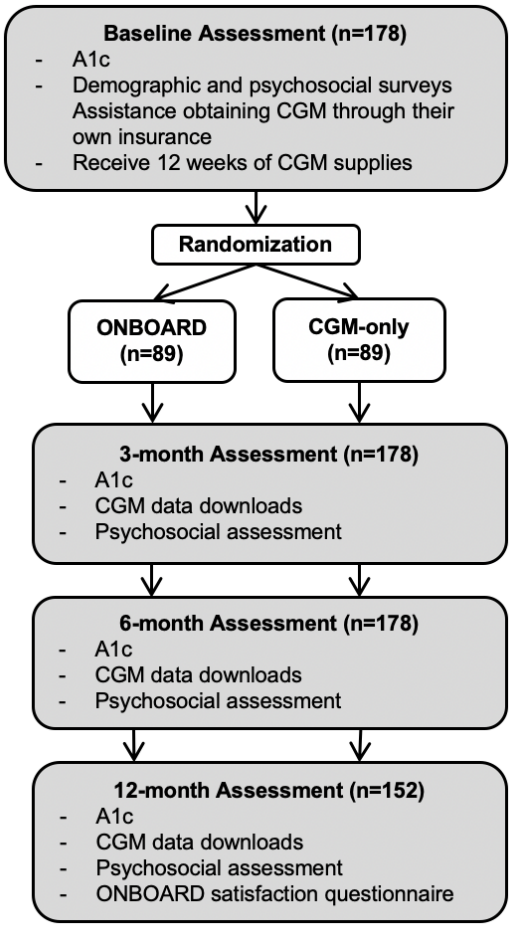
CHAPTER 2: STUDY PROTOCOL

2.1. Synopsis of study protocol

The primary objective of this randomized controlled trial is to examine the impact of a behavioral support intervention for adults with type 1 diabetes (T1D) who are starting on continuous glucose monitoring (CGM). This trial compares adults with T1D who are starting on CGM with behavioral supports (the intervention group) versus those who are starting on CGM without behavioral supports (the control group). We will examine group differences over a 3-month period on two sets of outcomes. The first set of outcomes includes glycemic variables (e.g. hemoglobin A1c, time in range). In this set of outcomes, A1c is the identified primary endpoint. The second set of outcomes includes psychosocial variables (e.g. diabetes distress, worry about hypoglycemia, technology attitudes), with diabetes distress as the primary endpoint. After the initial comparison of intervention to control across the first 3 months after starting CGM, we will conduct a longitudinal follow-up of glycemic and psychosocial outcomes at 6 and 12 months.

2.2. Study procedures

Participants will be recruited at Stanford University through a combination of in-clinic, in community locations and online through type 1 diabetes online communities. Eligible participants will be adults (ages 18-50) who have not been using CGM consistently (>5 days/week) for at least the past 6 months. Once identified in clinic or once someone has expressed interest in the study, study staff will approach potential participants to explain the study, determine eligibility, and obtain informed consent. All participants will complete their baseline visit remotely. This baseline visit will include 1) completing a hemoglobin A1c test kit that is mailed to them in advance; 2) completing a baseline assessment survey online via a secure site (REDCap) to obtain demographic and psychosocial data and 3) initiate use of CGM supplies. Participants will be given the choice of using Dexcom G6 or Libre 2 CGM. Participants will be mailed 12 weeks of CGM supplies of their choice and will receive initial standard CGM introduction and education from the study staff and will be provided with standard resources from the device manufacturer at this baseline visit. At baseline, participants will then be randomized. We will randomize at a 1:1 ratio, intervention to control. Those randomized to the intervention (ONBOARD) condition will schedule 4 60-minute sessions with study interventionist (every 2 weeks), with the first session scheduled for 2 weeks after CGM initiation. Sessions will be conducted via a secure, HIPAA-compliant, videoconferencing software (Zoom) and may be recorded to ensure consistency and quality of the intervention across participants and interventionists. Each participant will receive one unique Zoom link that they will use for all 4 of their study sessions. At the 3-, 6-, and 12-month time points, participants will be mailed A1c test kits for follow-up A1cs, and will complete a follow-up REDCap survey at these time points as well. The follow-up survey will assess psychosocial variables, technology satisfaction, and changes to demographic/medical information. Each follow-up survey is expected to take 30 minutes to complete. Of note, all study participants will



