STUDY PROTOCOL

Social Behavioral Template

Informatics-Based Digital Intervention to Promote Safe Exercise in Middle-Aged Adults with Type 1 Diabetes and Other Absolute Insulin Deficiency Diabetes – A feasibility study

Protocol Number

2000035846

Protocol Version

August 14, 2024

Version #7

Clinical Trials Registration Number (if applicable)

NCT06098729

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Synopsis

Purpose

PRIMARY PROBLEM ADDRESSED

Current evidence-based type 1 diabetes mellitus (T1D) self-management interventions target glycemic control but ignore other modifiable health concerns prevalent in T1D such as hypertension and obesity. Exercise interventions could provide a novel solution if they could innovatively address the diabetes management and psychosocial challenges around exercise posed by T1D. These include especially keeping blood glucose in a safe range during and after exercise (i.e., glycemic stability), and overcoming the fear of hypoglycemia.

PRIMARY PURPOSE

Develop a data-driven exercise intervention for T1D and evaluate its feasibility, acceptability, and mathematical robustness.

SECONDARY PURPOSE

Determine mechanisms underlying the link between T1D-related barriers (glycemic stability, fear of hypoglycemia) and physical activity behavior.

Objectives

PRIMARY OBJECTIVES

1-1. Evaluate the intervention for feasibility.

1-2. Evaluate the intervention for acceptability (i.e., user satisfaction).

1-3. Evaluate the intervention app algorithm's accuracy to predict lapses in exercise behavior ahead of time.

SECONDARY OBJECTIVES

2-1. Examine whether recognized T1D-related physical activity barriers (fear of hypoglycemia, glycemic variation) predict momentary and long-term variation in motivation states for physical activity.

2-2. Examine whether motivation states for physical activity predict momentary and long-term variation in physical activity behavior change, adherence, and maintenance resulting from a T1D motivational physical activity intervention.

2-3. Qualitatively identify determinants and sequalae of motivation states for physical activity among adults with T1D.

Study Population

Adults 30-65 years old with T1D and sedentary lifestyle at baseline, because people with T1D experience unique barriers to exercise that must be addressed by intervention. The age range was chosen because those below it have significantly different needs regarding exercise (exercise dependence, desire to improve body image) and self-management (transitions in care, residence, and professional life), while those above it have significantly different needs regarding exercise including mobility issues and substantial modifications to exercise.

Number of Participants

APPROVED BY THE YALE UNIVERSITY IRB 8/14/2024

This is a pilot study with primary objectives to test feasibility and acceptability, for which a typical sample size is 10-40 participants[1]. Within this range we chose 24 participants to first ensure thematic saturation of interviews and second achieve adequate power for one of the secondary objectives. Further detail in section 7.1.

Study Design

Single group completing familiarization (2 weeks), intervention (4 weeks) and follow-up (2 weeks) with longitudinal quantitative observations (surveys, wearable biosensors) and a descriptive qualitative interview.

Study Duration

16 months (data collection) plus 4 months (data analysis). Each subject participates for 9 weeks counting the time to consent and mail supplies.

Outcome Variables

Primary Objective #1 (Feasibility):

*Participant use metrics (i.e., % completion of diary, % wear-time of biosensors, frequency of video usage, % received of text messages)

Primary Objective #2 (Acceptability):

*Likert-style survey of satisfaction with specific components of this intervention

*Interview themes

Primary Objective #3 (Mathematical robustness):

*Biosensor readings of blood glucose and exercise

Secondary Objective #1 (prediction of motivation states):

*Predictors: Biosensor readings (blood glucose, physical activity, sleep), surveys (fear of hypoglycemia)

*Dependent variable: Motivation states for physical activity

Secondary Objective #2 (prediction of physical activity):

*Predictor variable: Motivation states for physical activity

*Dependent variable: physical activity behavior

Secondary Objective #3 (qualitative): *Interview themes
Locations/Facilities Physical center for coordination: *YSM, Section of General Internal Medicine, 200 West Campus Drive Online locations: *OneDrive for data storage *REDCap for weekly study visit survey capture *Ilumivu for mobile survey capture *Qualtrics for mobile survey capture *GlucoseZone mobile app for intervention delivery and capture of wearable device data from Dexcom and Fitbit *InPen user dashboard for insulin injection data capture *Keto-Mojo researcher dashboard for capture of ketone data

Abbreviations

Abbreviation	Explanation
API	Application programing interface
BG	Blood Glucose
CGM	Continuous glucose monitor
CRAVE	Cravings for Rest and Volitional Energy Expenditure (CRAVE) survey of motivation states for physical activity
EP	Exercise physiologist
JDAT	Joint Data and Analytics Team
RA	Research Assistant
SCT	Social Cognitive Theory
T1D	Type 1 Diabetes
WANT	Wants and Aversions for Neuromuscular Tasks
YSM	Yale School of Medicine

Glossary of Terms

Glossary	Explanation
Cravings for Rest and Volitional Energy Expenditure (CRAVE) survey of motivation states for physical activity	Survey asking about momentary motivation to move or be still. Construct relates to motive states, affective valence (pleasure/displeasure), and arousal/activation.
Ecological momentary assessment	Repeated sampling of behaviors and experiences in real-time, which serves to a) minimize recall bias and b) capture the effect of real-world surroundings.
Just-in-time adaptive messaging	“An intervention that adapts the provision of support (e.g., the type, timing, intensity) “over time to an individual’s changing status and contexts with the goal to deliver support “at the moment and in the context that the person needs it most and is most likely to be receptive.”[2]

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Protocol Revision History

Version Date	Summary of Substantial Changes
7/20/23	First submission
7/24/23	Added HIC protocol number
11/6/23	More precise safety guidance, formal template for goal-setting, increased compensation, recruitment wording and methods, audio recording frequency and method, additional research site, survey question corrections,
12/5/23	Raised blood pressure exclusion criteria
1/16/24	Added requirement for PCP confirmation of eligibility, further clarified exclusion criteria with specific conditions, replaced exercise coach with exercise physiologist, added surveillance protocol for monitoring symptoms, added data and safety monitoring board (DSMB)

1 Background

1.1 Background

PRIMARY AIMS: EXERCISE SUPPORT

Exercise for type 1 diabetes (T1D) is an important area for intervention development.
Intensive diet and insulin self-management are required for people with T1D to mitigate snacking, physical activity, and mental stress-associated glycemic fluctuations. There are several modifiable cardiovascular risk factors including overweight (60%), hypertension (40%), dyslipidemia (60%), and inadequate physical activity (67%-82%)[3] exacerbating their already elevated risk of cardiovascular morbidity and mortality[4]. Existing T1D self-management interventions (psychoeducation[5-7], diabetes devices[8-12], digital platforms[13-18]) have improved achievement of glycemic targets, however none of the current interventions are effective for cardiovascular risk factors or lifestyle behaviors when measured with reliable instruments[19,20]. For instance, intensive insulin therapy in the Diabetes Control and Complications trial while decreasing HbA1c increased risk of developing obesity, and this weight gain correlated with lipid panel and blood pressure deteriorations[21,22]. Thus, T1D self-management interventions that address health targets beyond glycemic control are needed. Physical activity interventions can improve health outcomes (e.g., aerobic capacity, lipid profile)[23]. Unfortunately, most people with T1D do not regularly engage in physical activity[24,25] indicating a need for novel interventions.

For purposes of describing this study, T1D will also refer to other types of diabetes that present similarly from the standpoint of behavioral self-management considerations. These types are the others with absolute insulin deficiency: latent autoimmune diabetes of adulthood and diabetes secondary to pancreatitis.

Physical activity with T1D has been linked to glycemic destabilization and fear of hypoglycemia.
Lack of engagement in physical activity stems from the unique challenges of physical activity with T1D[26]. Physical activity with T1D can dysregulate blood glucose, leading to hypo- and/or hyperglycemia during and up to 24hr later due to consumption of energy, increased insulin sensitivity, release of counterregulatory hormones, and various combinations thereof. The direction and magnitude of these glycemic fluctuations vary according to type of physical activity, personal insulin sensitivity, insulin-on-board, and hormone concentrations[27]. There is also high interindividual variation in these responses due to factors not well understood[27,28]. Predicting these fluctuations to adjust diet and insulin is challenging.

When these fluctuations bring blood glucose into clinically unsafe ranges, symptoms can require halting of physical activity. As well, a context where these symptoms are likely (e.g., downward-trending blood glucose or high insulin-on-board) can preclude the start of physical activity. Furthermore, repeated exposure to these symptoms leads to *fear of hypoglycemia,* the most reported barrier to physical activity among people with T1D[29]. This fear can motivate people with T1D to avoid physical activity due to remembering past symptoms and anticipating future occurrence of symptoms.

This investigation does not address exercise for type 2 diabetes (T2D) which faces different barriers compared to T1D. There is less risk of hypoglycemia due to the nature of the medication treatment, and therefore less fear of hypoglycemia. Meanwhile there is greater associated stigma, since the disease has etiology rooted in modifiable lifestyle behaviors. In addition, obesity as a comorbidity is more common and more severe. Therefore there is greater relevance of obesity-related barriers such as joint pain, exercise equipment being too small, and weight stigma.

Knowledge and technology are available that could support exercise for T1D.
Patients and their providers are encouraged to follow consensus statement guidelines for monitoring blood glucose levels and adjusting diet and insulin before, during, and after exercise to limit safety hazards and optimize benefits[26]. In addition, continuous glucose monitoring (CGM) is a now widely used (30%)[30] technology among people with T1D that can support them to follow these exercise recommendations. First, by giving glucose trends rather than "snapshot" values, CGM helps the patient identify risk of exercise-induced hypo- or hyper-glycemia and adjust insulin and diet accordingly and mitigate fear of hypoglycemia. Second, CGM presents users with time-series feedback of their glucose levels, allowing them to infer whether the timing of behaviors such as exercise (e.g., morning vs. afternoon, after vs. before insulin bolus) contributes to achievement of the target range[31]. Patients with *type 2* diabetes have shown greater motivation to increase exercise when presented with feedback on the intersection of exercise and CGM data[32]. Third, patients using CGM report better confidence in glycemic control and motivation to more carefully consider lifestyle choices[33]. This combination of knowledge and technology holds great potential to help people with T1D overcome barriers to exercise. Yet, evidence-based interventions to translate CGM feedback into sustainable adherence to exercise-related behaviors are lacking[34].

Translating this Knowledge and Technology to Practice
Most CGM users regularly view the real-time display of current blood glucose values and trending direction but few use mobile medical applications to comprehensively view CGM data (17%)[30]. These metrics are discussed with providers at clinic appointments[34], but provider discussions often do not translate to daily self-management decisions by patients. *Studies working with people with T1D to develop and test how they could independently use in-depth CGM information to promote safe, consistent, and effective exercise represent an underexplored, promising area for intervention development.*

We propose to address the gap between the available relevant medical information and translation to successful exercise by people with T1D by applying the Information-Motivation-Behavioral Skills (IMBS) model (Figure 1)[35]. The IMBS model has been successfully applied to self-management interventions for T1D[36,37] and other chronic diseases[38,39] and explained variance in self-management outcomes[35,40,41]. In the present application, we propose to develop mobile tools that leverage the diabetes literature, CGM data, and informatics to derive the needed components of IMBS for exercise (information about exercise, motivational encouragement to exercise, and feedback on long-term exercise outcomes) and deliver it to people with T1D.

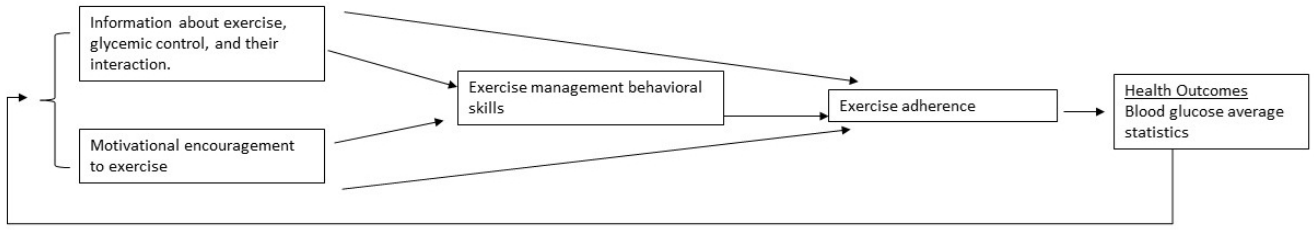


Figure 1. Information-motivation-behavioral skills (IMBS) model for exercise with type 1 diabetes.

SECONDARY AIMS: PSYCHOLOGICAL MECHANISMS FOR BEHAVIOR CHANGE

Rationale for determining real-time mechanisms underlying physical activity behavior and T1D-related barriers.
Fear of hypoglycemia has been measured as a "trait" (i.e., personality-specific) but in just one study as a "state" (i.e., situation-specific)[42]. Participants reported their state fear of having hypoglycemia over the next 12hr[42]. Responses had significant intraindividual variation and correlation with the related construct of blood glucose variability, indicating the need to further study fear of hypoglycemia as a state variable. Glycemic destabilization meanwhile is recognized to cause intense symptoms that acutely preclude physical activity, but no study has addressed the possible impact of more nuanced changes. E.g., downward-trending glucose could affect motivation to be active even if not projecting an excursion outside the clinically safe range.

Conceptual model of barriers to change.
Addressing this weakness, we and others have begun demonstrating that such affective (i.e., automatic) feeling states are the primary motivational factors driving humans to engage in physical activity[43-47]. Furthermore, these motivational factors have highly transient effects, exhibiting more state than trait qualities. Our team developed the Wants and Aversions for Neuromuscular Tasks (WANT) model to explain these relationships[48-52] based on Kavanaugh's model of affective motivation states determined by motive states, affective valence (pleasure/displeasure), and arousal/activation[53]. Past models by contrast have relied exclusively on social cognitive theory (SCT) constructs (i.e., self-efficacy, outcome expectations, sociocultural traits)[54-56]. Therefore, we must test not only SCT constructs but also WANT model real-time states to link T1D-related barriers to physical activity (Figure 2).

In sum, our secondary objectives will address underlying psychological mechanisms of the intervention. Knowledge of these mechanisms would improve tailoring. For example, if we find an individual's lack of motivation for physical activity is predicted by having below-average starting blood glucose, a below-average blood glucose reading an hour before opportunities for physical activity would trigger a reminder for additional carbohydrates. On the other hand, if we find the predictor is *fear* of hypoglycemia, the message would provide psychological support such as cognitive behavioral therapy for fear of hypoglycemia[57]. To generate the needed mechanistic knowledge, we have proposed the secondary aims of this study.

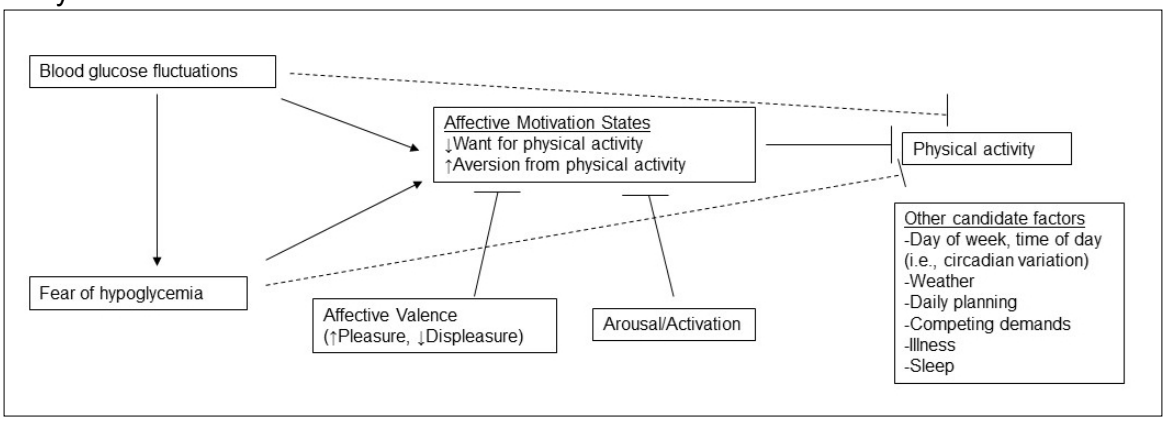


Figure 2. *Hypothesized conceptual model of factors influencing physical activity behavior change. Dotted lines indicate alternative hypothesis that T1D-related barriers directly impact physical activity without mediation by motivation states.*

1.2 Prior Experience (if applicable)

1.2.1. Pilot study of mobile exercise support for middle-aged adults with T1D[58,59] (Yale HIC #2000025992)

Working with an industry partner (GlucoseZone™, Fitscript[LLC], New Haven, CT) we customized a mobile digital application providing on-demand instructional exercise videos, access to a text-based exercise coach (Dr. Ash, an expert in T1D exercise), daily electronic self-monitoring diaries, and monthly reports of BG and exercise data discussed with Dr. Ash in a motivational enhancement therapy session. We evaluated its feasibility, safety, and acceptability in a pilot study. Participants were followed for 2 weeks of baseline and 10 weeks of application use and completed assessments by televideo that included wearable device setup, home-based clinical assessments, surveys, and interviews. Exercise was tracked by usage logs of the videos, electronic self-monitoring diaries for non-video guided exercise, and Apple Watch heart rate. All participants wore continuous glucose monitors (CGMs) and dispensed insulin by automated device (Bluetooth smartpen or continuous infusion pump); these data were captured by the "Share" feature of proprietary websites.

Recruitment. Using targeted Facebook news feed advertisements, word-of-mouth spread on Facebook and emails by role models with T1D, and approaching patients at clinical visits we recruited adults (N=20, 55% F, 42.3±15.0 years old, 20.5±15.3 years of T1D) with risk factors suggesting need for exercise intervention: body mass index 29.5±5.1 kg/m^2, median 3 (IQR 0,7) daily exercise minutes, and high avoidance of exercise due to fear of hypoglycemia (3.9±0.8 out of 5). News feed advertisements were more cost-effective than clinic recruitment ($41.11 vs $250.00 per eligible volunteer), captured higher-risk participants than role model word-of-mouth advertising (88% vs 25% obesity, 88% vs 25% elevated A1c), with faster yield than all other methods (8 participants enrolled over 20 days of advertising). Totally the eligibility rate was 20 / 47 = 43%.

