Study Title: **Evaluation of an Intervention for Young Adults With Diabetes: Resilient, Empowered, Active Living-Telehealth (REAL-T)**

NCT Number: **NCT04023487**

Version Date: **06/08/2022**

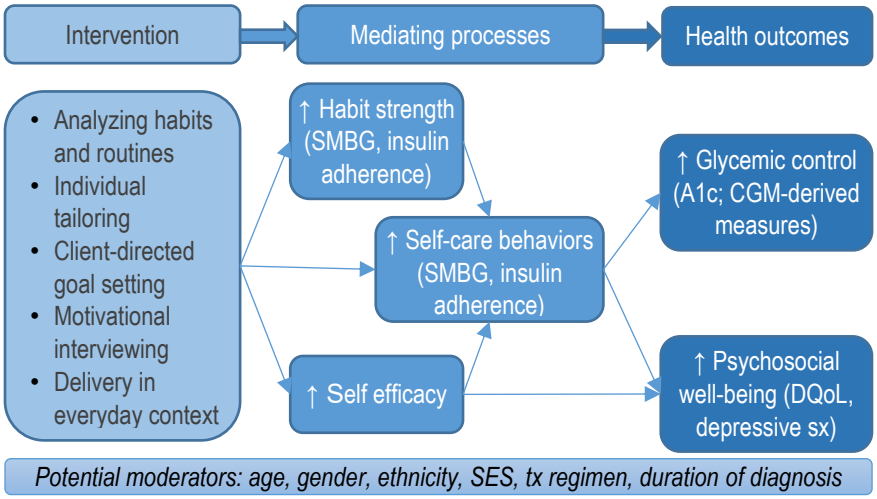
RESEARCH STRATEGY

Scientific Premise and Overall Impact. Young adults (YAs) with type 1 diabetes (T1D), in particular those from low-SES and racial/ethnic minority backgrounds, are widely recognized as one of the most vulnerable and difficult-to-reach populations with diabetes. In a previous mid-sized RCT, our study team obtained evidence for the efficacy of *Resilient, Empowered, Active Living (REAL),* a community-based intervention addressing self-management and psychosocial well-being in YAs with T1D.[1, 2] In this study, the REAL intervention improved hemoglobin A1c (p=0.01; clinically meaningful change of -0.81% in YAs with T1D) and diabetes-related quality of life (DQoL; p=0.04) among low-SES, primarily minority YAs with diabetes (N=81). In a subsequent proof-of-concept study, we demonstrated that REAL is feasible and acceptable to deliver via telehealth (REAL-T), which for several reasons (see below) provides an improved method of intervention delivery for YAs with T1D. The currently proposed R01 builds upon our prior work by evaluating, on a larger scale, the efficacy, long-term effects, mediating mechanisms, and cost implications of REAL-T. *In doing so, we lay the groundwork to shift the paradigm of diabetes care through an innovative, scalable intervention which has the potential to improve health and well-being among a highly vulnerable population whose needs have not been adequately addressed by traditional self-management interventions.*

Summary of Scientific Premise and Significance. Diabetes exacts enormous human and economic costs, and the need for effective interventions to combat its negative effects on health and well-being is especially acute among YAs and disadvantaged populations.[73] Further, with the cost of healthcare escalating, scalability and cost efficiency should be primary considerations in the development and adoption of innovative interventions. Therefore, this project will fill a critical gap by evaluating a telehealth-adapted self-management intervention with strong preliminary evidence demonstrating its efficacy among YAs with T1D, and which may potentially be extended to other populations including YAs with T2D and other age groups with T1D or T2D.

Conceptual Model. The conceptual model underlying REAL-T is outlined in Figure 1. This model was informed by a process evaluation of REAL RCT data (including statistical analysis of process variables, therapist treatment notes, and participant and therapist interviews) as well as by a review of existing literature.[83, 96-99] As suggested by the model, we expect that improvements in glycemic control (A1C, time in range) will be mediated primarily through increased performance of health behaviors (SMBG, insulin adherence), while improvements in psychosocial well-being (DQoL, depressive symptoms) will primarily be mediated by improvements in self-efficacy. Furthermore, we anticipate that changes in health behaviors will be mediated by changes in habit strength and self-efficacy. In addition to examining mediating pathways of intervention effects, we will examine whether intervention effects are moderated by key demographic or clinical variables including age, gender, ethnicity, SES, treatment regimen (multiple daily injections vs. pump; CGM yes/no), or duration of diagnosis.