receive instruction on how to work with their insurance to obtain coverage for continuing to use CGM after the first 12 weeks of the study. At the 3-, 6-, and 12-month timepoints, CGM data downloads will be obtained.

2.3. Study groups

There are two groups in this study: intervention (ONBOARD) and control (CGM-only). All participants will receive 12 weeks of CGM supplies and will receive standardized education about getting started with CGM. A person trained in delivering education about CGM will deliver education about CGM use and will be present during a virtual meeting while participant is inserting first sensor during training. This individual will be available to assist with questions from participants. In addition, Dexcom and Abbott representatives are available to participants for technical questions or issues with the system, just like the access any CGM user has. All participants in both groups will be required to actively use CGM for 12 weeks. After that time period, they can continue or discontinue use of CGM. If they decide to continue, the study team will provide information on working with insurance and with their provider to obtain CGM for both study groups.

After randomization, participants in the intervention group will receive 4 one-on-one sessions of ONBOARD (OvercomiNg Barriers & Obstacles to Adopting Diabetes Devices). Sessions will be held every 2-3 weeks over the 12-week period when participants are using CGM provided by the study. ONBOARD is a multicomponent intervention to provide tailored support for CGM adoption. Session content and strategies are outlined in Table 3. Sessions target four primary topics. Each participant will receive content in the same order, but the program is designed to be flexible depending on individual barriers and concerns. Some participants may spend more time on certain topics than others. ONBOARD will approach CGM data interpretation with the goal of reducing 'data overload' and to empower participants to use data in a way that works for them. Setting alerts/alarms, understanding trend arrows, reviewing the data for patterns and trends, and identifying common reactions that may arise with this quantity of glucose data. Participants will first increase comfort with data quantity, change arrows, and alarms, and then will learn to examine data for patterns and trends. Study personnel will not directly suggest insulin dosing and may encourage participants to talk with their care team when relevant. ONBOARD sessions will be delivered individually to participants by a doctoral level

Table 3. ONBOARD Intervention Topic Content

Barrier addressed	*Topic name*	*Strategies used*	*Goals*
	Introduction	- Psychoeducation; rapport building	- *Provide rationale for ONBOARD* - *Introduce concepts from Technology Acceptance Model to discuss CGM pros and cons*
Physical	Wearing Diabetes Device(s)	- Experiential wear	- *Troubleshooting device placement* - *Provide education and examples of problem solving for common concerns and strategies for navigating them: appearance, insertion, skin irritation, discomfort, interference with daily activities* - *Provide resources for adhesive, skin prep, and adhesive removal*
Data	Managing CGM Data	- Education - Behavioral: optimizing alert thresholds - Cognitive: Identifying thoughts & feelings	- *Provide information on trend arrows* - *Review options for customizing alert thresholds* - *Identify common thoughts and feelings that may arise from receiving data (e.g. managing reactions to double arrows) and identify helpful thoughts* *Demonstrate how to view data on Clarity or LibreView*
Social	CGM and Social Situations	- Problem solving	- *Demonstrate problem solving common issues that arise with using and wearing diabetes devices around others (e.g. answering questions about devices, engaging with diabetes around others* - *Practice using problem-solving exercise in session*
Trust	Building Trust	- Psychoeducation - Social problem solving	- *Demonstrate how others have developed trust and what they do when trust in a device is broken (e.g. listening to body, using meter)*
	Wrapping Up	- Goal-setting - Motivational Interviewing	- *Reviewing perceived benefits of the technology as they relate to, or are weighed against, perceived issues.* - *Anticipate future barriers that may lead to CGM discontinuation to brainstorm possible alternative actions.*

psychologist with diabetes expertise. Each session will include relevant first-person digital stories from adults with T1D, recounting how they managed relevant CGM barriers. Sessions will be delivered via a HIPAA-compliant videoconference program.