Feasibility. Assessment completion was 85%-100% for all outcomes. Participants exercised with the app an average of 2.4±1.7 times per week and attended 35 / 40 monthly discussions (88%). Participants were queried on each non-exercise day about their barriers to exercise, and app malfunction was reported as a barrier <1% of the time. CGM data capture was 92.5±7.2% during baseline and 88.3±9.8% during weeks 9-10, with 95% of timepoints meeting literature standard ≥75%[60]. Accelerometer wear time at baseline met the literature standard of ≥10 hours per day on 6.7±0.6 out of 7 days, with all participants above literature standard of ≥4 days per week, and accelerometer data at follow-up are pending analysis. Participants completed a median of 98% (IQR 88%, 100%) of the 84 possible mobile diaries, with 90% meeting literature standard ≥70%.

Safety. There were no episodes of ketoacidosis or severe hypoglycemia. Episodes of mild hypoglycemia were recorded on mobile diaries and reviewed by Drs. Ash, Weinzimer, and Nally biweekly for safety concerns.

Acceptability. The overall intervention rating was moderate (3.4±0.9 out of 5). Participants rated the monthly feedback and coaching discussions most acceptable of all components (4.4±0.8 out of 5) but requested more frequent feedback and coaching sessions. The elements designed for more frequent touchpoints were rated somewhat lower (exercise videos 3.8±0.9, text-based exercise coach 3.2±0.8, daily diaries 2.2±0.6), ***indicating need for more automated and frequent support as planned in the current study***.

Preliminary Efficacy. Participants increased their exercise from a median of 4 (IQR 0, 41) to 64 (20, 129) minutes per week (*d*= 0.71). Body mass index increased (*d*= 0.57). Systolic blood pressure (*d*= -0.45), HbA1c (*d*= -0.42), and mean sensor BG (*d*= -0.41) tended to slightly decrease while total daily insulin (*d*= 0.09) was not different. In summary, the intervention was safe and showed promising efficacy, ***supporting virtually delivered exercise guidance if it can be delivered more intensively and sustainably.***

1.2.2. Virtual exercise for other age groups with T1D

We have one clinical exercise trial for youth with T1D completed (Yale HIC #1605017843)[61,62] and two in progress (#2000030105, #2000033736). The latter two occurred in virtual settings. These trials have had similarly high feasibility and acceptability as our adult study detailed above. None have had instances of severe hypoglycemia or diabetic ketoacidosis.

1.2.3. We can use data from momentary surveys and continuous biometric monitoring to predict physical activity among adults with T1D.

Using data from the above study with adults (c.f sect 1.2.1, 1,125 person-days), we developed a deep neural network to predict the successful completion of physical activity on each day (≥10min sustained) using 95 possible predictive features derived from the prior 7 days of state fear of hypoglycemia, sleep quality, blood glucose variation, and demographics. The method showed promise to predict physical activity for the adults with T1D (80% accuracy, 82% precision, 85% sensitivity, 74% specificity)[63]. The secondary objectives of the current study will use our newfound WANT model[48-52] to elucidate psychological mechanisms of T1D physical activity, thus increasing success of prediction. We have evidence from the general population that higher want for physical activity is associated with 8%-19% greater odds of current or intended physical activity[52].

1.2.4. Summary of the team's qualifications

PI **Dr. Ash** is an exercise physiologist (EP) specializing in digital health, currently completing an NIDDK K01 on the development of an informatics-based digital intervention to promote physical activity by people with T1D. He has also collaborated on the psychometric development of the WANT model[**48-52**]. Besides being PI of the above prior studies, he coordinated a randomized trial of 120 individuals as a postdoc[64] and a smaller randomized trial for his doctoral dissertation[65]. He furthermore brings extensive experience leveraging physical activity trackers for health purposes, including Veterans Affairs investigator-level funding and lead authorship of global stakeholder panels[66,67]. His co-investigators on the present study include three of his mentors and one of his collaborators, all of whom he has published with extensively. **Dr. Fucito** is a behavioral psychologist-scientist with additional expertise in digital health tools and using technology to improve treatment access and engagement. She is PI of an R-series award utilizing smartphone tracking to anticipate vulnerabilities to substance abuse and adverse mental health states. **Dr. Weinzimer** is an endocrinologist-scientist, internationally recognized expert in continuous glucose monitoring[68], and PI of 10 awards from the U-, R-, and DP-3 series. **Dr. Nally** is an endocrinologist-scientist with expertise in exercise research[58,69]. **Dr. Jeon** is a biostatistician trained in epidemiology and recently focusing on methods for analyzing the circadian rhythmicity of continuous motor activity.

2 Rationale/Significance

2.1 Rationale and Study Significance

PRIMARY AIMS:

Current evidence-based T1D self-management interventions target glycemic control but ignore other modifiable health concerns prevalent in T1D such as hypertension and obesity. Exercise interventions could provide a novel solution if they could innovatively address the diabetes management and psychosocial challenges around exercise posed by T1D. Continuous glucose monitoring (CGM) allows patients and providers to comprehensively track the short- and long-term outcomes of exercise. Evidence-based interventions to translate CGM technology into sustainable adherence to exercise-related behaviors are lacking.

SECONDARY AIMS:

Physical activity with T1D has been linked to glycemic destabilization and fear of hypoglycemia, but there is a need to determine real-time mechanisms underlying this link. Fear of hypoglycemia has been measured as a "trait" (i.e., personality-specific) but in just one study as a "state" (i.e., situation-specific)[42]. Participants reported their state fear of having hypoglycemia over the next 12hr[42]. Responses had significant intraindividual variation and correlation with the related construct of blood glucose variability, indicating the need to further study fear of hypoglycemia as a state variable. Glycemic destabilization meanwhile is recognized to cause intense symptoms that acutely preclude physical activity, but no study has addressed the possible impact of more nuanced changes. E.g., downward-trending glucose could affect motivation to be active even if not projecting an excursion outside the clinically safe range.

Addressing this weakness, we and others have begun demonstrating that such affective (i.e., automatic) feeling states are the primary motivational factors driving humans to engage in physical activity[43-47]. Furthermore, these motivational factors have highly transient effects, exhibiting more state than trait qualities. Therefore, we must test these real-time states to link T1D-related barriers to physical activity (Figure 2 in section 1.1).

2.2 Risks

Confidentiality: Due to the collection of private identifiable information, there is a possibility of a security breach compromising subject confidentiality. Such breaches are extremely uncommon when proper IRB-approved precautions are taken.

Several steps will be taken to safeguard the confidentiality of subjects and their data. All research data collected outside of the mobile applications will be assigned a study participant number and that number will only identify participants in digital databases on REDCap or Actigraph Actilife software (downloads Actigraph GT9X blinded hip & wrist watch). Audio-recorded interviews and orientation sessions will be transcribed and names, places, and any other identifying information will be removed. The names of participants will not be associated with this data and assessments will be maintained according to participant study number. A master list connecting participant study numbers to participant names will be kept on a secure server where it can only be accessed by senior level project staff. Any information published as a result of the study will be such that it will not permit identification of any participant.

All research data that is collected via the mobile applications (CGM, diary responses, exercise performance, insulin usage, carbohydrates, GPS) will be stored on the relevant web application programming interface (API) platforms (Dexcom, Fitbit, GlucoseZone), researcher dashboard (Ilumivu, Qualtrics), or user dashboard (InPen) in accord with Yale Information Technology Services protocols (Table A1). After syncing the data, the data will be immediately deleted from the participants' biosensor devices and smartphones. Web-based application and user sessions are encrypted between the server and client browser through the use of industry standard SSL certificates. As soon as each participant completes the study protocol, their data will be immediately transferred from the API platform to Yale secure servers by secure file-protection strategies, assigned to the de-identified participant study number noted in the previous paragraph, and deleted from the API platform. All data is encrypted both at rest and in transit.

Table A1. Summary of devices and data pathways.

Device	**Identifiers**	**Data Capture**	**Data Export to Yale Server for Deidentified Analysis**
Actigraph GT9X Blinded Watch	None	Physical hookup to computer desktop with Actilife software	From Actilife Software
GlucoseZone	Name, email, GPS location	GlucoseZone API	From GlucoseZone API§
Dexcom G6 continuous glucose monitor	None*	Dexcom API → GlucoseZone API	From GlucoseZone API
Fitbit Inspire 3 smartwatch	None*	Fitbit API → GlucoseZone API	From GlucoseZone API
Keto-Mojo GK+ fingerstick ketone and glucose meter	None*	Keto-Mojo Researcher Dashboard	From Keto-Mojo Researcher Dashboard
Ilumivu mobile surveys	None	Ilumivu Researcher Dashboard	From Ilumivu Researcher Dashboard
Qualtrics mobile surveys	None	Qualtrics Researcher Dashboard	From Qualtrics Researcher Dashboard
InPen	None*	InPen User Dashboard†	From InPen User Dashboard
Participants' own insulin pump	Entered for routine care (not for research purposes)	Pump Manufacturer User Dashboard‡	Participant exports their own data and uploads to REDCap link

*Manufacturer platform registration requires email and date of birth. Research team will create participant account with fake details (e.g., YaleExerciseStudy01@gmail.com, date of birth 1/15/2000).
§Name and email removed by research team immediately when data reach Yale server. GPS removed by research team after aligning with National Weather Service to calculate weather at each timepoint.

†There is no researcher dashboard, but researcher can log into user dashboard to export data.
‡Any participants encountering difficulty with insulin upload or sharing will be provided written instructions or YouTube videos used at the Yale Children's Diabetes Program, assisted by the research team as needed, who will contact the manufacturer for troubleshooting as needed (as per our prior protocol helping adolescents upload their pumps, HIC#2000033736). Alternatively, the research team can create a participant account with fake details (e.g., YaleExerciseStudy01@gmail.com, date of birth 1/15/2000) on Tidepool.org which is a universal uploader server.

Right to privacy for participation in this research will be protected through alphanumeric coding of data (in place of names) and proper storage of research records, including interviews and data downloaded from the web API platforms. Collected materials will be maintained via an alphanumeric reference system maintained by Dr. Ash. Participants' names will appear only on the consent form, the HIPAA authorization form, and a master list maintained on REDCap that is separate from research data. Our data collection and management procedures are fully compliant with HIPAA. Access will be limited to personnel intimately involved in the study. Electronic data will be deidentified and password protected. Only members of the study team will have access to the physical or electronic data.

Hypoglycemia: There is risk of hypoglycemia due to exercise. The magnitude of these events can range from a few minutes of mild symptoms (e.g., dizziness, fatigue) to prolonged severe symptoms (e.g., loss of consciousness, diabetic ketoacidosis).

The T1D standard of care[70] recognizes the probability of these events as common in the context of daily living. Our previous pilot studies exercise for T1D (c.f. sect 1.2.1, 1.2.2) had some episodes of mild hypoglycemia around exercise, but they quickly resolved following appropriate rescue carbohydrates and there were no severe episodes, ketoacidosis, or other adverse events.

We will apply the same safety protocols to minimize these risks in the current study. To ensure safety, all participants will receive clearance to participate in the exercise by one of the study endocrinologists Drs. Weinzimer or Nally. They will self-monitor their blood glucose using a CGM. Those without their own monitor upon study entry will have one provided. CGM has reduced risk of hypoglycemia during and after exercise in randomized controlled trials compared to usual care (reviewed in[53]).

They will also be provided a comprehensive exercise safety orientation which is detailed in Appendix 22a. Briefly, the information includes review of devices, supplies, space, safe glucose ranges and carbohydrate snacking for exercise, reminders from CGM training pertinent to exercise, insulin adjustments around exercise, watching for symptoms, and who to call with concerns. They will be provided and instructed to keep carbohydrate-containing foods and drinks (eg, orange juice, glucose tablets) available to use when indicated by glucose testing or symptoms. In addition, they will be educated regarding the American Diabetes Association guidelines for self-monitoring blood glucose and urine ketones, if indicated, and appropriate adjustments of diet and insulin before, during, and after engaging in exercise[70,71]. For instance, if blood glucose is less than 90 mg/dL, they can consume 10-20g of fast-acting carbohydrates (eg, 4 oz of orange juice or 3 glucose tablets) and wait to commence with exercise until blood glucose is confirmed to be above 90 mg/dL. If blood glucose is greater

than 270 mg/dL and not associated with a recent meal, they must check their blood for ketones and avoid exercise if they have ketones ≥1.0 mmol/L.

Participants will be encouraged to be vigilant for symptoms of hypoglycemia during exercise and for the remainder of the day because exercise increases the risk for nocturnal hypoglycemia. The symptoms they will be encouraged to be vigilant for include cold, clammy skin, pallor, difficulty concentrating, shakiness, lack of coordination, irritability, hostility, and poor behavior, a staggering gait, fatigue, nervousness, excessive hunger, headache, blurred vision and dizziness, and abdominal pain or nausea. In these instances, they will be advised to refrain from exercise while checking blood glucose.

Participants will be monitored for exercise-associated events (hypo- and hyperglycemia, diabetic ketoacidosis, other health risks) as detailed in the Data and Safety Monitoring Plan (Sect 8.7). In brief, a research staff member will daily review each participant's CGM data, fingerstick glucose tests, ketone tests, exercise start times, and diary records of hypoglycemia and other clinical events (see Data and Safety Monitoring Plan "Tracking" section) each of the first 14 days of the trial for each participant. Instances of severe hypoglycemia, diabetic ketoacidosis, a missed ketone test, or other clinical event will result in immediate discontinuation of exercise until a physician has alerted the participant and the participant's primary diabetes care provider to the issue and developed a prevention strategy, consulting with the primary diabetes care provider as needed. For instances of a missed test, physician contact can be replaced initially by research assistant contact to query symptoms and troubleshoot testing procedures, followed by physician contact if symptoms were present.

The principal investigator Dr. Ash and a study physician (Drs. Weinzimer or Nally) will review the above data plus carbohydrate and insulin dosing around exercise, every 2 weeks during the clinical trial. Participants exhibiting patterns confirmed by the physician to be indicative of problematic exercise-induced hypo- or hyperglycemia will be alerted to the issue and referred to their diabetes care provider for follow-up (all patients will submit provider information to the study team at study start). Dr. Weinzimer will join at least every other occurrence of these meetings (i.e., at least every 4 weeks) and provide a second review of Dr. Nally's medical management decisions. Participants will be trained in allowing their provider to access their CGM data. Mild hypoglycemia will not be exclusionary since such individuals are in high need of exercise intervention. Any day-to-day decisions about clinical care, including adjustment of insulin dosing or CGM target ranges will be made by the participant's provider, not the study physicians. Clinical providers will not monitor CGM in real-time.

All participants participate in routine follow-up, consisting of quarterly visits to the clinic and 24-hour access to nurse and/or physician consultation. It is not anticipated that any of the data collection procedures or the intervention will cause any adverse effects. Nonetheless, the participants will continue to receive routine medical and nursing care throughout the study period, and intervention for adverse effects will be available.

These protocols have been utilized by Drs. Ash, Weinzimer, and Nally over four prior exercise clinical trials among youth and adults with T1D that had no instances of severe hypoglycemia or diabetic ketoacidosis (HIC #s 1605017843, 2000025992, 2000030105, 2000033736).

Hyperglycemia: There is a risk of hyperglycemia due to exercise from factors such as counterregulatory hormone response releasing glucose into the blood[26].

See above regarding blood glucose testing, blood glucose monitoring review by research staff, Drs. Ash, Nally, Weinzimer, and routine clinical support. Regarding hyperglycemia

specifically, participants will be encouraged to be vigilant before, during, and after exercise for signs or symptoms of hyperglycemia such as dry mouth, headache, heaviness, pressure behind the eyes, or unusual increase in thirst. They will be advised in these instances to reassess their blood glucose. If blood glucose is greater than 270 mg/dL and not associated with a recent meal, they should check their blood for ketones and avoid exercise if they have ketones ≥1.0 mmol/L.

Severe hypoglycemia and hyperglycemia: There is a risk of severe hypoglycemia or hyperglycemia due to exercise.

Severe hypoglycemia will be defined as any blood glucose level resulting in symptoms which require outside intervention to control (including but not limited to confusion and loss of coordination). Severe hyperglycemia will be defined as blood glucose >500mg/dL, presence of urine ketones or other signs and symptoms of diabetic ketoacidosis (including but not limited to weakness and fatigue, confusion, shortness of breath). Patients will be asked to contact emergency services should these events occur. Specifically, Yale-affiliated patients with T1D have access to a 24-hour hotline with access to nurse and/or physician advice or can choose to call 911. Non-Yale-affiliated patients will be asked to call 911 or contact their providers' after-hours staff (all patients will submit provider information to the study team at study start). The study team will be notified of the event within 24 hours via daily diaries; moreover all participants will have the PI's direct contact information should they choose to contact him earlier by phone or email. Our team will then notify the patient's primary diabetes provider (if not already notified) and all study-related exercise will be suspended until patient receives further advice from their diabetes provider regarding next steps which may include modified exercise routines or suspension of the study altogether. All serious adverse events such as severe hypoglycemia and hyperglycemia will be reported to the PI verbally within 24 hours of study staff being notified and to university's IRB committee in writing within 5 business days. In the case of >1 episode of severe hypoglycemia or 1 episode of diabetic ketoacidosis not closely related to pump site failure, the participant will be removed from the study and referred to their diabetes care provider for follow-up.

Exercise-related injuries: Exercise may cause muscle soreness/pain, muscle strain, cardiovascular events, and tiredness during or after the activity.

The probability and magnitude of such injuries varies based upon factors such as the individual participant's fitness level and the difficulty of the exercise routines. Our previous pilot studies (sect. 1.2) had no injuries or muscle strains. The American Heart Association Scientific Statement[114] notes that the frequency of exercise-related out-of-hospital cardiac arrest among the general population ages 35-90yr was measured at 3.0 per 100,000 person-years[115].

To minimize the risk of injuries or strains, participants will complete the GlucoseZone videos warm-up and cool-down routines. In addition, they will be coached to initially select classes from the "beginner" category and "short" to "medium" duration (15-40 minutes).