Figure 1. Conceptual Model of REAL-T Intervention



REAL-T Intervention. *Overview.* The REAL-T intervention applies theoretical principles and therapeutic strategies drawn from Lifestyle Redesign,[96] habit change theory,[83] patient empowerment,[98] the transtheoretical model,[99] and motivational interviewing[97] to address concrete self-care challenges encountered by YAs with diabetes.[3] Lifestyle Redesign is an intervention framework which applies principles of OT to the prevention and management of chronic conditions, and has been shown to cost-effectively improve physical and mental health outcomes among diverse populations and age groups.[72, 100-104] The intervention is client-centered and individually tailored, with treatment goals and activities developed collaboratively by the client and therapist. REAL-T emphasizes the integration of self-care within sustainable habits and routines through a client-directed process of activity analysis and evidence-based strategies to promote habit formation and maintenance, including chaining, repetition, creating environmental cues, and linking activities to rewards.[83] To meet the

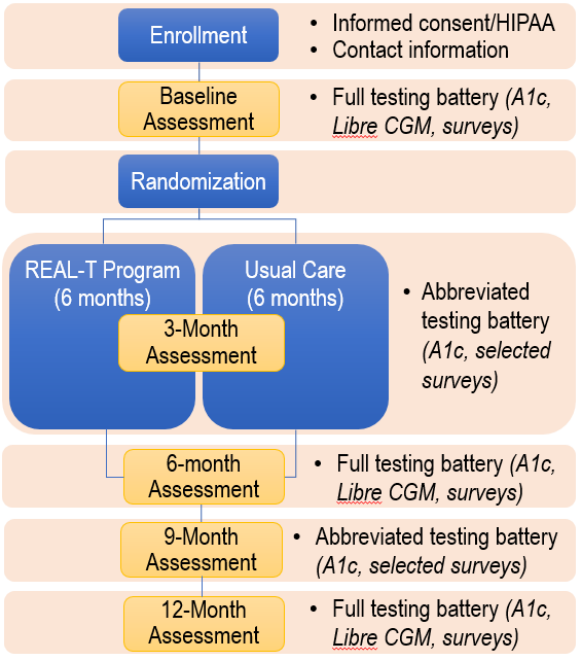
needs of clients at varying stages of readiness to change, REAL-T uses communication strategies drawn from motivational interviewing to address ambivalence, and tailors treatment activities to match the client's readiness to change. This process supports the development of self-efficacy by matching activities to clients' interests, motivation, and skills, thereby facilitating experiences of mastery in diabetes self-care.

REAL-T Intervention Process. REAL-T participants will receive approximately 12 hours of REAL-T over 6 months, delivered by a licensed occupational therapist (OTR/L) with a minimum of 12 continuing education hours in diabetes education and 12 hours in motivational interviewing training within the past 2 years, and 20 hours of training in the REAL-T intervention manual. An endocrinologist and a psychologist will be available for as-needed consultation with the OTR/L to address emergent medical and mental health issues that fall outside of the OT scope of practice. The first intervention session takes place in-person at a location of the client's choosing (client's home, local community setting, or the OTFP outpatient clinic). If an in-person meeting is not feasible, the initial evaluation will take place via telehealth (videoconferencing). Subsequent sessions will take place using a HIPAA-compliant telehealth platform, which clients can access through both a web browser and smartphone app. Clients who do not have a computer and who are within driving distance of the study office will be loaned a study-purchased laptop for the duration of their intervention period, and clients who have a computer without a webcam will be given a webcam to facilitate videoconferencing.

Intervention Fidelity will be documented through three strategies that were employed successfully in our initial RCT. First, therapists will document their adherence to the intervention protocol (e.g., timing and duration of sessions, use of manualized intervention content) in all treatment notes. Second, approximately 10% of sessions, chosen at random, will be observed and/or recorded, with participants' permission, by an investigator or second intervener trained in the intervention, who will complete a fidelity checklist and provide feedback to the treating therapist. Finally, weekly meetings will be held in which the Clinical Director and treating therapists will discuss client progress and conduct refresher training.

Communication with Providers. For several pragmatic reasons, REAL-T will not be integrated within a particular clinic or health system, but rather will be offered to any YA meeting eligibility criteria. Thus, we will draw on several strategies to facilitate open communication with providers. First, we will request clients' medical records prior to initiating OT services, to gain an accurate overview of their medical histories and current diabetes treatment regimens. Second, we will initiate several points of informational outflow with clients' providers. These will include (a) notice of the patient's enrollment in REAL-T; (b) an initial OT evaluation and plan of care; (c) summaries of quarterly lab and psychosocial survey results; (d) notification of significant medical events; and (e) a discharge summary upon the patient's completion of REAL-T. Clients who do not have a provider at the time of enrollment will be referred by the research team to one of the study's partnering clinical sites or another provider in their area.