2.4. Coordination of study procedures with clinical care

This study will not be directly connected to participants' clinical care. Participants will be encouraged to contact their care providers during the study to pursue initiating CGM use after study supplies run out and participants in the ONBOARD intervention will be provided education on how to advocate for getting the devices they need with their providers and with their insurance companies.

The study staff will have primary role of initiating CGM at the start of the study for all participants and providing training on insertion. Participants will also receive information from study staff on how to share their CGM data with their diabetes providers.

2.5. Study visits and assessments

All participants will attend a baseline study visit. Baseline is the date they complete their first assessment and begin using their CGM and will receive training from study staff on beginning to use CGM. After baseline, only participants randomized to ONBOARD will receive 4 additional study visits. Remaining assessments (A1c, CGM data downloads, and surveys) will be done via mail and electronically, respectively.

Study assessments for both groups will occur at baseline, 3 months, 6 months and 12 months post-baseline. We will conduct these assessments and obtain glucose data to examine changes over time in glycemic and psychosocial variables. Participants will receive a $25 gift card for each assessment they complete.

Assessment components are included in Table 4.

Table 4. Study Measures

Domain	Measure	Description	0 mos	3 mos	6 mos	12 mos
Demographic	History questionnaire	Medical, personal, device history	X			
	Demographic/medical update	Changes to baseline information		X	X	X
Psychosocial	Diabetes Distress Scale-T1D	28-item validated measure of T1D distress in adults	X	X	X	X
	Fear of Hypoglycemia - Worry	18-items; measure of fears related to severe low BG	X	X	X	X
	Hypoglycemic Confidence Scale	9 items; validated for adults with T1D	X	X	X	X
	Diabetes Self-Compassion Scale	19 items; validated for adults with T1D	X	X	X	X
	Patient Health Questionnaire-8	8 items; assesses depressive symptoms	X	X	X	X
	GAD-7	7 items; assesses anxiety symptoms	X	X	X	X
	Perceived Stress Scale	10 items; assesses stress and coping in past month	X	X	X	X
	World Health Organization-5	5 items; assesses emotional wellbeing	X	X	X	X
	Self Care Inventory-Revised	15 items; measure of a range of self-care activities	X	X	X	X
	Social Support Questionnaire	6 items; assesses availability of social support	X	X	X	X
	Diabetes Empowerment Scale-SF	8 items; assesses diabetes self-efficacy	X	X	X	X
	COVID-related impacts	Assesses general and diabetes-specific impacts of pandemic	X	X	X	X
Technology-specific	INSPIRE survey	Assesses closed loop attitudes	X			X
	Glucose Monitoring System Satisfaction Survey (GMSS-T1D)	15 items; validated measure of glucose monitoring device-related treatment satisfaction and quality of life	X	X	X	X
	Barriers to device use	19-item list of barriers	X	X	X	X
	A1c	Glycemic control	X	X	X	X

A1c and CGM data	% time in range; percent time in hypoglycemia and hyperglycemia; additional indices of variability including standard deviation	Glycemic control from CGM	X	X	X	X
	% time wearing CGM	Data from CGM	X	X	X	X
Satisfaction	Satisfaction survey (for ONBOARD participants only)			X		

2.6. Study population

The participant population is adults with type 1 diabetes ages 18-50. In order to have 76 participants per arm (152 total) we will enroll up to 178 adults with T1D and then randomize them to either the intervention (ONBOARD, n=89) or control group (CGM-only, n=89).