Though risk of serious injury is minimal, the research assistant will ask the participant weekly if they are having any of the symptoms overviewed on the consent form or any other injuries that could be made worse by exercising. In the event of positive responses, exercise physiologist (EP) Dr. Ash will contact them to ask follow-up questions, following protocols from the American College of Sports Medicine[113], to determine if they are indicative of pathology. If they are, Dr. Ash will report the episode to study physician Dr. Stuart Weinzimer and the participant's own PCP and suspend the participant's exercise participation unless receiving PCP clearance to continue.

Study questionnaires and interviews: Participants may experience some distress when discussing factors important to diabetes, diabetes management, and psychosocial stressors.

The probability of such responses is uncommon and the typical magnitude of responses is mild. No such instances were reported in our previous pilot studies (sect. 1.2).

Research participants who report negative psychological reactions to the research protocol, or negative emotional reactions to diabetes elicited during participation in the research study, will be referred to their regular clinical provider. If research staff determine that the degree of psychological reaction is severe, the physician staff of the study (Dr. Weinzimer or Dr. Nally) will be contacted to assess the participant and determine whether acute urgent referral is needed.

Continuous glucose monitoring (CGM): Participants will use Food and Drug Administration (FDA) approved Dexcom G6 CGM as part of the American Diabetes Association standard of care[70]. There is a low risk of developing a local skin infection at the site of the sensor needle placement. Itchiness, redness, mild bleeding, and or bruising may occur at the insertion site. Participants may develop localized reactions to adhesive used to secure the sensor.

Risks of glucose sensor insertion will be minimized because participants will be instructed to cleanse skin aseptically prior to insertion. Participants will receive training on sensor use if they have not used the sensor previously.

Fitbit: In a very small number of participants (~3% in a recent report[72]) the Fitbit may contribute to skin irritation or allergies. To minimize this risk, participants will be trained in manufacturer guidelines including keeping it dry, not wearing it too tight (loose enough that it can move back and forth on the wrist, moved 2-3 finger widths above wrist bone during exercise only), and giving the wrist a rest by removing the band for an hour every couple of days.

There are no potential social, cultural, financial, or legal risks to participants consenting to participate in this investigation.

Overall assessment: The risks associated with the current study are greater than minimal because exercise presents risk of hypoglycemia, hyperglycemia, and injuries. However, the exercise routines are within the scope normally performed by adults with T1D or other absolute insulin deficiency diabetes during daily living and the participants will benefit from our protocol measures described above that minimize exercise risks. In addition, the information to be gained will help develop an intervention supporting adults with T1D or other absolute insulin deficiency diabetes to become more physically active and overcome these risks of usual activity. Therefore, the value of the information to be gained outweighs the risks involved.

2.3 Anticipated Benefits

All participants in this study will receive a mobile health application that may help them increase their exercise.

Exercise is recommended by the American Diabetes Association for people with T1D due to its physical and mental health benefits.

The benefits to science and other people may include a better understanding of how to engage more people with T1D into exercise. There is a need to increase exercise among individuals with T1D.

The risks of our participants developing hypoglycemia, hyperglycemia, or exercise-related injuries during or after exercise in the context of the study are the same as those of them performing exercise under their normal conditions of daily living. The exercise routines in our instructional videos will target standard exercise recommendations by the American Diabetes Association for adults with T1D, which the association has determined have long-term health benefits that outweigh their risks. Furthermore, our participants will be supported in exercise safety by the measures outlined above (blood glucose monitoring review by Drs. Ash, Nally, Weinzimer, and routine clinical support) which further decreases the risk to benefit ratio.

The skin irritation risks associated with wearing commercially-manufactured biosensor devices including the CGM and Fitbit in the context of the study are also the same as those from wearing these devices under normal conditions of daily living. Wearing a CGM is recommended in the American Diabetes Association standard of care, and wearing a Fitbit device is a common and popular strategy to increase exercise. These benefits further decrease the risk to benefit ratio.

There are standard risks of research including confidentiality breach, and distress when completing study questionnaires and interviews. The principal investigator Dr. Ash has determined in consultation with his mentors Drs. Weinzimer and Fucito that these are outweighed by the benefits described in the first paragraph.

3 Study Purpose and Objectives

3.1 Purpose

PRIMARY

To trial a mobile intervention that promotes safe exercise in middle-aged adults with type 1 diabetes mellitus (T1D) and evaluate its feasibility, acceptability, and mathematical robustness.

SECONDARY

Determine real-time mechanisms underlying physical activity behavior and T1D-related barriers.

3.2 Hypothesis

PRIMARY

Hypothesis 1-1: The mobile intervention will meet standards of feasibility.

Hypothesis 1-2: The mobile intervention will generate positive user feedback and suggested refinements.

Hypothesis 1-3-1: The data will verify that a prior-constructed machine-learning algorithm that predicted exercise adherence in a prior dataset will continue to do so with acceptable accuracy (receiver-operator characteristic AUC .80, or precision-recall AUC .80 if <20% of days are lapses).

Hypothesis 1-3-2: The data will verify that prior detected patterns in blood glucose safety hazards will continue to appear with expected frequency (≥1 of the above patterns occurring in ≥80% of person-weeks).

Hypothesis 1-3-3: The data will verify that small or greater (d≥0.1) changes in blood glucose resulting from exercise are detectable by a Bayesian model.

SECONDARY

Hypothesis 2-1-1: Fear of hypoglycemia and blood glucose trends over the past 3 hours will predict momentary motivation states for physical activity (timepoints T1-T2).

Hypothesis 2-1-2: Fear of hypoglycemia and glycemic metrics over the past week will predict motivation states for physical activity over the past week (timepoints T0-T2).

Hypothesis 2-2-1: Motivation states for physical activity over the past week will predict physical activity behavior change and adherence over the 4-week intervention period (T0-T1).

Hypothesis 2-2-2: Motivation states for physical activity over the past 3 hours will predict physical activity maintenance, over the 2 weeks following the intervention (T1-T2).

Hypothesis 2-3: We expect interview themes among the proposed T1D population will include perception of connection among glycemic variation, fear of hypoglycemia, motivation states for physical activity, and performance of physical activity.

3.3 Objectives

Primary Objective 1. Evaluate the intervention for feasibility

Primary Objective 2. Evaluate the intervention for acceptability (i.e., user satisfaction)

Primary Objective 3. Evaluate the mathematical robustness of the intervention data-driven tools.

Secondary Objective 1. Examine whether recognized T1D-related physical activity barriers (fear of hypoglycemia, glycemic variation) predict momentary and long-term variation in motivation states for physical activity.

Secondary Objective 2. Examine whether motivation states for physical activity predict momentary and long-term variation in physical activity behavior change, adherence, and maintenance resulting from a T1D motivational physical activity intervention.

Secondary Objective 3. Qualitatively identify determinants and sequalae of motivation states for physical activity among adults with T1D.

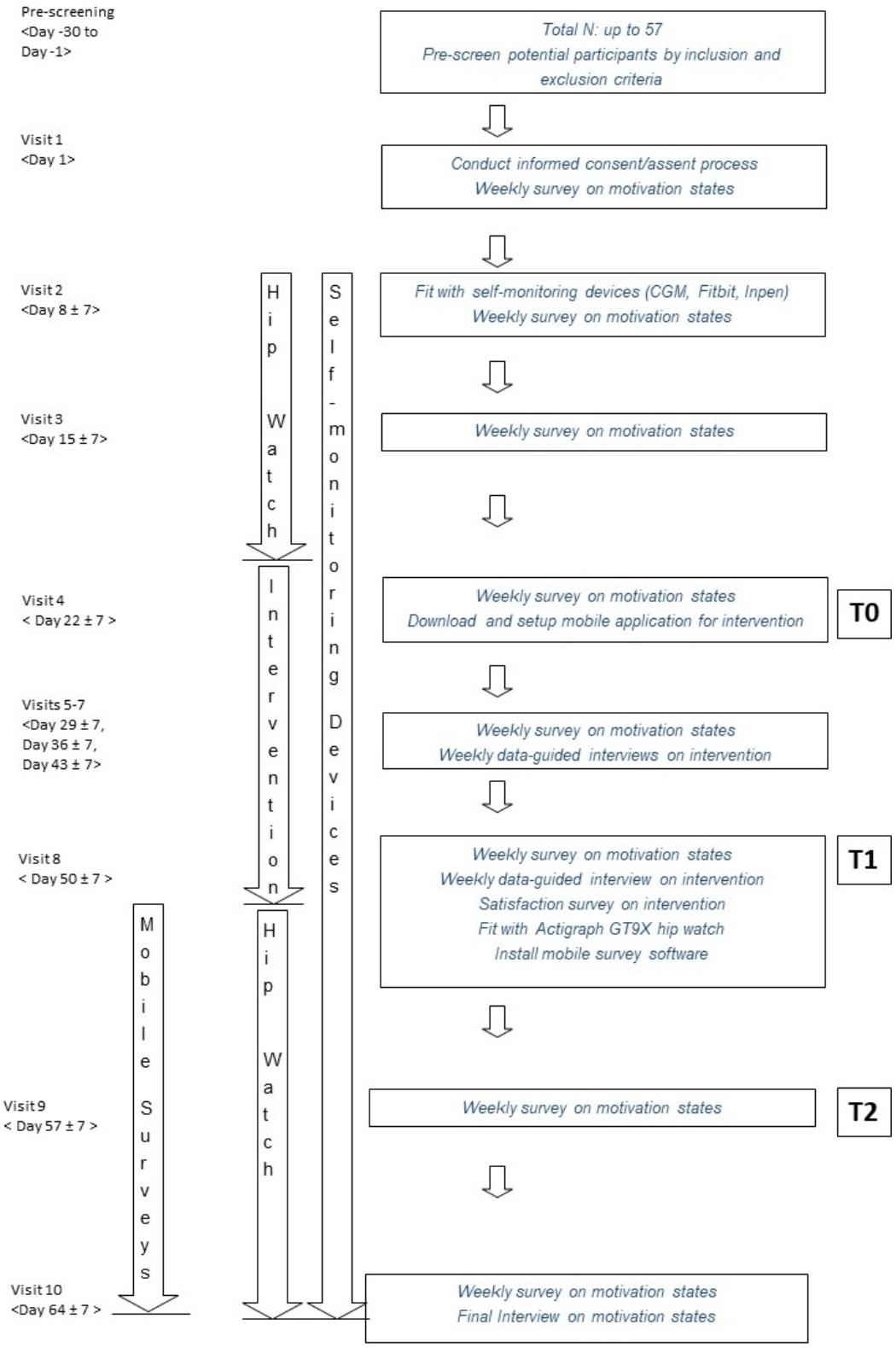
4 Study Design

Single group completing familiarization (2 weeks), intervention (4 weeks) and follow-up (2 weeks).

The primary objectives are addressed by observation of feasibility and weekly satisfaction interviews.

The secondary objectives are addressed by longitudinal quantitative observations (surveys, wearable biosensors) during all phases and a descriptive qualitative interview at follow-up.

Figure 3. *Study design flow chart.*



4.1 Study Duration

Subjects will each participate for 9 weeks. Totally data collection will be 16 months and data analysis 4 months, for a total study period of 20 months.

4.2 Outcome Variables/Endpoints

4.2.1 Primary Outcome Variables/Endpoints

PRIMARY AIMS

Primary Objective 1. Evaluate the intervention for feasibility

> **Outcome Variable 1-1-1.** Participant use metrics (i.e., % completion of diary, % wear-time of biosensors, frequency of video usage, % received of text messages).

Primary Objective 2. Evaluate the intervention for acceptability (i.e., user satisfaction)

> **Outcome Variable 1-2-1.** System usability scale (10 Likert-style items assessing aspects such as ease of use and degree of technical support needed, α=.91)[73] augmented with Likert-style survey items specially designed for this intervention.

Primary Objective 3. Evaluate the mathematical robustness of the intervention by evaluating its predictive performance upon exercise behavior.

> **Outcome Variable 1-3-1.** Prediction accuracy for exercise adherence (receiver-operator characteristic, precision-recall).
>
> **Outcome Variable 1-3-2.** Frequency of expected patterns in blood glucose safety hazards around exercise.
>
> **Outcome Variable 1-3-3.** Changes in blood glucose resulting from exercise.

4.2.2 Secondary and Exploratory Outcome Variables/Endpoints (if applicable)

Secondary Objective 1. Examine whether recognized T1D-related physical activity barriers (fear of hypoglycemia, glycemic variation) predict momentary and long-term variation in motivation states for physical activity.

> **Outcome Variable 2-1-1. Cravings for Rest and Volitional Energy Expenditure (CRAVE) survey of motivation states for physical activity**
>
> **2-1-1-a.** “right now” want for physical activity
>
> **2-1-1-b.** “right now” aversion for physical activity
>
> **2-1-1-c.** “past week” want for physical activity
>
> **2-1-1-d.** “past week” aversion for physical activity

Secondary Objective 2. Examine whether motivation states for physical activity predict momentary and long-term variation in physical activity behavior change, adherence, and maintenance resulting from a T1D motivational physical activity intervention.

Outcome Variable 2-2-1. Physical activity, total counts

Outcome Variable 2-2-2. Physical activity, minutes of moderate-to-vigorous

Outcome Variable 2-2-3. Sedentary behavior, minutes

Secondary Objective 3. Qualitatively identify determinants and sequalae of motivation states for physical activity among adults with T1D.

Outcome Variable 2-3-1. Interview themes.

5 Study Participants

5.1 Study Population

Middle-aged adults with T1D and sedentary lifestyle.

5.2 Number of Participants

We will screen up to 57 participants to meet our goal of selecting 24 participants.

5.3 Eligibility Criteria

In order to be eligible for inclusion in the study, an individual must meet all of the following criteria:

- 30-65 years old inclusive
- Diagnosis with type 1 diabetes (T1D) or other insulin deficiency diabetes (latent autoimmune disease of adulthood, diabetes secondary to pancreatitis)
- Sedentary (<1.0 exercise sessions/wk as assessed by question #6 of Paffenbarger Physical Activity Questionnaire)[74,75]
- Smartphone ownership
- English literacy
- Under regular care by a healthcare provider (defined as attending at least one appointment in the past year, plus access to verified 24hr phone number to reach the provider's team for insulin dose adjustments if assistance is needed)
- Home Broadband wireless Internet or cell phone network (≥25 mbps downloads, ≥3 mbps uploads on google Internet speed test). This is used in ~98% of US households[112].
-

Any individual who meets any of the following criteria will be excluded from participation in this study:

- Diabetic ketoacidosis not clearly related to pump site failure in past 6 months
- >1 episode of severe hypoglycemia (altered mental and/or physical status requiring assistance from another person for recovery) in past 6 months
- A1c ≥10.0%
- Resting blood pressure >160mmHg systolic or >100 mmHg diastolic
- Myocardial infarction or angina in past 12 months
- Uncontrolled arrhythmia (e.g., Afib with RVR, new onset Afib, ventricular tachycardia, escape rhythms)
- Congestive heart failure (stage 3 or 4)
- Exercise-induced asthma (not controlled on inhalers)

- Chronic obstructive pulmonary disease (requiring home oxygen)
- Renal failure
- Pregnancy
- Cognitive impairment
- Severe retinopathy or neuropathy.
- Other chronic disease or physical disability that would influence exercise intervention (e.g., recent spinal surgery)

No vulnerable populations will be targeted.

5.4 Recruitment Procedures

The research team will identify study candidates by manually examining the EPIC database for diabetes status and age or requesting a report from the Joint Data and Analytics Team (JDAT). Candidates will be reviewed to determine eligibility at the recommendation of their primary diabetes providers, who will be made aware of the study and eligibility criteria and introduce the study to the patients. The provider will be contacted to determine whether contact from the study team is appropriate. Eligible patients are contacted by the research team either via face-to-face meeting, phone, email, via video (Zoom), or approached at their regular clinic appointments to discuss their potential participation. Alternatively, the diabetes provider will send the patient a direct mailer or a MyChart message if they have a MyChart account (Appendix 13). These will only be sent once per patient.

The study will also be advertised so candidates may contact us proactively. Research flyers will be posted at the Yale Diabetes Center and public pharmacies. Internet postings, mass emails, and social media advertisements (e.g., Facebook, Google, Instagram) will also be used, particularly targeting T1D support groups such as BeyondType1.org. Leaders of private groups will be contacted and asked to consider posting advertisements. Study candidates identified on EPIC using the Joint Data and Analytics Team (JDAT) will receive a direct mailer, and those among them who have a MyChart account will receive a MyChart message. Lastly, the study will be posted on clinicaltrials.gov and our departmental website. Images and text for these advertisements are given in appendices 14 and 15 respectively. Full layouts are given in Appendix 15a.

Interested individuals viewing these advertisements will be invited to inquire about the study by a) contacting investigators by telephone or by email to learn more about the study, or b) providing their eligibility web questionnaire answers (Appendix 1b1) and contact details on a secure HIPAA-compliant Qualtrics webform (not capturing IP address or GPS location) so investigators may contact them by telephone or email. These individuals (i.e., inquirers) will be provided a brief description of the study and invited to ask questions. Among the inquirers, those wishing to volunteer will complete a brief eligibility interview (Appendix 1a, 1b, 1c). If they meet criteria, their primary care provider (PCP) will be contacted for confirmation (Appendix 24). If eligible, the participant will be invited to schedule a consenting televideo visit on Zoom, which they will be asked to complete from as private a physical setting as possible. They will be emailed a pdf of the consent form the same day as screening, to review in advance of the consenting visit. Consent will be documented by REDCap eConsent framework as detailed below.

5.5 Consent/Assent Procedures/HIPAA Authorization

- Consent/assent will use the standard IRB-approved compound consent / HIPAA research authorization form.

- A pdf of each IRB-approved form will be converted to an electronic survey on YCCI's approved REDCap e-consent framework. The framework adds to REDCap's typical survey framework by (a) a final screen displaying all responses as a pdf that participants are asked to certify, (b) storage of the form as a pdf rather than exportable data fields, and (c) fields allowing for "wet" signatures (hand-traced using the mousepad).

- The forms listed in the first bullet describe in detail the study intervention, study procedures, and risks. They are given to the participant and written electronic documentation of informed consent on these forms is required prior to starting study assessments and administering study intervention. Written electronic documentation on each form includes the signature of the researcher obtaining consent and the signature of the participant on the compound consent/authorization form.

- The participant will be asked to read and review the documents. The principal investigator, a co-investigator, or a research assistant will explain the research study to the participant (in terms suited to their comprehension) and answer any questions that may arise. This conversation will take place over a Zoom televideo call, which the participant will complete from as private a physical setting as possible.

- Participants will have the opportunity to carefully review the electronic written forms and ask questions prior to signing. To identify and clarify any misconceptions, participants will be encouraged to describe the research procedures and their associated risks in their own words, followed by correction of any errors by the researcher. A quiz is used to ensure understanding of study procedures. The participants will have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate.

- Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A pdf of the signed consent/assent documents will be sent by encrypted email to the participants for their records.

This study does not involve children

STUDY PROTOCOL

Social Behavioral Template

6 Study Methods/Procedures

6.1 Study Procedures

Table 1. Visit Schedule

	Pre-screening (Pre-consent)	*Visit 1 Day 1*	*Visit 2 Day 8 ±7*	*Visit 3 Day 15 ±7*	*Visit 4 Day 22 ±7*	*Visits 5 Day 29 ±7*	*Visit 6 Day 36 ±7*	*Visit 7 Day 43 ±7*	*Visit 8 Day 50 ±7*	*Visit 9 Day 57 ±7*	*Visit 10 Day 64 ±7*	*Unscheduled Visit*
Screening Phone Call	X											
Contact primary care provider for confirmation	X											
Informed Consent		X										
Demographics		X										
Clinical history		X										
Blood pressure			X	X	X	X	X	X	X	X	X	
Monitor symptoms		X	X	X	X	X	X	X	X	X	X	
Devices												
InPen (if multiple daily injection user)			*Continuous* ---------->									
CGM			*Continuous* ---------->									
Fitbit			*Continuous* ---------->									
Morning survey monitoring daily living (Appendix 8a)			*Continuous* ---------->									
Actigraph GT9X (hip during day, wrist during night)			*Continuous* ---------->						*Continuous* ---------->			
Intervention												
Mobile App					*Continuous* ---------->							
Outcome Evaluation												
Interview on App Features						X	X	X	X			
Exit Survey on App Features									X			

Momentary Surveys on Motivation States									5x/day---------->			
Weekly Survey on Motivation States			X	X	X	X	X	X	X	X	X	
Interview on Motivation States											X	
Adverse Events Reporting												
Adverse Events Reporting			X	X	X	X	X	X	X	X	X	X
Total Time (minutes)	15	30	45	35	65	65	65	65	85	35	80	15
**The total time commitment for the study is the sum of these visits (575min) + mobile surveys (2min/survey * 5 surveys/day * 14 days = 140min) = 715 min, along with the target 150 minutes of exercise per week during the intervention and follow-up (150 min/week * 6 weeks = 900min), for a total of 1625min or 27 hours.*												

STUDY PROTOCOL

Social Behavioral Template

6.1.1 Data Collection

STUDY DESIGN OVERVIEW

The study is a single-group longitudinal study with periods of familiarization with devices, intervention using devices and mobile app, and maintenance follow-up (Figure 4). The primary aim is observing the intervention for feasibility, acceptability, and mathematical robustness. The secondary aim is observing psychological and biometric outcomes through assessments (Table 2) which are completed 1x/weekly during the entire study to test long-term effects (hypothesis 2-1-2 & 2-2-1) and 5x/daily during maintenance follow-up to test momentary effects (hypothesis 2-1-1 & 2-2-2). The secondary aim also includes an interview at the end of the study (hypothesis 2-3).

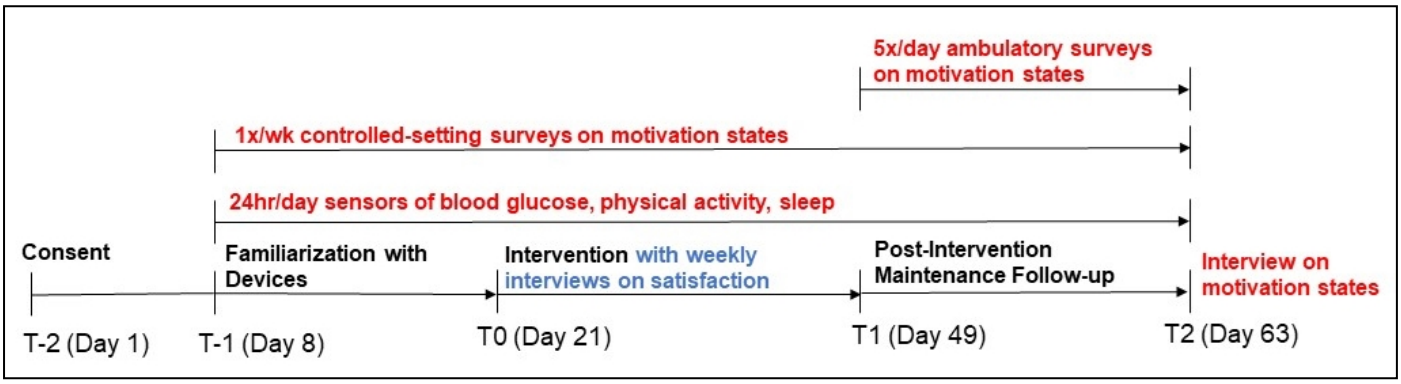


Figure 4. Individual participant timeline. Blue indicates measures for primary aims and red indicates measures for secondary aims.

Table 2. Surveys used for secondary aims. Appendix has instruments for dependent variable (#2a,2b), independent variables fear of hypoglycemia (#3a, 3b), exercise self-efficacy (#4), exercise self-regulation (#5), and covariates affective valence (#6), daily intention and competing demands and illness (#7)

PHASE	**Momentary** (Hypotheses 2-1-1, 2-2-2) (Timepoints T1-T2)	**Weekly** (Hypotheses 2-1-2, 2-2-1) (Timepoints T0-T2)
ASSESSMENT SCHEDULE	5x daily at random times within 3hr bins under ambulatory conditions of daily living	Weekly in controlled setting (tele-video in quiet room)
DEPENDENT VARIABLE††		
Cravings for Rest and Volitional Energy Expenditure (CRAVE) survey of motivation states for physical activity*	Score of 1-item want "right now" and 1-item aversion "right now"	Score of 5-item want "past week" and 5-item aversion "past week"
INDEPENDENT VARIABLES		
Fear of hypoglycemia†	Score of 1-item "next 3 hours" version	Weekly score of 18-item "past week" version
Fear of hyperglycemia††	Score of 1-item "next 3 hours" version	Weekly score of 24-item "past week" version
Blood glucose metrics‡	Past 3 hours averages and slope	Weekly averages
Exercise self-efficacy[76]	N/A	Weekly score of 9-item "past week" version
Exercise self-regulation[77]	N/A	Weekly score 15-item "past week" version
COVARIATES		
Non-T1D-related affective valence states previously associated with CRAVE score (pleasure/displeasure[78], activation/arousal[79]).§	Score of 1-item "right now" versions	Weekly score of 1-item "past week" versions
Day of week, time of day	Timestamp	N/A
Weather (temperature, humidity, windchill for GPS location by National Weather Service)	Momentary value	Weekly averages

Physical Activity Daily Intention[80] multiple choices (exercise in morning, occupational activity, etc[81])	Daily state||	Weekly frequencies
Competing Demands "How busy is today's schedule?"[82]	Daily state||	Weekly averages
Illness "Were you sick yesterday?"	Daily state||	Weekly frequency
Sleep (total, waketime after sleep onset)**	Daily state||	Weekly averages
††Dependent variable for aim 2-1. For aim 2-2, this is an independent variable and the dependent variable is Actigraph-measured physical activity. *Validated in ref[83] for 5-item versions and ref[84] for 1-item versions. †1-item is emerging new instrument[42] and 18-item widely validated (α=.89)[85]. ††1-item parallels fear of hypoglycemia item one row up, and 24-item is validated (α=.92)[111]. ‡Assessed by Dexcom G6 continuous glucose monitor (mean error 9%-10%[86]). Quantified as consensus metrics[60] (Coefficient of variation, mean, time in target range [70-180 mg/dL], time above range, time below range i.e. hypoglycemic). §.41-.88 convergent validity[87,88]. ||assess at wakeup and apply to all timepoints that day. **Assessed by Actigraph GT9X. Each 60-s epoch will be scored as wake or sleep (Sadeh's algorithm[89,90]).		

PROCEDURES FOR EACH VISIT ARE GIVEN BELOW:

VISIT 1 (Day 1)

On REDCap: consenting, medical history (verify from eligibility interview Appendix 1c), demographics form (Appendix 1d), contact information (Appendix 1e).

When possible, research staff will compare the collected medical and demographic information with EMR data accessed through EPIC (Yale patients) or Share Everywhere (non-Yale patients who have a MyChart account). In the event of any discrepancies, the staff will ask the participant for clarification to resolve the discrepancy.

Monitor Symptoms

The research assistant will ask the participant if they are having any of the symptoms overviewed on the consent form or any other injuries that could be made worse by exercising. In the event of positive responses, exercise physiologist (EP) Dr. Ash will contact them to ask follow-up questions, following protocols from the American College of Sports Medicine[113], to determine if they are indicative of pathology. If they are, Dr. Ash will report the episode to study physician Dr. Stuart Weinzimer and the participant's own PCP and suspend the participant's exercise participation unless receiving PCP clearance to continue.

Mailing

After visit 1, participants will be mailed a package containing:

a. Blood pressure monitor (Omron BP760N)
b. CGM transmitter plus 6 sensors (Dexcom G6). If not already using. Issued by Dexcom under a research contract, not involving a prescription.
c. Bluetooth ketone meter and test strips (Keto-Mojo GK+). The device also acts as a glucometer for CGM calibrations and sensor changes.
d. Prepackaged snacks containing 15g fast-acting carbohydrates (e.g., Nestle Juicy Juice 125mL boxes, Glucose Tablets)
e. Fitness smartwatch (Fitbit Inspire 3)
f. Bluetooth Smart Insulin Pen (Companion Medical Inpen). If not a pump user. Issued by Medtronic under a research contract, not involving a prescription. A prescription for the participant's normal insulin in the correct cartridge for the InPen (3mL, U-100) will be obtained from the participant's primary diabetes care provider, or sent by a study physician through EPIC.
g. Smartphone. If not already owned

h. Actigraph GT9X Accelerometer. Programmed to run days 8-22, plus box to mail back so research team can download, reprogram for days 50-64, and mail to participant a second time.

In the event of lost items, up to 1 replacement will be provided, except items that are not essential for safety and have resale value (scale, fitness smartwatch, smartphone). Regardless of lost items, participants will be allowed to continue with other aspects of the study. For example, if they lose the smartwatch they can still use the exercise app with feedback missing the heart rate, steps, and sleep. Or if they lose the scale, they can still attend the weekly visits and complete the surveys and blood pressure readings. Participants will not be responsible for the cost of any lost or damaged items.

VISIT 2 (Day 8)

Devices

Participants not currently using a Dexcom G6 CGM will be trained over tele-video by Research Associate James Lukasik or PI Dr. Ash. The training protocol incorporates information from the manufacturer setup protocol plus additional guidance provided by the study endocrinologists Drs. Weinzimer and Nally (Appendix 21). Participants will log into either their own Dexcom account (current users) or an anonymous account set up by research staff with a generic username, generic email address, and password (new users) and pair the device. They will be guided to create a "share code" that gives the holder access to CGM data in real-time; research staff will record the code on Yale's secure server for transmission to their primary diabetes care provider. The CGM is validated against venous blood glucose (mean absolute percentage error 9%-10%[86,91]). For the 2-week familiarization period until visit 4, the trainer will review CGM data after days 1, 3, 7, 10, and 14 days to check if data are being transmitted consistently with reasonable values and if the first sensor change (day 10) was completed as scheduled). The trainer will also talk with the participant at each weekly visit and query if there are any issues with skin irritation, sensor dislodgement, or values suspicious or inconsistent with fingerstick checks. At the visit 2 weeks after initiation (visit 4), they will ask if there were any issues with the first sensor change. Trainer will follow up with participant to troubleshoot as needed. We will start with a bank of standard troubleshooting techniques from our procedure manual, then involve Dexcom customer service or a senior clinician from the research team as needed.

Participants will set up the Fitbit Inspire 3 to track steps (typical ~5% overestimation)[92,93] and heart rate (typical ~3% underestimation)[92]. It will arrive to participants linked to an account set up by research staff with a generic username, generic email address, and password. Participants will be guided to place it on their non-dominant wrist and taught to mark exercise start-stop times using the side button, advised that marked bouts will have logged timing on the dashboard but all bouts are counted toward daily totals. Fitbit non-wear is defined as ≥60 seconds without registering a pulse[96]. Participants will be instructed to wear the Fitbit at least 22 hours per day and charge it for 2 hours when the battery is low (expected every 5-7 days).

Participants will set up the Keto-Mojo GK+ which uses fingerstick strips to track blood ketones and blood glucose, the latter replacing CGM values when needed (i.e., during CGM calibrations and sensor changes). It will arrive to participants linked to an account set up by research staff with a generic username, generic email address, and password. Participants will receive a demonstration with explanation that it works like a standard glucometer, with blue strips testing ketones and brown strips testing glucose.

Participants will set up the insulin smartpen (Companion Medical InPen), over tele-video with training guided by Research Associate James Lukasik or PI Dr. Ash (Appendix 23). It will arrive to participants linked to an account set up by research staff with a generic username, generic email address, and password. The account will be disabled for all features and alerts that guide insulin dosing and timing. The trainer will review the participant's use of their normal insulin pen, ensure they use it correctly, then orient them to the parts of the InPen so they can use it the same way as their normal pen. The trainer will also note that the InPen is reusable and train the participant to change cartridges. Patients already owning the device will be asked to use their own, or otherwise one will be provided by the research team. Patients who administer insulin in their usual care by a subcutaneous insulin infusion pump rather than multiple daily injections will continue using their

pump and will not use a smartpen. Thus, in this study the pen introduces more comprehensive record-keeping where needed but does not alter care practices.

For the 2-week familiarization period until visit 4, the trainer will review InPen data after days 1, 3, 7, 10, and 14 days to check if data are being transmitted consistently with reasonable values. The trainer will also talk with the participant at each visit and query of there are any issues or concerns. Trainer will follow up with participant to troubleshoot as needed. We will start with a bank of standard troubleshooting techniques from our procedure manual, then involve Medtronic customer service or a senior clinician from the research team as needed.

Participants will set up the Actigraph GT9X hip accelerometer (i.e., blinded hip and wrist watch) on their own belt, elastic waistband, or a belt we provide. They are asked to wear the device on the hip for all waking hours except bathing, and on the dominant wrist (i.e., opposite wrist of the Fitbit) for sleep. The device samples data at 30Hz and aggregates it into 60-second epochs. Non-wear periods are defined by Troiano's algorithm[94] confirmed against participant logs of non-wear periods; previously our wear time exceeded literature standards (14.1±1.9 waking hours per day for 5.4±1.0 out of 7 days)[58]. Participants will receive a daily morning SMS survey through Ilumivu or Qualtrics asking them to log that morning's attachment time and previous night's removal time.

Participants will measure blood pressure by standard home monitoring procedures[95]. We will take the average of 2 brachial artery measurements after ≥12 hours abstention from acute blood pressure confounders (exercise, caffeine, alcohol, tobacco, nicotine) and ≥5 minutes of quiet rest using the Omron BP760N, which includes a rigid cuff that minimizes fitting errors. If the measurements differ by >5 mmHg, then a third will be taken and the closest two will be averaged. In the event of a result meeting the home BP monitoring criteria for uncontrolled accelerated hypertension (systolic >160 mmHg and/or diastolic >100 mmHg), the participant will be withheld from exercise participation until BP can be reassessed at least one day later. In the event of a second occasion meeting these values, the participant will be removed from the study and referred to their healthcare provider for follow-up.

Daily morning survey that captures daily morning context during app intervention is started at this visit -- Appendix 8a: 1) prior day hypoglycemia episodes; 2) recent clinical events (asked every day for 2 weeks, then every 2 weeks); 3) fear of hypoglycemia previous night and coming day; 4) sleep quality and nocturia previous night; 5) competing demands and exercise plan for the day.

Surveys

Participants will complete the first weekly "long-term" survey (Table 2, third column) on REDCap.

Communication to primary diabetes provider

The research team will send a letter by secure clinic fax to diabetes care provider (Appendix 19) that informs them of their patient's participation, contains share code to view real-time glucose values, advises that biometric data including CGM and insulin are available upon request when the participant completes the protocol, and that our Data and Safety Monitoring Plan includes contacting them if there are any exercise-associated concerns related to hypoglycemia, diabetic ketoacidosis, or health risks.

Monitor Symptoms

Same as visit 1.

VISIT 3 (Day 15)

Surveys

Participants will complete the second weekly "long-term" surveys (Table 2, third column).

Blood pressure
Repeat visit 2 procedures.

Monitor Symptoms

Same as visit 1.

VISIT 4 (Day 22)

Monitor Symptoms

Same as visit 1.

Start of Intervention

Participants will download and be oriented to use the GlucoseZone™ (New Haven, CT) mobile application that delivers the digital intervention. The intervention is designed to target 150 minutes of weekly exercise, in accord with recommendations[70,71]. Participants utilize exercise videos with biometrically-driven feedback coaching.

Data Captured by App

Daily context each morning -- Appendix 8a: 1) prior day hypoglycemia episodes; 2) recent clinical events (asked every 2 weeks only); 3) fear of hypoglycemia previous night and coming day; 4) sleep quality and nocturia previous night; 5) competing demands and exercise plan for the day.

Pre- and mid-exercise context captured in conjunction with videos – Appendix 8b & 8c and passive data from app and sensors: 1) carbohydrates taken; 2) insulin dosing; 3) weather; 4) day of the week; 5) exercise instructional video selected; 6) exercise performance metrics.