2.6.1. Eligibility criteria

To be eligible for the study, an adult must meet the following criteria:

1. Clinical diagnosis of type 1 diabetes
2. Age between 18 and 50 years at time of screening
3. Comprehension of written and spoken English
4. Lack of consistent continuous glucose monitoring use (>5 days/week) for past 6 months
5. No severe medical conditions, which in the opinion of the investigators are likely to hinder participation in this clinical trial

2.6.2. Exclusion criteria

The presence of any of the following is an exclusion for the study:

1. Subject has a medical disorder that in the judgment of the investigator will interfere with completion of any aspect of the protocol (e.g. pregnancy, kidney disease, skin condition that may hinder sensor application).
2. Subject has a neurologic disorder that in the judgment of the investigator will affect completion of the protocol.

2.7. Data analysis plan

Our team has extensive experience in the use of web-based assessment, data management and data anlysis. Quantitative data will be entered into an online encrypted, HIPAA-compliant data management system, REDCap, with secure access for unique study IDs assigned to each participant. REDCap survey data is then ready for download by study staff and will be imported into SPSS for data cleaning and analysis. CGM data will be downloaded via Dexcom Clarity and LibreView which create a CSV file for transfer to REDCap and data analysis programs.

Demographic, medical, psychosocial variables, and some outcome measures are surveys and multi-item scales that participants will answer in REDCap. Psychometric properties of scales will be assessed before proceeding to investigate the proposed aims. These psychometric properties include item-total correlations and Cronbach's α to assess reliability. Total scores and subscale scores, when available, will be calculated and used for statistical analyses. Descriptive statistics will calculate frequencies, means and standard deviations for study variables. Independent samples t-tests and χ^2 analyses will assess potential differences between groups at baseline in demographic, psychosocial and diabetes variables. Analyses for Hypotheses 1&2 will follow the intention-to-treat principle.

To test Hypotheses 1&2, we will first conduct a treatment group comparison (ONBOARD vs. CGM-only) of the change in A1c, the primary outcome, from baseline to 3, 6, and 12 months. Specifically, we will use linear mixed models to model changes in A1c as a function of time, intervention assignment, and group-by-time interaction. These models will include a subject-specific random effect to account for the correlation of

outcomes over time within a subject. We will examine change from baseline for each outcome as the dependent variable. We will begin by fitting models with minimum covariates prior to considering additional covariates. Similar models will be used to examine secondary outcomes of time in range, days of CGM wear (Hypothesis 1), diabetes distress, and perceived CGM benefit (Hypothesis 2). We will reference information criteria (e.g., Akaike's) to inform model selection decisions. Beyond testing the groups-by-time interaction term, custom contrasts will assess group differences at each time point. Exploratory analyses will examine differences between subgroups over time after primary, intent-to-treat analyses are completed. Additional exploratory analyses will examine patient-level predictors of CGM wear (e.g. age, gender, diabetes duration). For the CGM-continuer subgroup, we will conduct exploratory longitudinal analyses using CGM data to look at changes in time in range. We will adjust for multiple comparisons by using the Benjamini-Hochberg procedure and a false discovery rate of 0.05 (78). Analyses will initially be conducted without imputation for missing values, using the missing-at-random approach (79) and then multiple imputation will be used to supply values for missing data. We will conduct sensitivity analysis by multiple imputation to compare the effects.

Enrolling and randomizing a sample of 178 adults with T1D (1:1 randomization; 89 per arm) will be sufficient to investigate the hypotheses in this study. Based on our previous related work, we estimate 15% attrition, yielding a final sample size of 76 participants per arm (152 total). This target sample size is based on the following pieces of data. First, effect sizes comparing CGM to non-use in adults with T1D are in the moderate (d=.40-.50) range (8, 75, 76), showing improvements in A1c and time in range during CGM use. Further, standardized effects of diabetes behavioral interventions for adults are in the small to moderate range with .35 to .40 SD unit differences (43, 77). In the proposed study, we hypothesize group differences in A1c of a similar or greater magnitude will be driven by a combination of greater sustained use of CGM over the 12-month follow-up period in the ONBOARD program and added utility and benefits from use resulting from the ONBOARD program. Sample size estimates for comparison of ONBOARD and CGM-only are based on intent-to-treat analyses, alpha=.05, 80% power, autocorrelation of .50 (7), a repeated measures ANOVA on change between the 2 groups from baseline to 3, 6 and 12 months. A sample of 89 participants assigned to ONBOARD and 89 to CGM-only will provide power to exceed 0.80 for the primary outcome of A1c for moderate effects of d=.35 or greater. The sample size allows detectable mean differences in the magnitude of A1c≥0.5% (conservatively assuming 1.2 SD; recent registry data suggests our SD will be closer to 1.0). A 0.5% A1c is the minimum clinically significant difference regarded by physicians and stakeholders. Treatment guidelines and algorithms from ADA/EASD and UK National Institute for Clinical Excellence have recommended evaluating new treatment regimens by whether A1c is lowered by 0.5% or more**.** Between clinic and wider T1D community, we will have ample ability to reach our recruitment goal.

2.8. Expected duration of study participation

Duration of study participation is expected to be 1 year.

CHAPTER 3: ADVERSE EVENT REPORTING AND SAFETY MONITORING

3.1. Overview of Safety Monitoring

Safety monitoring will be performed by Drs. Tanenbaum (PI) and Hood (Mentor) on an ongoing basis. Safety data will be gathered and reviewed periodically by the study investigators. Reviews will occur every two months during the course of the trial and the study staff will examine occurrence of adverse events and whether participants are satisfied with their participation. The PI will be responsible for evaluating each unanticipated problem and determining whether it affects the risk/benefit ratio of the study and whether modifications to the protocol and consent forms are required. The PI will be responsible for reporting unexpected problematic events involving any aspect of the study to the NIH and local IRB per institutional guidelines. Unanticipated problems to be assessed include adverse events, deviations from the study protocol, problems with informed consent, and confidentiality violations. The PI will report unanticipated problems to the NIH and IRB within 3 business days of their occurrence. The local IRB will review such cases and determine what actions must be taken to address or resolve the situation. As this study employs an FDA-approved device and the team is providing additional support, it was determined that there is no need for a Data Safety and Monitoring Board (DSMB).

3.2. Definition of an Adverse Event

Reportable adverse events in this study include any untoward medical occurrence that meets criteria for a serious adverse event or any medical occurrence (expected or unexpected) in a study participant that is study-related.

Hypoglycemic events are recorded as adverse events if the event required assistance of another person due to altered consciousness and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the subject was impaired cognitively to the point that he/she was unable to treat his or herself, was unable to verbalize his or her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

Hyperglycemic events are recorded as adverse events if the event involved diabetic ketoacidosis (DKA), as defined by the DCCT, and had all of the following:

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Serum ketones > 1.0 mmol/L or large/moderate urine ketones;
- Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15; and
- Treatment provided in a health care facility

Skin irritation from sensor wear will be recorded in specific sections of the case report forms. An adverse event form is only completed if skin irritation is severe.

Distress or discomfort experienced by participants as they complete surveys is not considered an adverse event. However, we have trained psychologists on staff who will be available to address any distress or discomfort and initiate referrals if requested.

3.2. Recording of adverse events

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

The investigator will elicit reports of adverse events from the participant at each visit and phone call and complete all adverse event forms online. The study investigator will assess whether an adverse event is related or unrelated to the study by determining if there is a reasonable possibility that the adverse event may have been caused by the study procedures.

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

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

3.3. Reporting serious or unexpected device-related adverse events

A serious adverse event is any untoward occurrence that:

- Results in death
- Is life-threatening; (a non life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in significant disability/incapacity
- Is a congenital anomaly/birth defect

3.4. Unanticipated adverse device event

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

Serious or unexpected adverse events must be reported to the coordinating center immediately via completion of the online serious adverse event form.