24hr passive data from sensors – 1) Continuous blood glucose; 2) Physical activity outside of exercise videos

The app uses this biometric data to give exercise guidance, as described in the funded grant submission (1K01DK129441) and below

Tool #1: Access to a library of 200 exercise videos following brief human orientation consultation (Appendix 18b). Our ~200 exercise videos (GlucoseZone™, New Haven, CT) include a combination of aerobic, resistance, flexibility, and balance exercises, in accord with American Diabetes Association recommendations[70,71]. They can be filtered by difficulty level, duration, type of exercise (aerobic vs. resistance), muscle groups, mobility limitations (knee-friendly, shoulder-friendly, chair-based), indoor/outdoor, and home equipment availability. Using these filters, participants can select single sessions or 30-session series that progress in difficulty and duration. Participants self-schedule exercise time in their home environment or outdoor guided walking routes. Participants may select routines requiring no equipment, use a $10 set of resistance bands we recommend, use their dumbbells or household items like frozen water bottles. A trained exercise physiologist (EP) from the research team (Dr. Ash,) will guide downloading the app, discuss exercise levels, goals and safety (Appendix 22a), and recommend starting videos and series. This orientation will be audio-recorded and combined with later interviews for qualitative analysis (Sect 7.2.1, hypothesis 2-3). A consultant from the manufacturer of GlucoseZone (Fitscript LLC; Mr. Charles O'Connell or Ms. LaurieAnn Scher) will be available for assistance with downloading, navigating, or troubleshooting the app.

Tool #2: Daily just-in-time adaptive text messages to overcome exercise barriers on vulnerable days. Just-in-time adaptive messaging is "an intervention that adapts the provision of support (e.g., the type, timing, intensity) over time to an individual's changing status and contexts with the goal to deliver support "at the moment and in the context that the person needs it most and is most likely to be receptive."[2] From "data captured by app" (above, Appendix 8) the app will extract data to generate just-in-time adaptive messages. Specifically, the app organizes these data on a dashboard accessible to Yale staff. When a Yale staff member monitors this dashboard daily for exercise safety as described in the DSMP (Sect 8.7, "tracking") they export the contents onto the Yale Secure Server and enter them into our machine-learning code using Python to generate a supportive message (or confirmation that no message is needed that day). The staff member relays this information to the EP Dr. Ash who edits the message as needed according to standard of care T1D exercise guidelines[26,70,71] then sends the message to the participant through the GlucoseZone app.

The exported data include firstly exercise adherence, by tracking usage of exercise guidance (videos or guided outdoor walking). Fitbit heart rate readings verify exercise timing, duration, and intensity. The Borg Rating of Perceived Exertion prompt captures intensity for non-aerobic exercises such as weightlifting (Appendix 8c). The extracted data also include contextual variables that may predict vulnerability to missing exercise: 1) 24hr blood glucose derived from interstitial vales sampled every 5min by the CGM and expressed by consensus metrics (coefficient of variation, mean, % time >180, 70-180, <70mg/dL)[60]. 2) Fear of hypoglycemia the previous night and coming day (Appendix 8a). 3) Sleep Quality the previous night from self-report (Appendix 8a) and Fitbit (sleep time overestimation ~10%)[96]; 4) Competing demands and exercise plan (Appendix 8a); 5) Weather; (temperature, humidity, windchill) captured using GPS location and the National Weather Service API; 6) Day of the week (weekday vs. weekend). 7) Insulin dosing (including entered carbohydrates) from the participant's device (InPen, Tandem, Omnipod, or Medtronic). 8) Physical activity outside of exercise videos; captured by the proprietary Fitbit algorithm (intensity classification accuracy 85%[97], step counts ±3%[92];).

The above markers of individual context, day of the week, and between-participant characteristics, including demographics and clinical characteristics that can impede exercise (body composition, mobility limitations), will be exported from GlucoseZone to our Yale Secure Server for processing by our machine-learning code. The code is programmed to identify predictors of exercise "lapse," defined as the 3rd missed day of the week or 2nd consecutive missed day given that the goal is 150 min/week spread over ≥5 days[70]. Thereafter, when the code detects these predictors, the research assistant running the code will signals the exercise coach to edit then send a specific encouragement message. E.g., if high blood glucose variability is a vulnerable state predictor, the just-in-time message meeting its occurrence would read: "Sometimes blood glucose can go up and down. You can still be active using the strategies you and your provider have discussed." This encouragement does not extend to suggestions of specific exercises or managing low blood glucose.

The mathematical basis of the code is a binary classification model of exercise lapse using Python scikit-learn package v. 0.19.0[98], including random forests and gradient boosted tree ensembles (such as XgBoost[99]). We have completed analyses that train the model at the group level which was aim 2 of our prior protocol (HIC #2000025992). Briefly, we collected data on blood glucose, insulin dosing, fear of hypoglycemia, sleep, illness, and exercise occurrence. We ran two types of machine learning – random forest and dense neural network -- to predict exercise lapses (i.e., days without exercise) based upon prior days' blood glucose, fear of hypoglycemia, sleep, and illness. The data were randomly split where 80% of person-days were used to train the model and the other 20% were used to test the model. The present study will use the random forest model which had the highest accuracy (79%). Its sensitivity to predict exercise lapses was 83% and specificity was 71%. A **confidential** draft of the full manuscript describing the development is included (Appendix 20). These accuracy metrics, while limited, are better than the non-AI alternative of sending an encouraging message every day without any attempt to select for the most vulnerable days. Doing so can lead the participants to develop alarm fatigue and silence the notifications.

These models have been pruned to reduce the complexity of the final classifiers and avoid overfitting the training data. This group-level model (Appendix 9a) will be the starting point for training a person-level model for each participant via supervised transfer learning methods during the present study to give the participant tailored prompts. This strategy mitigates the shortness of the timeframe (4 weeks) to train each

person's model. At the end of the study, the data will first be used as an independent sample to validate the pilot group-level model. Second, they will be combined with the pilot data for a larger sample size to assess potential covariates, including pump vs. injection users, prior CGM usage, and age. If needed, separate models for subgroups can be established in the subsequent beta version of the app. Models are evaluated by the number of lapses required to train person-level models to reach acceptable accuracy (receiver-operator characteristic AUC .80, or precision-recall AUC .80 if <20% of days are lapses), thus estimating a "learning window" before users can expect adaptive feedback. We can anticipate this learning window by programming the app to utilize a simplified algorithm (e.g., chosen from a bank according to an *a priori* hierarchy of barriers present) until adaptive feedback starts. For instance, the example at the end of the previous paragraph would be utilized based on the detection of high blood glucose variability, even if the model has not yet established high blood glucose variability as a vulnerable state predictor.

The messages will go through expert human review and edits by the EP prior to sending to the participants. Differences between the algorithm-generated and human-edited messages will be tabulated for analysis at the end of the study (Sect 7.2, Hypothesis 1-3-1).

Tool #3: Personalized review of safety hazard occurrences around exercise and tips to avoid them. The GlucoseZone cloud will apply heuristic codes to the exercise and CGM data to recognize common patterns that contribute to glycemic regulation (Table 3). These patterns were selected using a list in international consensus guidelines for the entire T1D population[26] pared down to ones observed occurring in our pilot study. The GlucoseZone cloud will send participants weekly reports to summarize their patterns, corresponding follow-up tips, daily CGM tracings with indicated exercise times, and weekly summary statistics. The above patterns may occur less commonly than expected (≥1 of the above patterns occurring in ≥80% of person-weeks) or differ in occurrence by covariates noted above like pump vs. injection users, prior CGM usage, and age. In that case, we will examine the data for other more commonly occurring patterns to include in this tool in the next version. CGM tracking of people with T1D in the earliest stages of exercise uptake is novel, so some new patterns are expected.

Table 3. Example summary of exercise safety hazards with tips to avoid them.

Pattern	Definition	Times of occurrence	Follow-up Tip
Failure to take adequate carbohydrate supplementation relative to start values	(Blood glucose <70 mg/dL at the start of exercise) OR (blood glucose 70-100 mg/dL at the start of exercise AND <70 mg/dL during or within 1hr after exercise)	Monday 9:43am Wednesday 11:16am	A
Nocturnal hypoglycemia following exercise	Blood glucose <70 mg/dL for 30min of consecutive nocturnal readings	Wednesday 2:00-3:15am	A
Failure to adequately reduce pre-exercise bolus insulin	Insulin bolus <120min before start of exercise AND blood glucose <70 mg/dL during or within 1hr after exercise	Thursday 7:14pm Saturday 3:44pm	A
Starting exercise with elevated blood glucose values	Blood glucose >270 mg/dL at the start of exercise	Friday 4:45pm Sunday 4:17pm	B

A, Based on this blood glucose data, it may be a good idea to review the recommendations from your healthcare professional about how you would adjust your food intake or insulin dosing around exercise. If you do not remember, it would be a good idea to reach out. B, If your blood sugar is high (more than 270 mg/dL) before starting exercise, check your blood or urine for ketones. If you test positive for ketones, avoid vigorous activity. If you do not have ketones in your blood or urine and you feel well, it should be fine to exercise.

Tool #4: Health outcome feedback regarding the causal impact of exercise upon blood glucose (Appendix 18). The GlucoseZone cloud will draw CGM metrics (coefficient of variation, mean, % time >180, 70-180, <70mg/dL)[60] and covariates (insulin-on-board, carbohydrates self-reported into insulin device, exercise metrics including video selected and Fitbit minutes / heart rate / distance / calories / sleep / activity at sub-exercise intensity). The app organizes these data on a dashboard accessible to Yale staff. A Yale staff member exports the contents onto the Yale Secure Server weekly and enters them into our Bayesian R-code (Appendix 9b)[100]. The EP reviews the results and accompanying visualizations documenting a positive, neutral, or negative effect of exercise once per 1-4 weeks as insights are generated. The EP will message the client by encrypted emailed pdf relaying the most representative results and/or visualizations and any recommended adjustments by interpretating and applying exercise guidelines[26,70,71] (e.g., "You have done purely resistance exercise for the past 28 days, and it has had the causal impact of increasing blood glucose time above target range. Consider more aerobic exercise.") If these EP's recommendations indicate repeating certain videos, they will accordingly appear on the home-screen the following week.

The mathematical basis of the R-code is our Bayesian time series model. Briefly, it compares CGM metrics over each 1-4 week period against a counterfactual predicted based upon the CGM during the 1-4 weeks before the period and the covariates over the 1-4 week period. The full formalism and an example of this analysis is available in our manuscript[100]. The advantage over linear modeling frameworks is the flexibility to evaluate the intervention's effect strength at all points in the intervention period. If p-values do not reach significance (α=.05) then the next version of the app will extend the length of the testing window before providing feedback, though even 1 week of CGM data at minimal adherence (70%) yields k=1,411 observations resulting in 96% power to detect a small effect size ($d \geq 0.10$) at α=.05. The maximum window of 4 weeks was chosen as a typical minimal frequency of health coaching sessions for long-term maintenance of lifestyle change[101].

Surveys

Participants will complete the third weekly "long-term" surveys (Table 2, third column).

Blood pressure

Repeat visit 2 procedures.

VISITS 5-7 (Days 29, 36, 43)

Monitor Symptoms

Same as visit 1. For complaints that are musculoskeletal issues that can be temporarily avoided by the EP Dr. Ash recommending GlucoseZone videos that avoid the injured area, then such videos can be continued without PCP clearance.

Surveys

Participants will complete the fourth - sixth weekly "long-term" surveys (Table 2, third column).

Interviews

Participants will complete weekly audiotaped 30min semi-structured interviews about the app (Appendix 10).

Blood pressure
Repeat visit 2 procedures.

VISIT 8 (Day 50)

Monitor Symptoms
Same as visit 1.

Surveys
Participants will complete the seventh weekly "long-term" survey (Table 2, third column).

Interviews
Participants will complete the same interview as Visits 5-7.

Quantitative Satisfaction Survey (Appendix 11)
The above weekly semi-structured interviews will be supplemented by a quantitative survey at the end of the 4 weeks. It will include the system usability scale[109] (10 Likert-style items assessing aspects such as ease of use and degree of technical support needed, α=.91) for each of the above tools and each biosensor, Likert-style survey items specially designed for each of the novel mobile tools based upon the above questions, net promoter score[102], and implementation outcome measures (acceptability, appropriateness, feasibility; α=.85-.91)[103]. We will evaluate participant use metrics to determine intervention component feasibility (i.e., diary and biosensor adherence, use of videos, receipt of text messages).

Start Ecological Momentary Assessments
Ecological momentary assessments are repeated sampling of behaviors and experiences in real-time, which serves to a) minimize recall bias and b) capture the effect of real-world surroundings.

Participants will download Ilumivu or Qualtrics software. They will start momentary surveys 5x daily (Table 2, second column) and continue through the end of Visit 10. For each participant we will establish five windows programmed to cover their self-expected wake window. For example, a participant who normally wakes up at 7am and goes to bed at 10pm would have windows of 7-10am, 10am-1pm, 1pm-4pm, 4pm-7pm, 7pm-10pm. Ilumivu or Qualtrics will push one survey at a random time within each window. The survey remains accessible for 40min then expires if not completed. Participants will be instructed not to answer surveys while driving.

Blood pressure
Repeat visit 2 procedures.

Put Actigraph GT9X (i.e., blinded hip and wrist watch) back on
Repeat visit 2 procedures.

VISIT 9 (Day 57)

Monitor Symptoms
Same as visit 1.

Surveys
Participants will complete the eighth weekly "long-term" survey (Table 2, third column).

Blood pressure
Repeat visit 2 procedures.

VISIT 10 (Day 64)

Monitor Symptoms
Same as visit 1.

Surveys
Participants will complete the nineth weekly "long-term" survey (Table 2, third column).

Interview
Interview on Motivation States (Appendix 12). The interview will be conducted by personnel from Case Western Reserve University over HIPAA-compliant Zoom. All other procedures are conducted by personnel from Yale University.

Blood pressure
Repeat visit 2 procedures.

Data Transfer
Participants using their own insulin pump will upload to the manufacturer's site they normally use in clinical care, generate an export .csv file, and upload the export file to a secure REDCap link.
Any participants encountering difficulty with insulin upload or sharing will be provided written instructions or YouTube videos used at the Yale Children's Diabetes Program, assisted by the research team as needed, who will contact the manufacturer for troubleshooting as needed (as per our prior protocol helping adolescents upload their pumps, HIC#2000033736). Alternatively, the research team can create a participant account with fake details (e.g., YaleExerciseStudy01@gmail.com, date of birth 1/15/2000) on Tidepool.org which is a universal uploader server.

PAYMENT FOR PARTICIPATION
From consent form:
First, you will be paid for each weekly visit. These payments start at $5, increase by $3 for each week in a row that you complete, and returning to $5 if you miss a week. Second, you will be paid $1 for each day you wear the CGM, each day you wear the Fitbit, each day you complete the daily survey, each day you wear the blinded watch on your hip, and each night you wear it on your wrist. Third, you will be paid $100 if you complete 50%-79% of the 5x daily surveys, and $200 if you complete 80%-100% of them. This third payment is released once you mail back the study supplies using a prepaid label. Therefore, the total possible compensation is $577.

You may be responsible for paying state, federal, or other taxes for the payments you receive for being in this study. Taxes are not withheld from your payments.

Please note payments are only provided for completion of research assessments, not the exercise. So we do not consider them to impact exercise outcomes.

STUDY PROTOCOL

Social Behavioral Template

6.2 Method of Assignment/Randomization (if applicable)

Not applicable (not a randomized study)

6.3 Adverse Events Definition and Reporting

Every event that is reported to either the principal investigator or the designated research associates by the subject or medical staff caring for the subject and which meets the criteria will be documented.

An adverse event report will be generated for each event. The report will include
*description of the event
*likelihood of being related to the study
*when and how it was reported
*any official chart records or documentation to corroborate the event

The report will be supplied to the principal investigator, the study physicians Drs. Nally and Weinzimer, the data and safety monitoring board (DSMB), the Yale University IRB, and the NIDDK program official responsible for the award Maureen Monaghan Center, PhD. The DSMB is chaired by Denise Esserman, PhD (statistician at Yale Center for Analytical Sciences) who currently chairs a DSMB for the National Institute of Aging and has served on 10+ DSMB boards. The other members are Sarah Chhabra, MD (board-certified endocrinologist at University of Virginia) and Sean Fournier, MS (exercise physiologist at Yale-New Haven Hospital Heart and Vascular Center). No DSMB members are affiliated with the study or investigators.
Timeline for reporting
Events that may require a temporary or permanent interruption of study activities by the Principal Investigator or sponsor to avoid potential harm to subjects will be verbally reported immediately (if possible) with a written report filed within 5 calendar days.

Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related to study procedures) will be filed as a written report within 5 calendar days.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) will be filed as a written report within 5 calendar days. UPIRSOs applicable to this study include:

• Adverse device effects from any of the biosensors (continuous glucose monitor, smartwatch, insulin smartpen, hip accelerometer) beyond the ones expected (sect 2.2, last 2 bolded sections).
• Adverse events or injuries that are serious, unexpected, *and* related;
• Breaches of confidentiality involving risks;
• Interim analyses altering the risk/benefit profile by identification of increased risks;
• Revisions to safety information, such as MedWatch Reports, that meet the definition of a UPIRSO;
• New information indicating an unexpected increase in risks or decrease in potential benefits (e.g., literature/scientific reports or other published findings);
• Protocol deviations, violations, or other accidental or unintentional changes to the protocol or procedures involving risks or with the potential to recur;

• Unapproved changes made to the research to eliminate an apparent immediate hazard to a subject;
• Other problem or finding (e.g., loss of study data or forms) that an investigator or research staff member believes could influence the safe conduct of the research.

Events that do not require prompt reporting and are only documented at regular reports (twice yearly to DSMB, annual renewals to the Yale IRB, and annual progress reports to NIDDK) are:

• Anticipated adverse events (described in section 2.2)
• Adverse device effects that are non-serious, anticipated, *or* unrelated;
• Adverse events or injuries that are non-serious, expected, *or* unrelated;
• Deaths not attributed to the research (e.g., from "natural causes," accidents, or underlying disease when the Principal Investigator and the DSMB have ruled out any connection between the study procedures and the subject's death);
• Interim analyses not altering the risk/benefit profile;
• Protocol deviations or violations unlikely to recur or not involving risks to subjects;
• Subject complaints that were resolved or complaints not involving risks
• Problems or findings not involving risk (unless the PI believes the information could affect subjects' willingness to continue in the research)

Any action resulting in a temporary or permanent suspension of this study (e.g., IRB actions, or actions by the investigators) will be immediately reported to the appropriate NIDDK program official.

6.4 Reaction Management

This protocol is listed in section 2.2 risks and pasted here for reference.