The principal investigator will notify all participating investigators of any adverse device event that is both serious and unexpected. Notification will be made within 10 days after the PI becomes aware of the event.

The PI is responsible for informing their IRB of serious study-related adverse events and abiding by any other reporting requirements specific to their IRB.

3.5. Potential risks and side effects

Loss of confidentiality is a potential risk and is protected by the safeguards discussed above. Hypoglycemia, hyperglycemia, and ketone formation are always a risk in subjects with type 1 diabetes. Subjects will be closely monitored for this. When wearing CGM sensors there are risks of skin rashes, allergic reactions to tape, infections at the insertion site, or small pieces of the sensor breaking off or remaining under the skin. These risks will be monitored, but study staff will not oversee insertions, tracking of sensor information, and other diabetes device information.

3.5.1. Hypoglycemia

There is always a risk of hypoglycemia for patients with insulin-dependent diabetes. The frequency of hypoglycemia during this study is not expected to be greater than the risk incurred during daily living. If severe hypoglycemia occurs, it is readily treated with either oral glucose or glucagon injection. To minimize the risk of hypoglycemia due to "stacking" insulin doses, study participants will be instructed in their initial education not to take rapid acting insulin injections to correct hyperglycemia more than once every 3 hours. The low alert level

will be set at 75 mg/dL for all study participants at the outset of the study; however, participants can change these alerts if they would like.

3.5.2. Hyperglycemia

Hyperglycemia and ketonemia can occur if insulin delivery is attenuated or suspended for an extended period. This is a risk of type 1 diabetes that is not expected to be greater during the study period than it is during daily living. If severe hyperglycemia occurs, participants will be advised to treat with insulin therapy or to seek medical attention from their diabetes care team.

3.5.3. Lancing risks

Finger lancing is part of the usual care for people with diabetes and should not be a significant contributor to risks in this study. A small drop of blood will be obtained by finger stick to measure blood glucose and HbA1c. This is a standard method to obtain blood for routine hospital laboratory tests. Pain is common at the time of lancing. In about 1 in 10 cases, a small amount of bleeding under the skin will produce a bruise. A small scar may persist for several weeks. The risk of local infection is less than 1 in 1000.

3.5.4. Sensor site risks

There is a possibility of CGM sensor site risk. Whenever the skin is broken there is the possibility of an infection. CGM sensors are inserted under the skin. There may be bleeding where the sensor is inserted, which can cause bruising. CGM site infections occur very infrequently, but, if an infection was to occur, oral and/or topical antibiotics can be used. The risk of skin problems could be greater if a sensor is left in longer than recommended. On rare occasions, the sensor wire may break or detach from the sensor pod. There is a remote chance that sensor fragments could remain under the skin if the sensor breaks during normal wear. Subjects may also develop skin irritation or allergic reactions to the adhesives used to secure the CGM. If these reactions occur, different adhesives (such as with IV 3000, Tegaderm, etc.) will be tried, sites will be rotated frequently, and a mild topical steroid cream or other medication may be required. All participants will be carefully instructed about proper use of sensors.

3.5.5. Other potential risks

A potential source of risk in this study is the risk of gathering sensitive social, behavioral, and medical information. Data collection via the internet will be conducted through secure applications (REDCap). There are no known psychological risks to subjects completing self-report attitude and behavior rating scales. or participating in intervention sessions. However, the survey and intervention topics may contain items or questions that make the subjects feel uncomfortable in that they ask about their physical and psychological health and feelings/emotions. Subjects will be informed that any items on questionnaires or topics discussed in the intervention modules that produce these effects may be skipped or ignored. Subjects will also have the option of not participating in conversations or exercises in the interventions that cause them discomfort. They will also be free to withdraw at any time. All intervention modules will be carried out by a highly trained, doctorate level psychologist. There are no known risks to audio recording intervention sessions. All audio recorded information will remain confidential and will only be accessed by study team members. Use of BG meter downloads offers no increased risk over standard care. Data downloaded from CGM and the home glucose meter will be collected for the study as measures of diabetes self-management behaviors. Some people may be uncomfortable with the researchers' having such detailed information about their daily diabetes habits. The respondent burden for completion of all data collection at each assessment point is approximately 30-45 minutes total. All participants will be clearly informed of the time required for participation, the study duration, and the nature of the data to be collected. It is not anticipated that any of the data collection instruments will cause any adverse effects.