Study questionnaires and interviews: Participants may experience some distress when discussing factors important to diabetes, diabetes management, and psychosocial stressors.

The probability of such responses is uncommon and the typical magnitude of responses is mild. No such instances were reported in our previous pilot studies.

Research participants who report negative psychological reactions to the research protocol, or negative emotional reactions to diabetes elicited during participation in the research study, will be referred to their regular clinical provider. If research staff determine that the degree of psychological reaction is severe, the physician staff of the study (Dr. Weinzimer or Dr. Nally) will be contacted to assess the participant and determine whether acute urgent referral is needed.

6.5 Withdrawal Procedures

- Participants may withdraw at any time without penalty by telling study staff or writing to the PI (Garrett Ash, Yale School of Medicine, Section of General Internal Medicine, PO Box 208025, New Haven, CT, 06520-8025)
- Upon withdrawal, no further information will be collected.
- Researchers may still use information collected prior to withdrawal.
- Participants withdrawing will be asked to return all supplies using the packing tape and prepaid label included in the box (see section 6.1.1 visit 1, “mailing”)
- Participants withdrawing may request copies of their Fitbit and blood glucose data up to the point of withdrawal
- Researchers may withdraw participants from the study if they have not followed instructions, suffer injury or illness making further exercise unsafe, meet individual stopping criteria (>1 episode of severe hypoglycemia, 1 episode of diabetic ketoacidosis not closely related to pump site failure, or blood pressure >160/100mmHg), or the researchers otherwise believe it is not in their best interest to continue.

6.6 Locations/Facilities

All work and data storage occurs on the online venues mentioned: OneDrive, REDCap, Actigraph Actilife software, web application programming interface (API) platforms (Dexcom, Fitbit, GlucoseZone), researcher dashboard (Keto-Mojo, Ilumivu, Qualtrics), or user dashboard (InPen) in accord with Yale Information Technology Services protocols (Table A1).

The PI has office space at 200 West Campus Drive, Orange, CT, 06477.

7 Statistical Design

7.1 Sample Size Considerations

This is a pilot study with primary objectives to test feasibility and acceptability, for which a typical sample size is 10-40 participants[1]. Within this range we chose 24 participants to first ensure thematic saturation of interviews (aims 1-2, 2-3), and second achieve adequate power for one of the secondary objectives, specifically hypothesis 2-1-1. Based on my past retention and adherence among sedentary adults with and without T1D (88% participants completed, they provided 83% of ecological momentary assessments on longer surveys than the present study, 90% continuous glucose monitor wear, and 95% accelerometer wear)[58,104] I expect 21 completers with an average of 50 complete observations each over T1-T2. Thus, using previous psychometrics of the CRAVE wants and aversions (.28/.39 ICC, 9.9/12.3 total variances)[52] I expect design effects of 14.21/20.11 and standard errors of 0.37/0.48, yielding 91%/81% power to detect predictors having ≥ .34 correlation (e.g., pleasure[52], fear of hypoglycemia[42]). For other secondary objective hypotheses (2-1-2, 2-2-1, 2-2-2) the study is not designed to detect statistical significance but calculate effect sizes (Cohen's f^2) for purposes of determining whether the WANT[48-52], SCT model[54-56], or both generate a signal for prediction of physical activity behavior.

7.2 Planned Analyses

Primary Objective 1 (DESCRIPTIVE). Evaluate the intervention for feasibility

Hypothesis 1-1. Participant use metrics (i.e., % completion of diary, % wear-time of biosensors, frequency of video usage, % received of text messages) will be summarized with descriptive measures.

Primary Objective 2 (DESCRIPTIVE). Evaluate the intervention for acceptability (i.e., user satisfaction)

Hypothesis 1-2. Results of acceptability survey will be summarized with descriptive measures. Weekly interviews about app usage will be transcribed, reviewed, and analyzed by content analysis[105].

Primary Objective 3 (MACHINE LEARNING). Evaluate the mathematical robustness of the intervention by evaluating its performance to predict exercise behavior, assess exercise safety hazards, and measure exercise glycemic response.

Hypothesis 1-3-1. Predicting Exercise Behavior. The mathematical basis of the code is a binary classification model of exercise lapse using Python scikit-learn package v. 0.19.0[98], including random forests and gradient boosted tree ensembles (such as XgBoost[99]). We have completed analyses that train the model at the group level using the previous pilot dataset (section 1.2.3). These models have been pruned to reduce the complexity of the final classifiers and avoid overfitting the training data. This group-level model (Appendix 9a) will be the starting point for training a person-level model for each participant via supervised transfer learning methods during the present study to give the participant tailored prompts. This strategy mitigates the shortness of the timeframe (4 weeks) to train each person's model. At the end of the study, the data will first be used as an independent sample to validate the pilot group-level model. Second, they will be combined with the pilot data for a larger sample size to assess potential covariates, including pump vs. injection users, prior CGM usage, and age.

If needed, separate models for subgroups can be established in the subsequent beta version of the app. Third, model-generated messages will be validated against the human-edited messages that are released to participants during the study (c.f. Sect 6.1.1, tool #2). Models are evaluated by the number of lapses required to train person-level models to reach acceptable accuracy (receiver-operator characteristic AUC .80, or precision-recall AUC .80 if <20% of days are lapses), thus estimating a "learning window" before users can expect adaptive feedback. Third,

Hypothesis 1-3-2. Detect Exercise Safety Hazards. Tabulate the occurrence of the common safety hazards (Table 3) and report them by frequency statistics.

Hypothesis 1-3-3. Assessing Exercise Glycemic Response. The mathematical basis of the R-code is our Bayesian time series model. Briefly, it compares CGM metrics over each 1-4 week period against a counterfactual predicted based upon the CGM during the 1-4 weeks before the period and the covariates over the 1-4 week period. The full formalism and an example of this analysis is available in our manuscript[100]. The advantage over linear modeling frameworks is the flexibility to evaluate the intervention's effect strength at all points in the intervention period. If p-values do not reach significance (α=.05) then the next version of the app will extend the length of the testing window before providing feedback, though even 1 week of CGM data at minimal adherence (70%) yields k=1,411 observations resulting in 96% power to detect a small effect size (d≥0.10) at α=.05. The maximum window of 4 weeks was chosen as a typical minimal frequency of health coaching sessions for long-term maintenance of lifestyle change[101].

7.2.1 Secondary Objective Analyses (if applicable)

All statistical models for secondary objectives 1 and 2 will estimate intraclass correlation coefficient (ICC) to assess the proportion of variance explained by participant ID.

Secondary Objective 1 (STATISTICAL, MULTILEVEL MODELING). Examine whether recognized T1D-related physical activity barriers (fear of hypoglycemia, glycemic variation) predict momentary and long-term variation in motivation states for physical activity

Hypothesis 2-1-1. Momentary predictors of motivation states. We will develop two multilevel models for the dependent variables of want and aversion for physical activity (CRAVE 2-item "right now") respectively. The independent variables and covariates (Table 2) will be separated into momentary states for level 1, daily states for level 2, and demographics for level 3.

Hypothesis 2-1-2. Week-to-week changes in motivation states. We will develop two generalized linear mixed models for the dependent variables of want and aversion for physical activity (CRAVE 10-item "right now") respectively. A random intercept will incorporate correlations within-subject. We will include long-term assessed independent variables and covariates (Table 2, last column) along with a time categorical variable to estimate the contribution of changes coinciding with intervention (T0 to T1) and maintenance follow-up (T1 to T2).

Secondary Objective 2 (STATISTICAL, MULTILEVEL MODELING). Examine whether motivation states for physical activity predict momentary and long-term variation in physical activity behavior change, adherence, and maintenance resulting from a T1D motivational physical activity intervention.

Hypothesis 2-2-1 – Predictors of physical activity behavior change and adherence over the intervention. We will develop a generalized linear mixed model for physical activity behavior testing WANT and SCT constructs as independent variables. A random intercept will incorporate correlation within-subject. We will include long-term assessed independent variables and covariates (Table 2, last column) along with a time categorical variable to estimate the contribution of changes from intervention (T0-T1) and maintenance follow-up (T1-T2).

Hypothesis 2-2-2 – Predictors of acute physical activity behavior. We will develop a multilevel logistic model where the dependent variable is a binary physical activity behavior outcome, defined as absence vs. presence within 3hr window of 10+ min bout of moderate-to-vigorous physical activity with no more than 2min interruption[106]. The models will include the same levels as hypothesis 2-1-1. We will estimate unadjusted and adjusted odds ratios of physical activity behaviors.

Secondary Objective 3 (QUALITATIVE). Qualitatively identify determinants and sequalae of motivation states for physical activity.

Hypothesis 2-3. De-identified transcripts will be imported into NVivo by Dr. Stephanie Griggs from Case-Western Reserve University or designee. Drs. Griggs and Ash will collaboratively identify general coding categories. Dr. Griggs, a research assistant (RA) from Case-Western Reserve University, and Dr. Ash will meet to establish consensus on the coding. Drs. Griggs and Ash will identify subthemes and the RA will conduct the remaining coding of excerpts into subthemes in NVivo. This process is recommended for descriptive studies as it involves immersion in the data prior to specific coding, emphasizing theorizing, synthesizing, and recontextualizing[105]. We will incorporate field notes with interviewer impressions and observations[107]. We will use inductive, directed qualitative content analysis[108]. Emerging findings will inform continual refinement of questions and probes[109]. Results will be reviewed with mentor Dr. Fucito every 2 weeks.

7.2.2 Analysis of Subject Characteristics (if applicable)

Demographics (age, sex, gender, race, ethnicity, household income, education level, public vs private insurance, duration of T1D), descriptive characteristics (HbA1c, height, weight, insulin regimen, total daily insulin dose), and derived indices (body mass index defined as weight divided by height squared, total daily insulin dose per kg body weight) will be tabulated. Categorical variables will be reported as proportions, continuous variables will be reported as mean±standard deviation if normally distributed or median (25^{th} %'ile, 75^{th} %'ile) if non-normally distributed.

7.2.3 Interim Analysis (if applicable)

The sole stopping rule will be clear evidence of harm.

There is no possibility of futility of treatment or overwhelming evidence of the benefit of treatment. This is because the present study is evaluating treatment feasibility and psychological mechanisms, but not treatment effect.

As such, no interim analyses are planned.

7.3 Data Relevance

The primary research question is whether a data-driven exercise intervention for T1D is feasible, acceptable, and mathematically robust. The data from this study will include provide performance metrics of the intervention on all these points.

The secondary research question is to determine mechanisms underlying the link between T1D-related barriers (glycemic stability, fear of hypoglycemia) and physical activity. The data from this study will include continuous biometric and survey data that measure these\ constructs, so that their relationship can be assessed.

7.4 Data Coding

All data will be coded by anonymous participant ID numbers. For web applications participants do not use in their routine care (Fitbit, GlucoseZone) staff will guide and verify that participants do not enter personal details for their username or email address, but rather their anonymous number and email address that is created and assigned by the study team (e.g., MOVE.CGM.01@gmail.com).

For electronic medical records, identifiers will be redacted prior to saving a screenshot.

During analysis, race and ethnicity will be assigned numerical codes and combined as needed (e.g., white Hispanic).

7.5 Data Analysis Tools

Statistical analysis will utilize SAS (Cary, NC). Machine learning will utilize Python. Qualitative analysis will use NVivo.

7.6 Data Monitoring

<u>Data Collection Forms</u>

Continuous glucose monitoring data will be monitored every 2 weeks through the Dexcom application programing interface, and mobile diaries will be monitored daily through the GlucoseZone application programming interface. This monitoring will include audits for completeness. Other biosensors that continuously sync with their web application programming interface (Fitbit, insulin devices) will be monitored every 2 weeks through the relevant application programming interface. Actigraph watch data will be audited for completeness when the device is downloaded after each 2-week assessment period. Dr. Ash will also perform quarterly audits for conformance with source document completion.

<u>Data Integrity and Protection of Databases</u>

Databases will be exported quarterly from REDCap, Ilumivu, Qualtrics, and Actigraph Actilife onto Yale University secure servers and audited for completeness and aberrant values using

frequency statistics. Datasets from biosensors will be checked in on REDCap checklists as they are downloaded, and the checklists will be audited quarterly. Original reports of all biosensor downloads will be retained for verification and further data analysis.

7.7 Handling of Missing Data

Missing patterns will be screened for whether the missingness is associated with predictors under examination and previous values (i.e., Missing at Random). Informed by this screening we have several options for final models including Rubin's multiple imputation method and Monte Carlo Markov Chain estimation.

8 Data/Specimen Handling and Record Keeping

8.1 Subject Data Confidentiality

Participant confidentiality and privacy is strictly held in confidence by the participating investigators, their staff, and the sponsor(s)/funding agency. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. While there is a possibility of a security breach compromising subject confidentiality, several steps will be taken to safeguard the confidentiality of subjects and their data as detailed below.

All research activities will be conducted in as private a setting as possible.

All research data collected outside of the mobile applications will be assigned a study participant number and that number will only identify participants in digital databases on REDCap or Actigraph Actilife. Audio-recorded interviews and orientation sessions will be transcribed and names, places, and any other identifying information will be removed. Recordings will then be promptly destroyed. The names of participants will not be associated with these data and assessments and transcriptions will be maintained according to participant study number. A master list connecting participant study numbers to participant names will be kept on a secure server where it can only be accessed by senior level project staff. Any information published as a result of the study will be such that it will not permit identification of any participant.

All research data that is collected via the mobile applications (CGM, diary responses, exercise performance, insulin usage, carbohydrates, GPS) will be stored on the relevant web application programming interface (API) platforms (Dexcom, Fitbit, GlucoseZone), researcher dashboard (Keto-Mojo, Ilumivu, Qualtrics), or user dashboard (InPen) in accord with Yale Information Technology Services protocols (Sect 2.2, Table A1). After syncing the data, the data will be immediately deleted from the participants' biosensor devices and smartphones. Web-based application and user sessions are encrypted between the server and client browser through the use of industry standard SSL certificates. As soon as each participant completes the study protocol, their data will be immediately transferred from the API platform to Yale secure servers by secure file-protection strategies, assigned to the de-identified

participant study number noted in the previous paragraph, and deleted from the API platform. All data is encrypted both at rest and in transit.

Yale Information Technology Services has reviewed all devices that transmit data for the study. They have determined that the Actigraph GT9X blinded watch, Dexcom G6 CGM, Fitbit Inspire 3 smartwatch, Ilumivu mobile surveys, Qualtrics mobile surveys, InPen, and participants' own insulin pumps will not collect or transmit any HIPAA-covered health information for study purposes. They have determined that GlucoseZone in this study will collect and transmit HIPAA-covered health information, in a manner meeting the HIPAA privacy and institutional standards, including GlucoseZone's specific data use agreement with Yale University.
Right to privacy for participation in this research will be protected through alphanumeric coding of data (in place of names) and proper storage of research records, including interview transcripts and data downloaded from the web API platforms. Collected materials will be maintained via an alphanumeric reference system maintained by Dr. Ash. Participants' names will appear only on the consent form, the HIPAA authorization form, and a master list maintained on REDCap that is separate from research data. Our data collection and management procedures are fully compliant with HIPAA. Access will be limited to personnel intimately involved in the study. Electronic data will be deidentified and password protected. Only members of the study team will have access to the physical or electronic data.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in a password-protected OneDrive folder at the Yale School of Medicine Section of General Internal Medicine. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used will be secured and password protected. At the end of the study, all study databases will be de-identified and archived indefinitely at the Yale School of Medicine Section of General Internal Medicine.

Data availability: Individual deidentified participant data (including data dictionaries) will be shared. This includes individual participant data that underlie the results reported in any aspect of a published article (text, tables, figures, and appendices). Other documents that will be available include the study protocol, statistical analysis plan, informed consent form, and analytic code. The data will be available immediately following publication with no end date. Data will be shared with researchers who provide a methodologically sound proposal to achieve aims in the approved proposal. Proposals should be directed to Dr. Garrett Ash at Yale University (garrett.ash@yale.edu). To gain access, data requesters will need to sign a data access agreement. Data will also be uploaded to NIH per the NIH data sharing agreement.

Representatives of the Institutional Review Board (IRB), regulatory agencies or study sponsor/funding agency may inspect all documents and records required to be maintained by the investigator for the participants in this study. The study site will permit access to such records.

8.2 Data Quality Assurance

As stated in Section 7.6:

Data Collection Forms

Continuous glucose monitoring data will be monitored every 2 weeks through the Dexcom application programing interface, and mobile diaries will be monitored daily through the GlucoseZone application programming interface. This monitoring will include audits for completeness. Other biosensors that continuously sync with their web application programming interface (Fitbit, insulin devices) will be monitored every 2 weeks through the relevant application programming interface. Actigraph hip watch data will be audited for completeness when the device is downloaded after each 2-week assessment period. Dr. Ash will also perform quarterly audits for conformance with source document completion.

Data Integrity and Protection of Databases

Databases will be exported quarterly from REDCap onto Yale University secure servers and audited for completeness and aberrant values using frequency statistics. Datasets from biosensors will be checked in on REDCap checklists as they are downloaded, and the checklists will be audited quarterly. Original reports of all biosensor downloads will be retained for verification and further data analysis.

8.3 Data or Specimen Storage/Security

For data storage and security, REDCap and Yale OneDrive are password-protected and only members of the research team will be given authorized access by the PI. All research team members will complete standard IRB trainings in protection of human subjects before being added to the protocol. All data is coded by anonymous study ID number which is linked in one section of the REDCap database to identifiers.

Certificate of Confidentiality

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information or documents that may identify participants in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless the participant has consented for this use. Information or documents protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if the participant has consented to the disclosure, including for their medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the National Institutes of Health (the United States federal government agency sponsoring the project) that is needed for their auditing or program evaluation. A Certificate of Confidentiality

does not prevent participants from voluntarily releasing information about themselves or their involvement in this research. If participants want their research information released to an insurer, medical care provider, or any other person not connected with the research, they must provide consent to allow the researchers to release it.

8.4 Study Records

Study records will be maintained by the PI and accessed by research staff on a Yale OneDrive folder. These include all IRB documents maintained on Yale OneDrive and IRES, an internal standard operating procedure manual, AE forms that follow a standard departmental template containing the items detailed in section 6.3, and confidential data sources (listed in section 8.1 paragraphs 3-4 and below in section 8.5). In addition, e-Consent forms are stored on REDCap and can be exported as pdfs for audits when necessary.