3.6. Adequacy of protection against risks

3.6.1 Informed Consent and Assent.

Interested participants may contact members of the study team directly or may be asked during a clinic visit if they wish to learn more about the study and be approached by a member of the study team. Either by phone or in person, a member of the study team will conduct screening for eligibility and enter this information into the secure server (REDCap). Eligible adults who are interested in participating will be provided with an informed consent form and HIPAA waiver, either electronically or hard copy. The study team member will then explain the purposes, benefits and risks of the project and offer them an opportunity to ask questions and/or decline participation. If still interested in participating, a full description of the nature of the study, the requirements of their participation in it, and the risks and benefits of the study will be explained to potential participants by the principal investigator or a trained research assistant. If an individual declines participation, the reasons for this will be documented and permission to record relevant demographic data from clinic records will be requested. This procedure allows for comparisons to be made between those who do and do not participate. If they consent to participate, they may do so either in written form or electronically.

All minorities will be encouraged to participate. Economically and educationally disadvantaged people, and participants who are employed at the clinical center (Stanford) will be eligible to enroll in this study if they meet all the study criteria. Subjects will be recruited from our clinics, through T1D community organizations, and through IRB approved patient recruitment lists. We will also use IRB approved recruitment materials to post the study on clinicaltrials.gov and to Stanford's research and department websites. Participants may self-select to join the research by responding to advertisements on social media. These posts will provide contact information for the research staff at each site. We will not interact with potential participants or enrolled participants through these media. We will actively work to prevent harm to all subjects enrolled in the study. We will work to avoid coercion by allowing equal enrollment opportunities for employees, as well as non-university affiliated subjects. We will ensure that all participants are informed that their participation is voluntary, that they will receive no ill treatment should they decide to not participate, and that they will receive no special advantages, aside from those mentioned in the "benefits" section of the consent, for participating in the study.

Participation will be voluntary. All participants must provide consent prior to inclusion in this research study. The primary investigator or a trained research coordinator will explain the nature, purpose, expected duration, and risks of study participation to each eligible participant. The primary investigator or trained research coordinator will also obtain consent and authorization for the release of personal information.

3.6.2. Protections Against Risk

All protocols and consent documents will be approved by Stanford's IRB. All members of the research team have and will maintain current training in the ethical conduct of research. Dr. Tanenbaum has completed rigorous training in the protection of human subjects, including CITI training, and graduate coursework at Yeshiva University. Research assistants and mentors/advisors working on the project will also complete standardized training in the protection of human subjects. The plan for protecting privacy and confidentiality recognizes that the protection of privacy in studies involving sensitive data is of utmost importance. We will attempt to do this in several ways. The PI or a trained RA will introduce the study to eligible participants and explain the purposes, benefits, and risks of the project to the subjects, and offer them an opportunity to ask questions and/or decline participation. The voluntary and confidential nature of the research, as well as limits to confidentiality, will be highlighted during informed consent process. Study participation will not interfere with clinical care and all patients have standard access to their treatment team on a routine (clinical care) and emergency basis. All responses to interview items will be given by subjects in private. Internet data collection will only occur through tools and resources that have acceptable security features. We will minimize all communications that involve names or other identifying information. All clinically relevant and study information will be kept in locked files in locked offices or password protected files.

Audio recordings of intervention sessions will be for quality control purposes only to ensure that sessions are delivered in a consistent way across participants. These audio recordings will be saved on a password-

protected secure server, will be reviewed by the PI, and will be deleted upon review. Information about subjects will not be accessible to any nonauthorized study personnel without the written consent of the subject. In all datasets we will use ID numbers only. A separate dataset linking names with ID numbers will be accessible only to authorized study personnel under the direction of the PI.

There will be an endocrinologist on call 24/7 for any severe events that should occur. Likewise, a licensed clinical psychologist is available for any concerns on the psychological side. Severe events are not anticipated but will be monitored. Study personnel are always available for questions. Hyperglycemia and ketone formation are always a risk in subjects with type 1 diabetes and subjects will be closely monitored for this. Subjects will have blood ketone meters provided through routine clinical care. Insulin can be given as a subcutaneous injection to treat hyperglycemia. Participants will be encouraged to contact their diabetes clinical care team and will also have access to phone numbers for a study physician. Participants in both groups will receive instruction about inserting and calibrating the sensor and will receive standardized introductory education about CGM. Participants are free to check blood glucose via fingerstick at any time and encouraged to do so if/when they notice a potential discrepancy between CGM and fingerstick values. A person trained in delivering education about CGM will deliver the education about CGM use and will assist with inserting the first sensor. This individual will be available to assist with questions from participants. In addition, Dexcom representatives are available to the participants for technical questions or issues with the system, just like the access any Dexcom user has.

3.7. Study stopping criteria

Individual subjects will be removed from the study for the following reasons: pregnancy, study-related adverse events (i.e. severe hypoglycemia, loss of consciousness, hypoglycemia related seizure, DKA related to study-related event requiring hospitalization), severe skin infection requiring systemic antibiotics, severe reaction to sensor tape, or other reasons that develop during the study that in the judgment of the investigator make it unadvisable for the subject to continue with the study

CHAPTER 4: MISCELLANEOUS CONSIDERATIONS

4.1. Potential Benefits

There are known benefits to people with T1D from using continuous glucose monitoring (CGM), including increased time in target range, decreased time in hypoglycemia, decreased A1c, and improvements in diabetes distress (7, 8, 75, 76). The potential benefit of this study is the provision of new knowledge about methods of optimizing the way that adults with T1D are introduced to CGM technology, with the long-term goal of informing methods for increasing device uptake and technology acceptance in the future in this population. Participants may find intervention sessions interesting and relevant. Collection of the psychosocial and clinical data may provide information for diabetes clinicians and other stakeholders to help optimize the way that new beneficial technology is introduced to their patients. The low risk of this minimally-invasive study appears to be far outweighed by the more compelling potential benefits.

4.2. Importance of the Knowledge to be Gained

Considering the relatively low uptake of CGM technology among adults with T1D and known benefits to using this technology, combined with ADA recommendations for robust training and support for CGM use, there is an urgent need to develop tailored, innovative interventions that patients can receive at the appropriate time to support uptake and prevent discontinuation of CGM. The knowledge gained from this study will lead to the development of a comprehensive behavioral recommendation to optimize CGM use in adults with T1D. This study will inform future, larger-scale studies that evaluate CGM training programs and promote ways of increasing benefit from the device and key problem-solving skills to work through hassles and barriers to device use.

4.3. Subject compensation

There will be no cost to the participants for taking part in this research study. Participants will receive $25 for the completion of each of the four assessments for up to $100 total. All participants will receive 12 weeks of CGM supplies free of charge.

4.4. Subject withdrawal

Participation in the study is voluntary and a subject may withdraw at any time. The investigator may withdraw a subject who is not complying with the protocol. For subjects who withdraw, their data will be used up until the time of withdrawal.

4.5. Confidentiality

For security and confidentiality purposes, subjects will be assigned an identifier that will be used instead of their name.

4.6. Level of risk

This research proposal is considered to have no more than minimal risk (e.g. blood draws, data collection, surveys, behavioral interventions, using FDA approved devices as recommended).

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