8.5 Access to Source

As stated in section 8.1:

Participant confidentiality and privacy is strictly held in confidence by the participating investigators, their staff, and the sponsor(s)/funding agency. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. While there is a possibility of a security breach compromising subject confidentiality, several steps will be taken to safeguard the confidentiality of subjects and their data as detailed below.

All research activities will be conducted in as private a setting as possible.

All research data collected outside of the mobile applications will be assigned a study participant number and that number will only identify participants in digital databases on REDCap or Actigraph Actilife. Audio-recorded interviews and orientation sessions will be transcribed and names, places, and any other identifying information will be removed. Recordings will then be promptly destroyed. The names of participants will not be associated with these data and assessments and transcriptions will be maintained according to participant study number. A master list connecting participant study numbers to participant names will be kept on a secure server where it can only be accessed by senior level project staff. Any information published as a result of the study will be such that it will not permit identification of any participant.

All research data that is collected via the mobile applications (CGM, diary/survey responses, exercise performance, insulin usage, carbohydrates, GPS) will be stored on the relevant web application programming interface (API) platforms (Dexcom, Fitbit, GlucoseZone), researcher dashboard (Keto-Mojo, Ilumivu, Qualtrics), or user dashboard (InPen) in accord with Yale Information Technology Services protocols (Sect 2.2, Table A1). After syncing the data, the data will be immediately deleted from the participants' biosensor devices and smartphones. Web-based application and user sessions are encrypted between the server and client browser through the use of industry standard SSL certificates. As soon as each participant completes the study protocol, their data will be immediately transferred from the API platform to Yale secure servers by secure file-protection strategies, assigned to the de-identified

participant study number noted in the previous paragraph, and deleted from the API platform. All data is encrypted both at rest and in transit.

Yale Information Technology Services has reviewed all devices that transmit data for the study. They have determined that the Actigraph GT9X blinded watch, Dexcom G6 CGM, Fitbit Inspire 3 smartwatch, Ilumivu Mobile Surveys, Qualtrics Mobile Surveys, InPen, and participants' own insulin pumps will not collect or transmit any HIPAA-covered health information for study purposes. They have determined that GlucoseZone in this study will collect and transmit HIPAA-covered health information, in a manner meeting the HIPAA privacy and institutional standards, including GlucoseZone's specific data use agreement with Yale University.

Right to privacy for participation in this research will be protected through alphanumeric coding of data (in place of names) and proper storage of research records, including interview transcripts and data downloaded from the web API platforms. Collected materials will be maintained via an alphanumeric reference system maintained by Dr. Ash. Participants' names will appear only on the consent form, the HIPAA authorization form, and a master list maintained on REDCap that is separate from research data. Our data collection and management procedures are fully compliant with HIPAA. Access will be limited to personnel intimately involved in the study. Electronic data will be deidentified and password protected. Only members of the study team will have access to the physical or electronic data.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in a password-protected OneDrive folder at the Yale School of Medicine Section of General Internal Medicine. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used will be secured and password protected. At the end of the study, all study databases will be de-identified and archived indefinitely at the Yale School of Medicine Section of General Internal Medicine.

Data availability: Individual deidentified participant data (including data dictionaries) will be shared. This includes individual participant data that underlie the results reported in any aspect of a published article (text, tables, figures, and appendices). Other documents that will be available include the study protocol, statistical analysis plan, informed consent form, and analytic code. The data will be available immediately following publication with no end date. Data will be shared with researchers who provide a methodologically sound proposal to achieve aims in the approved proposal. Proposals should be directed to Dr. Garrett Ash at Yale University (garrett.ash@yale.edu). To gain access, data requesters will need to sign a data access agreement. Data will also be uploaded to NIH per the NIH data sharing agreement.

Representatives of the Institutional Review Board (IRB), regulatory agencies or study sponsor/funding agency may inspect all documents and records required to be maintained by the investigator for the participants in this study. The study site will permit access to such records.

8.6 Retention of Records

Identifiers and consent forms will be retained on REDCap for 3 years following the completion of live data collection and anonymous data will be retained indefinitely.

8.7 Data and Safety Monitoring Plan

I. OVERVIEW

This clinical study is a feasibility study of the alpha version of an informatics-based digital application to promote safe exercise.

The Data and Safety Monitoring Plan (DSMP) outlined below for the study will adhere to the protocol approved by the Yale University IRB.

II. ADVERSE EVENTS

A. Adverse event assessment

The expected risks of this protocol are:

Confidentiality: Due to the collection of private identifiable information, there is a possibility of a security breach compromising subject confidentiality.

Hypoglycemia: There is risk of hypoglycemia due to exercise.

Hyperglycemia: There is a risk of hyperglycemia due to exercise. Hyperglycemia can lead to diabetic ketoacidosis.

Exercise-related injuries: Exercise may cause muscle soreness/pain, muscle strain, cardiovascular events, and tiredness during or after the activity.

Study questionnaires and interviews: Participants may experience some distress when discussing factors important to diabetes, diabetes management, and psychosocial stressors.

Continuous glucose monitoring (CGM): Participants will use Food and Drug Administration (FDA) approved Dexcom G6 CGM as part of the American Diabetes Association standard of care[70]. There is a low risk of developing a local skin infection at the site of the sensor needle placement. Itchiness, redness, mild bleeding, and or bruising may occur at the insertion site. Participants may develop localized reactions to adhesive used to secure the sensor.

Fitbit: In a very small number of participants (~3% in a recent report[72]) the Fitbit may contribute to skin irritation or allergies.

The approved protocol and consent form will address these risks.

Tracking

A. Daily monitoring during first 2 weeks for ketoacidosis, severe hypoglycemia, and other health risks associated with exercise:

We will detect any diabetic ketoacidosis or severe hypoglycemia within 24hr and suspend exercise until a personalized preventive strategy can be formed. To achieve this level of monitoring, a research assistant will monitor daily the biometric dashboard which contains Bluetooth-captured glucose, ketones, and exercise start/stop times. Safety signals include any of the following during or within 1hr of exercise: 1) Diabetic ketoacidosis (glucose ≥270 mg/dL + ketones ≥1.0 mmol/L), 2) Possible diabetic ketoacidosis (glucose ≥270 mg/dL and failure to test ketones), and 3) Possible severe hypoglycemia (glucose <55 mg/dL). Research staff will respond to each of these events within 24hr of its occurrence by informing the participant to immediately suspend the exercise program (app account will be suspended) until the participant has been contacted by a study physician. The physician will alert the participant and the participant's primary diabetes care provider to the issue and develop a prevention strategy, consulting with the primary diabetes care provider as needed. The exercise suspension will then be lifted, unless the participant has met the protocol's stoppage criteria (>1 episode of severe hypoglycemia, 1 episode of diabetic ketoacidosis not closely related to pump site failure).

In the event of the "possible" occurrences (#2, #3), physician contact can be replaced initially by research assistant contact to query symptoms. Then, if possible diabetic ketoacidosis is supported by the participant reporting symptoms, or possible severe hypoglycemia is supported by the participant reporting altered mental and/or physical status requiring assistance from another person for recovery, physician contact will be required as in paragraph #1 above.

We will detect any other exercise-associated health risks within 24-36hr and suspend exercise until a personalized preventive strategy can be formed. To achieve this level of monitoring, the morning survey question about prior day's clinical events (Appendix 8a, last question) will be asked of participants and monitored by research staff daily. If the participant reports a clinical event, the PI will complete Adverse Event review and summary (c.f. Protocol Sect 6.3) the same day (i.e., within 24-36hr of the reported event). If the event may be exercise-related, the participant will be informed to immediately suspend the exercise program (app account will be suspended) until the participant has been contacted by a study physician. The physician will alert the participant to the issue and develop a prevention strategy, consulting with the participant's primary diabetes care provider as needed. The exercise suspension will then be lifted, unless the participant has met the protocol's stoppage criteria.

B. Biweekly monitoring for mild hypo- or hyperglycemia:

Data on glucose, ketones, exercise timing, carbohydrate consumption, and insulin will be compiled by a research assistant and reviewed for each subject every 2 weeks at study team meetings by the principal investigator Dr. Ash and one of the study endocrinologists Drs. Weinzimer or Nally. The data will firstly be reviewed for patterns indicative of mild hypo- or hyperglycemia related to exercise. The most common are failure to take adequate carbohydrate supplementation relative to starting glucose values, nocturnal hypoglycemia following exercise, failure to adequately reduce pre-exercise bolus insulin, or starting exercise with elevated glucose values (Table 3, Sect 6.1.1). Safety issues will be noted and communicated to participant. Participant will be referred to their diabetes care provider if insulin dose adjustments are needed. The data will secondly be reviewed for adverse events. The study timetable has been set so that no more than 11 participants are active at one time, making this auditing manageable. Adverse events will be defined as severe hypoglycemia (an event that required assistance from another person to administer carbohydrate, glucagon,

or other resuscitative actions), diabetic ketoacidosis, and serious adverse events regardless of causality. Dr. Weinzimer will join at least every other occurrence of these meetings (i.e., at least every 4 weeks) and provide a second review of Dr. Nally's medical management decisions. Dr. Weinzimer is a world expert in CGM for T1D glycemic management in adult patients 18-25 years old, whose glycemic patterns are similar to those 30-65 years old. As a preeminent CGM authority he frequently advises adult endocrinologists on CGM issues. Regarding non-glycemic medical issues related to older age (e.g., angina history), Dr. Ilias Spanakis, an adult endocrinologist at the University of Maryland and previous collaborator of Dr. Ash (Dr. Ash's manuscripts[58,110] and Dr. Spanakis' own clinical trial NCT04800471), will be available for consultations. Participant histories will be de-identified prior to Dr. Spanakis' viewing and commenting.

C. Weekly monitoring for elevated blood pressure (BP) and symptoms

The protocol also includes tracking of blood pressure (BP) so that participants developing uncontrolled accelerated hypertension can be removed from the study and referred for follow-up. Weekly tracking protocols are based upon Dr. Ash's dissertation[65] and a prior exercise clinical trial conducted in the same laboratory[111] overseen by Dr. Paul Thompson, Chief of Cardiology, Hartford Hospital. In those trials, participants with pre- to stage 1 hypertension safely performed moderate to maximal exercise. Those trials utilized office BP criteria of uncontrolled accelerated hypertension (systolic > 160 mmHg and/or diastolic >100 mmHg) for study exclusion which are cutoffs where consensus guidelines recommend more careful monitoring[95]. We will use these cutoffs. The specific procedures are below:

BP will be checked by all participants at all weekly visits (visits 2-10) by standard home monitoring procedures[95]. Briefly, we will take the average of 2 brachial artery measurements after ≥12 hours abstention from acute blood pressure confounders (exercise, caffeine, alcohol, tobacco, nicotine) and ≥5 minutes of quiet rest using the Omron BP7350 (Omron Healthcare), which includes a rigid cuff that minimizes fitting errors. If the measurements differ by >5 mmHg, then a third will be taken and the closest two will be averaged. In the event of a result meeting the home BP monitoring criteria for uncontrolled accelerated hypertension (systolic >145 mmHg and/or diastolic >90 mmHg), the result will be faxed to the participants' primary diabetes healthcare provider as a possible early indicator of true uncontrolled accelerated hypertension. In the event of a result meeting uncontrolled accelerated hypertension (systolic >160 mmHg and/or diastolic >90 mmHg) the participant will be withheld from exercise participation until BP can be reassessed at least one day later. In the event of a second occasion meeting these values, the participant will be removed from the study and referred to their healthcare provider for follow-up.

The research assistant will ask the participant if they are having any of the symptoms overviewed on the consent form or any other injuries that could be made worse by exercising. In the event of positive responses, exercise physiologist (EP) Dr. Ash will contact them to ask follow-up questions, following protocols from the American College of Sports Medicine[113], to determine if they are indicative of pathology. If they are, Dr. Ash will report the episode to study physician Dr. Stuart Weinzimer and the participant's own PCP and suspend the participant's exercise participation unless receiving PCP clearance to continue. For complaints that are musculoskeletal issues that can be temporarily avoided by the EP Dr. Ash recommending GlucoseZone videos that avoid the injured area, then such videos can be continued without PCP clearance.

Steps to Minimize

Among enrolled subjects, steps will be taken to minimize risks of hypoglycemia and hyperglycemia as detailed in section 2.2, "Protection against Risks". Briefly, these include

instructions to participants regarding safe blood glucose testing habits, regular tracking of hypoglycemia and hyperglycemia as described above, blood glucose monitoring review by Drs. Ash and Nally every 2 weeks with clinical referrals by Dr. Nally as appropriate, second check of Dr. Nally's medical management decisions by Dr. Weinzimer at least every 4 weeks, and routine clinical support. Regarding non-glycemic medical issues related to older age (e.g., angina history), Dr. Spanakis will be available for consultations.

Participants will be instructed to call the Yale 24-hour access to nurse and/or physician consultation or 911 if they have any instances of severe hypoglycemia, diabetic ketoacidosis, or other severe clinical event. Non-Yale-affiliated participants will be required to submit information regarding their providers and will be instructed to call 911 if they do not have access to 24-hour consultation and experience an adverse event. Any such instances noted on participant diary surveys will be reviewed by our study team and forwarded to their diabetes provider. Patients will be instructed to suspend exercise until they have a chance to connect with their provider who will then determine the next steps regarding resumption of exercise and ongoing mobile application usage. Any day-to-day decisions about clinical care including adjustment of insulin doses or CGM target ranges will be made by the participant's provider, not the study physicians.

These protocols have been utilized by Drs. Ash, Weinzimer, and Nally over four prior exercise clinical trials among youth and adults with T1D that had no instances of severe hypoglycemia or diabetic ketoacidosis (HIC #s 1605017843, 2000025992, 2000030105, 2000033736).

***Exercise-related injuries*:**

To minimize adverse events during exercise we will exclude patients who have chronic disease or physical disability that would influence treatment intervention or preclude participation in regular exercise. Information to make this determination will be collected by Dr. Ash administering the Physical Activity Readiness Questionnaire, a consensus instrument endorsed by the American College of Sports Medicine designed to capture medical history pertinent to exercise[112]. This information is then processed in three steps. First, individuals meeting any of the following conditions will be excluded: diabetic ketoacidosis not clearly related to pump site failure in past 6 months, >1 episode of severe hypoglycemia in past 6 months, home blood pressure >160 mmHg systolic or >100 mmHg diastolic, chronic renal failure, pregnancy, cognitive impairment, inability to read and/or understand English, severe retinopathy, neuropathy or nephropathy, history of uncontrolled arrhythmia (e.g., Afib with RVR, new onset Afib, ventricular tachycardia, escape rhythms), congestive heart failure (stage 3 or 4), exercise-induced asthma (not controlled on inhalers), chronic obstructive pulmonary disease (requiring home oxygen), myocardial infarction and (or) angina in the past 12 months. Second, one of the study physicians Drs. Weinzimer or Nally will review any positive responses from the questionnaire not listed in the previous sentence. If they determine any of the positive responses would influence treatment intervention or preclude participation in regular exercise (e.g., recent spinal surgery), that individual will also be excluded. Third, the individual's primary care provider (PCP) will be contacted for confirmation (Appendix 24). Individuals passing this screening will be considered medically cleared to enroll, although Dr. Weinzimer or Nally or the individual's own PCP can revoke clearance at any time during the study, for example if the patient has a change in clinical status and/or a response to exercise that EP Dr. Ash, Dr. Weinzimer or Dr, Nally determines warrants a stoppage of usage of the mobile application. At any stage of this process, Dr. Spanakis will be available for Drs. Ash, Weinzimer or Nally to consult on medical issues related to older age (e.g., angina history).

Also to minimize the risk of injuries or strains, participants will complete the GlucoseZone videos warm-up and cool-down routines. In addition, they will be coached to initially select

classes from the “beginner” category and “short” to “medium” duration (15-40 minutes). Though risk of serious injury is minimal, if pain persists or prevents daily activities, participants will be encouraged to contact their healthcare provider.

In addition, symptoms and blood pressure are monitored and evaluated weekly (see above “Tracking”, section C).

Study Questionnaires and Interviews
Research participants who report negative psychological reactions to the research protocol, or negative emotional reactions to diabetes elicited during participation in the research study, will be referred to their regular clinical provider. If research staff determine that the degree of psychological reaction is severe, the physician staff of the study (Dr. Weinzimer or Dr. Nally) will be contacted to assess the participant and determine whether acute urgent referral is needed.

Continuous glucose monitoring (CGM)
Risks of glucose sensor insertion will be minimized because participants will be instructed to cleanse skin aseptically prior to insertion. Participants will receive training on sensor use if they have not used the sensor previously.

Fitbit
In a very small number of participants (~3% in a recent report[72]) the Fitbit may contribute to skin irritation or allergies. To minimize this risk, participants will be trained in manufacturer guidelines including keeping it dry, not wearing it too tight (loose enough that it can move back and forth on the wrist, moved 2-3 finger widths above wrist bone during exercise only), and giving the wrist a rest by removing the band for an hour every couple of days.

B. Adverse event reporting

Every event that is reported to either the principal investigator or the designated research associates by the subject or medical staff caring for the subject and which meets the criteria will be documented.

An adverse event report will be generated for each event. The report will include
*description of the event
*likelihood of being related to the study
*when and how it was reported
*any official chart records or documentation to corroborate the event

The report will be supplied to the principal investigator, the study physicians Drs. Nally and Weinzimer, the data and safety monitoring board (DSMB), the Yale University IRB, and the NIDDK program official responsible for the award. The DSMB is chaired by Denise Esserman, PhD (statistician at Yale Center for Analytical Sciences) who currently chairs a DSMB for the National Institute of Aging and has served on 10+ DSMB boards. The other members are Sarah Chhabra, MD (board-certified endocrinologist at University of Virginia) and Sean Fournier, MS (exercise physiologist at Yale-New Haven Hospital Heart and Vascular Center). No DSMB members are affiliated with the study or investigators.

Timeline for reporting

Events that may require a temporary or permanent interruption of study activities by the Principal Investigator or sponsor to avoid potential harm to subjects will be verbally reported immediately (if possible) with a written report filed within 5 calendar days.

Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related to study procedures) will be filed as a written report within 5 calendar days.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) will be filed as a written report within 5 calendar days. UPIRSOs applicable to this study include:

• Adverse device effects from any of the biosensors (continuous glucose monitor, smartwatch, insulin smartpen, hip accelerometer), since no adverse effects are expected from any of the devices used in the study.
• Adverse events or injuries that are serious, unexpected, *and* related;
• Breaches of confidentiality involving risks;
• Interim analyses altering the risk/benefit profile by identification of increased risks;
• Revisions to safety information, such as MedWatch Reports, that meet the definition of a UPIRSO;
• New information indicating an unexpected increase in risks or decrease in potential benefits (e.g., literature/scientific reports or other published findings);
• Protocol deviations, violations, or other accidental or unintentional changes to the protocol or procedures involving risks or with the potential to recur;
• Unapproved changes made to the research to eliminate an apparent immediate hazard to a subject;
• Other problem or finding (e.g., loss of study data or forms) that an investigator or research staff member believes could influence the safe conduct of the research.

Events that do not require prompt reporting and are only documented at regular reports (twice yearly to DSMB, annual renewals to the Yale IRB, and annual progress reports to NIDDK) are:

• Anticipated adverse events (described in Section II-A)
• Adverse device effects that are non-serious, anticipated, *or* unrelated;
• Adverse events or injuries that are non-serious, expected, *or* unrelated;
• Deaths not attributed to the research (e.g., from “natural causes,” accidents, or underlying disease when the Principal Investigator and the DSMB have ruled out any connection between the study procedures and the subject’s death);
• Interim analyses not altering the risk/benefit profile;
• Protocol deviations or violations unlikely to recur or not involving risks to subjects;
• Subject complaints that were resolved or complaints not involving risks
• Problems or findings not involving risk (unless the PI believes the information could affect subjects’ willingness to continue in the research)

Any action resulting in a temporary or permanent suspension of this study (e.g., IRB actions, or actions by the investigators) will be immediately reported to the appropriate NIDDK program official.

III. Safety Review Plan and Monitoring

Oversight of participant safety includes review of adverse events as well as study progress, data integrity and study outcomes.

A. Justification of sample size

As described in section 7.2:

This is a pilot study with primary objectives to test feasibility and acceptability, for which a typical sample size is 10-40 participants[1]. Within this range we chose 24 participants to first ensure thematic saturation of interviews (aims 1-2, 2-3), and second achieve adequate power for one of the secondary objectives, specifically hypothesis 2-1-1. Based on my past retention and adherence among sedentary adults with and without T1D (88% participants completed, they provided 83% of ecological momentary assessments on longer surveys than the present study, 90% continuous glucose monitor wear, and 95% accelerometer wear)[58,104] I expect 21 completers with an average of 50 complete observations each over T1-T2. Thus, using previous psychometrics of the CRAVE wants and aversions (.28/.39 ICC, 9.9/12.3 total variances)[52] I expect design effects of 14.21/20.11 and standard errors of 0.37/0.48, yielding 91%/81% power to detect predictors having ≥ .34 correlation (e.g., pleasure[52], fear of hypoglycemia[42]). For other secondary objective hypotheses (2-1-2, 2-2-1, 2-2-2) the study is not designed to detect statistical significance but calculate effect sizes (Cohen's f^2) for purposes of determining whether the WANT[48-52], SCT model[54-56], or both generate a signal for prediction of physical activity behavior.

B. Safety and study progress reviews

Dr. Ash will have primary responsibility for ongoing monitoring of adverse events and submitting reports according to the timetables in section II-B to the study physicians Drs. Nally and Weinzimer, the DSMB, the Yale University IRB, and the NIDDK program. The DSMB will review all adverse events and make recommendations. Dr. Ash will notify NIDDK of IRB-approved revisions to the study protocol that indicate a change in risk entity as appropriate and (if applicable) the action plan for the response, as well as notice of any actions taken by the IRB or regulatory bodies regarding the research and any responses to those actions.

Dr. Ash and the DSMB will review reports of safety as they are made according to the timetables in section II-B; thus, serious events will be reviewed within 5 days of their occurrence, and events that do not require prompt reporting will be reviewed at regular meetings occurring twice per year between Dr. Ash and the DSMB. The DSMB will not provide real-time feedback.

Dr. Ash will review study progress every 3 months. This will include recruitment (number of participants approached, number eligible, number enrolled, reasons for ineligibility and non-enrollment), retention (percentage of participants completing baseline and follow-up assessments, reasons for dropouts), and adherence (biosensor wear time, percentage of daily mobile diaries completed).

Dr. Ash will hold a research meeting every 2 weeks with study physician Dr. Nally as well as Dr. Weinzimer's research nurses and coordinators involved with the study to review the status of all enrolled participants and discuss the eligibility of potential participants. At this biweekly

meeting, they will review study progress (i.e., recruitment goals, retention, protocol adherence). Any adverse events will be reviewed at this meeting including serious adverse events that may have been attended to outside of this biweekly meeting. Dr. Weinzimer will join at least every other occurrence of these meetings (i.e., at least every 4 weeks) and provide a second review of Dr. Nally's medical management decisions. Dr. Spanakis will be available for consultations on medical issues related to older age (e.g., angina history).

An annual progress report will be submitted to NIDDK and the Yale University IRB that lists and summarizes adverse events; documents whether adverse event rates are consistent with pre-study assumptions; summarizes recruitment and retention and reason for dropouts; and summarizes study progress related to the stated aims.

C. Stopping Rules

The sole stopping rule will be clear evidence of harm.

There is no possibility in the present study of futility of treatment or overwhelming evidence of the benefit of treatment. This is because the purpose of the study is to develop and improve an intervention that will not be tested in a randomized controlled trial against usual care until a future study.

IV. Informed Consent

Informed consent will be obtained from each subject at entry into the study. The informed consent process is described in section 5.5. Briefly, written consent to participate will be obtained from all participants after the research procedures and risks associated with participation have been explained. The entire consent form will be reviewed in detail with the participant via one-on-one HIPAA-compliant televideo (Zoom, San Jose, CA). They will be asked to take the video call from a private setting which the researcher will verbally verify before starting the consent process. The consent form will provide clear and explicit language about the intervention components, assessments, and study procedures. Any questions the participant may have will be addressed. In order to identify and clarify any misconceptions, subjects will be encouraged to describe the research procedures and their associated risks in their own words, followed by correction of any errors by the research staff member completing the consent. An Informed Consent Quiz is used to ensure understanding of study procedures. All research staff will receive extensive training from Dr. Ash in appropriate procedures to obtain informed consent, including administering these measures of capacity to provide informed consent. If participants wish, they may keep the consent form and consider it further before signing. They may also request to speak to anyone on the research team about questions they have or to consult others, including their physician and family members.

Following resolution of any questions or concerns, the participant will be asked to sign the eConsent form on REDCap, if he/she agrees to participate.

Dr. Ash will perform monthly audits for conformance with informed consent requirements.

V. Data Quality and Management

Dr. Ash will be responsible for data quality and management.

Data Collection Forms

As described in section II-A, continuous glucose monitoring data will be monitored every 2 weeks through the Dexcom application programing interface, and mobile diaries will be monitored daily through the GlucoseZone application programming interface. This monitoring will include audits for completeness. Other biosensors that continuously sync with their web application programming interface (Fitbit, insulin devices) will be monitored every 2 weeks through the relevant application programming interface. Actigraph hip watch data will be audited for completeness when the device is downloaded after each 2-week assessment period. Dr. Ash will also perform quarterly audits for conformance with source document completion.

Data Integrity and Protection of Databases

Paper source documents will be entered into REDCap on a quarterly basis. Databases will be exported quarterly from REDCap, Ilumivu, Qualtrics, and Actigraph Actilife onto Yale University secure servers and audited for completeness and aberrant values using frequency statistics. Datasets from biosensors will be checked in on REDCap checklists as they are downloaded, and the checklists will be audited quarterly. Original reports of all biosensor downloads will be retained for verification and further data analysis.

VI. Confidentiality

As described in Section 2.2 Risks:

While there is a possibility of a security breach compromising subject confidentiality, several steps will be taken to safeguard the confidentiality of subjects and their data. All research data collected outside of the mobile applications will be assigned a study participant number and that number will only identify participants in digital databases on REDCap, Ilumivu, or Actigraph Actilife. Audio-recorded interviews and orientation sessions will be transcribed and names, places, and any other identifying information will be removed. The names of participants will not be associated with this data and assessments will be maintained according to participant study number. A master list connecting participant study numbers to participant names will be kept on a secure server where it can only be accessed by senior level project staff. Any information published as a result of the study will be such that it will not permit identification of any participant.

All research data that is collected via the mobile applications (CGM, diary responses, exercise performance, insulin usage, carbohydrates, GPS) will be stored on the relevant web application programming interface (API) platforms (Dexcom, Fitbit, GlucoseZone), researcher dashboard (Ilumivu, Qualtrics), or user dashboard (InPen) in accord with Yale Information Technology Services protocols. After syncing the data, the data will be immediately deleted from the participants' biosensor devices and smartphones. Web-based application and user sessions are encrypted between the server and client browser through the use of industry standard SSL certificates. As soon as each participant completes the study protocol, their data will be immediately transferred from the API platform to Yale secure servers by secure file-protection strategies, assigned to the de-identified participant study number noted in the previous paragraph, and deleted from the API platform. All data is encrypted both at rest and in transit.

Right to privacy for participation in this research will be protected through alphanumeric coding of data (in place of names) and proper storage of research records, including interviews and data downloaded from the web API platforms. Collected materials will be maintained via an alphanumeric reference system maintained by Dr. Ash. Participants' names will appear only on the consent form, the HIPAA authorization form, and a master list maintained on REDCap that is separate from research data. Our data collection and management procedures are fully compliant with HIPAA. Access will be limited to personnel intimately involved in the study. Electronic data will be deidentified and password protected. Only members of the study team will have access to the physical or electronic data.

9 Study Considerations

9.1 Institutional Review Board (IRB) Review

The protocol will be submitted to the IRB for review and approval. Approval of the protocol must be obtained before initiating any research activity. Any change to the protocol will require an approved IRB amendment before implementation. The IRB will have final determination whether informed consent and HIPAA authorization are required.

Study closure will be submitted to the IRB after all research activities have been completed.

Other study events (e.g. data breaches, protocol deviations) will be submitted per Yale policies.

9.2 Research Personnel Training

Research Associate James Lukasik will learn to train participants in CGM use. He will complete practice sessions with Dr. Ash, receive feedback, and repeat until all feedback has been incorporated successfully.

The study physicians Drs. Weinzimer and Nally hold endocrinology board certifications as well as extensive experience with safety review of BG data for our prior exercise studies (see section 1.2).

The qualitative analysis overseer Dr. Griggs and mentor Dr. Fucito are investigators with extensive qualitative research experience and publication track record.

The RA from Case-Western Reserve assisting Dr. Griggs will complete standard training protocols from her laboratory. Quality check steps with Dr. Griggs are also instilled into data analysis (sect 7.2.1, hypothesis 2-3).

9.3 Study Monitoring

Safety monitoring will be handled by the PI and study physician (section 6.3).

Data quality monitoring will be handled by the PI (section 8.2).

9.4 Unanticipated Problems and Protocol Deviations

A protocol deviation is any noncompliance with the protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site investigator to identify and report deviations within 5 working days of identification of the protocol deviation. All deviations must be addressed in study source documents, reported to the study sponsor, and the reviewing Institutional Review Board (IRB) per their policies.

Unanticipated problems involving risks to participants or others include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

If the study team becomes aware of an unanticipated problem (e.g. data breach, protocol deviation), the event will be reported to the IRB by a Report of New Information (RNI).

The UP report will include the following information:

Protocol identifying information: protocol title and number, PI's name, and the IRB project number;

- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs will be reported to the IRB within 5 days of the investigator becoming aware of the event.

9.5 Study Discontinuation

The sole stopping rule is clear evidence of harm.

The study may also be discontinued as a corrective action to an Unanticipated Problem (UP) as defined above, if deemed warranted by the PI, the study physician, or the IRB.

9.6 Study Completion

The expected completion date is February 28, 2025. The IRB will be notified by submission of a closure request. The sponsor will be notified in the next annual report.

9.7 Conflict of Interest Management Plan

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the appropriate conflict of interest review committee has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

All investigators will follow the applicable conflict of interest policies.

Consultant Mr. Charles O'Connell is the managing member and a shareholder of Fitscript LLC, the manufacturer of GlucoseZone. He is also the inventor of GlucoseZone and related patents on algorithms for diabetes exercise therapy. As his study responsibilities are limited to assisting with downloading, navigating, and troubleshooting the app, there is no conflict of interest.

Consultant Ms. LaurieAnn Scher is a paid employee of Fitscript LLC. Like Mr. O'Connell, her study responsibilities are limited to assisting with downloading, navigating, and troubleshooting the app, so there is no conflict of interest.

Otherwise, the PI and study team have no financial, intellectual property, recognition, or other interest from GlucoseZone or any other entity providing devices for this study.

9.8 Funding Source

Parent award is funded: 1K01DK129441-01

Also a supplement award is funded**:** 3K01DK129441-01A1 (GRANT13855443)

9.9 Publication Plan

The PI is responsible for presenting and publishing the study results, and held accountable for this responsibility by the sponsor, department, and university. Academic channels will be used to disseminate the results as widely as possible. We plan to present our results extramurally at the American Diabetes Association Scientific Sessions or the Society of Behavioral Medicine. We will also present the data intramurally at the Yale Diabetes Research Center Works in Progress Seminar. We also plan to publish at least 1 manuscript based on the results of this research. We will target journals that have published our previous similar manuscripts such as Pediatric Diabetes and Journal of Medical Internet Research, along with similar ones such as Diabetes Care, Diabetes Technology and Therapeutics, and Journal of Medical Internet Research Diabetes.

10 Appendices

Note: Highlighted appendices are instruments previously validated in the literature

Appendix #	Title	Section	Topic
1a	**Phone Screen Intro**	**5.4**	Study questionnaires, measures, focus groups/interview questions
1b	**Phone Screen Eligibility**	**5.4**	Study questionnaires, measures, focus groups/interview questions
1c	**Phone Screen Clinical History**	**5.4**	Study questionnaires, measures, focus groups/interview questions
1d	**Demographics**	**6.1.1 (Visit 1)**	Study questionnaires, measures, focus groups/interview questions
1e	**Contact Details**	**6.1.1 (Visit 1)**	Study questionnaires, measures, focus groups/interview questions
2a	**CRAVE Past Week**	**6.1.1 (Table 2)**	Study questionnaires,

			measures, focus groups/interview questions
2b	**CRAVE Right Now**	**6.1.1 (Table 2)**	Study questionnaires, measures, focus groups/interview questions
3a	**Fear of hypoglycemia past week**	**6.1.1 (Table 2)**	Study questionnaires, measures, focus groups/interview questions
3b	**Fear of hypoglycemia right now**	**6.1.1 (Table 2)**	Study questionnaires, measures, focus groups/interview questions
4	**Exercise Self-Efficacy**	**6.1.1 (Table 2)**	Study questionnaires, measures, focus groups/interview questions
5	**Exercise Self-Regulation**	**6.1.1 (Table 2)**	Study questionnaires, measures, focus groups/interview questions
6a	**Pleasure & Displeasure Past Week**	**6.1.1 (Table 2)**	Study questionnaires, measures, focus groups/interview questions

6b	**Pleasure & Displeasure Right Now**	**6.1.1 (Table 2)**	Study questionnaires, measures, focus groups/interview questions
6c	**Arousal & Activation Past Week**	**6.1.1 (Table 2)**	Study questionnaires, measures, focus groups/interview questions
6d	**Arousal & Activation Right Now**	**6.1.1 (Table 2)**	Study questionnaires, measures, focus groups/interview questions
7	**Daily Intention, Competing Demands, Illness**	**6.1.1 (Table 2)**	Study questionnaires, measures, focus groups/interview questions
8	**Daily survey in app**	**6.1.1 (Visit 4)**	Study questionnaires, measures, focus groups/interview questions
9a	**Code for tool #2 (just-in-time adaptive messaging)**	**6.1.1 (Visit 4)**	Other
9b	**Code for tool #4 (health outcome feedback regarding the causal impact of**	**6.1.1 (Visit 4)**	Other

	exercise upon blood glucose)		
10	**Interview Guide for weekly app satisfaction**	**6.1.1 (Visits 5-8)**	Study questionnaires, measures, focus groups/interview questions
11	**Exit survey**	**6.1.1 (Visit 8)**	Study questionnaires, measures, focus groups/interview questions
12	**Interview Guide for motivation states**	**6.1.1 (Visit 10)**	Study questionnaires, measures, focus groups/interview questions
13	**MyChart Recruitment Message**	**5.4**	Recruiting Text
14	**Recruitment Images**	**5.4**	Recruiting Images
15	**Recruitment Text**	**5.4**	Recruiting Text
15b	**Recruitment Flyers and Social Media Postings, full layouts**	**5.4**	Recruiting Text and Images
16	**Data and Safety Monitoring Plan**	**8.7**	Data and Safety Monitoring Plan
17	**Daily encouragements to exercise**	**6.1.1 (Visit 4, tool #2)**	Participant-facing intervention

18	**Biometric Report**	**6.1.1 (Visit 4, tool #4)**	Participant-facing intervention
18b	**Exercise videos**	**6.1.1 (Visit 4, tool #1)**	Participant-facing intervention
19	**Letter to diabetes care provider of participant**	**6.1.1 (Visit 1)**	Provider-facing intervention
20	**Machine-learning manuscript**	**6.1.1 (Visit 4, tool #2)**	Other
21	**CGM training and manual**	**6.1.1 (Visit 2)**	Participant-facing intervention
22a	**Exercise Safety Orientation and Handout**	**6.1.1 (Visit 4, Tool #1)**	Participant-facing intervention
22b	**Exercise Data Monitoring**		
23	**InPen Training and Manual**	**6.1.1 (Visit 2)**	Participant-facing intervention
24	**Eligibility confirmation form for primary care provider of participant**	**5.4**	Provider-facing intervention
25	**Process for notifying and reconsenting participants of changes**		Other

11 List of Tables

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