Figure 2. Participant Flow Diagram



Overview of Study Design. Our primary aim is to analyze the efficacy of the 6-month REAL-T intervention in a large-scale two-arm RCT. To achieve this aim, N=210 YAs with T1D will be randomized evenly to two conditions: REAL-T or usual care control. The primary outcome is A1c, with key secondary outcomes pertaining to psychosocial well-being (depressive symptoms, diabetes distress, and DQoL). In addition, we will examine the effects of REAL-T after 3- and 6-month no-treatment follow-up periods. Furthermore, we will analyze mediating mechanisms of the intervention's effects on outcomes through structural equation modeling, and conduct exploratory analyses to evaluate the cost-effectiveness, cost impact, and change in QALYs associated with the REAL-T intervention relative to usual care. Quarterly data collection visits, performed over a 12-month period, will enable longitudinal modeling of changes in glycemic control, psychosocial well-being, and other primary and secondary endpoints. In addition, blinded CGM data collected at baseline, 6 months (immediately post-intervention), and 12 months (long-term follow-up) will facilitate a more robust analysis of the impact of the REAL-T intervention on glycemic control, through

an examination of changes in glycemic variability, percent time in range, percent time in hypoglycemia, and percent time in hyperglycemia. Figure 2 provides an overview of data collection throughout the study period.

Participants. Eligibility criteria, as outlined in Table 3, were chosen to ensure a medically stable pool of participants and maximize the potential of therapeutic benefit. In addition, the intervention is most appropriate for those with demonstrated diabetes care challenges and risk of developing complications, as evidenced by an elevated A1c level. Because of key differences in the pathophysiology and management of T1D and T2D, we have elected to restrict participation to YAs with T1D only.

Table 3. Study Eligibility Criteria

Inclusion	Exclusion
• T1D for ≥12 months • A1c ≥7.5% at time of study enrollment • Age 18-30 yrs. at time of study enrollment • English or Spanish speaking • Resides in a state where our OT clinicians are licensed where the participant has access to a local healthcare provider in the event of emergency and can complete data collection in person (when permitted), or via mailings (when required during period of social distancing or due to distance from study site), or via contactless data collection in the community • Participant has access to a laptop or desktop computer, either their own or loaned by the study (if geographically feasible and permitted given COVID-19 social distancing distractions) • Willing to participate in 6-month intervention	• Currently pregnant or planning to become pregnant within the next 12 months • Previously received REAL intervention • Cognitive impairment or severe disability limiting life expectancy

To verify eligibility, we need to confirm A1C. Estimated A1C will be used for initial enrollment, and verified through A1C test results received from our laboratory. Estimated A1C will be identified through: (1) recent A1C from participant's medical records (directly from EMR or self-report); (2) GMI (estimated A1c) from participant's CGM software; or (3) participant self-reports that A1C has consistently been >7.5%.

- If the A1C value in the participant's electronic medical record (EMR) is 7.5% or higher **and** within the last two weeks, we will proceed with the informed consent process and use the EMR A1C as the baseline value.
- If the estimated A1C value (defined above) is 7.5% or higher, we will proceed with the informed consent process and test their A1C. If the study A1C value is less than 7.5%, they will not be eligible to participate in the study, but they will be compensated for their time with a $50 gift card. If the study A1C value is greater than or equal to 7.5%, they will be eligible to participate in the study and we will proceed with the remainder of the baseline testing session.
- If there is no estimated A1C value available, we will provide them with the screening consent and proceed with the A1C screening. If we are unable to test A1C in person, we will provide the participant with a mail-in kit where they will prick their finger and mail the kit to a laboratory. Based on the A1C test results we receive from the laboratory, if the study A1C value is 7.5% or higher, we will proceed with the informed consent process and use the study A1C as the baseline value. If the study A1C value is less than 7.5%, the participant is not eligible to enroll in the study and will not be compensated.
- In the event that in-person A1c testing is not feasible, A1c mailing testing kits will also be made available to participants.
- In the event that in-person recruiting and consenting of participants is not feasible, we will conduct recruitment activities virtually through phone calls or videoconferencing, and will send consent forms electronically to participants using DocuSign or a REDCap eConsent form to review and complete.

Recruitment, Enrollment, and Retention are outlined in brief below. During a 24-month recruitment period, we will enroll an average of 10 participants per month to attain our targeted sample size of 210. We will utilize four recruitment strategies: social media advertising, in-person invitations at partnering clinics, mass mailings to patients who are treated at our partnering clinics as well as outreach via convenience sampling and referrals from community clinicians, and Keck data request. A website will complement recruitment efforts by providing study information to prospective participants and allowing them to share their contact information for follow-up by study personnel. Table 4 illustrates our site-specific recruitment estimates for REAL-T, as derived from available information from participating clinics and preliminary data from the REAL RCT. Overall, our estimates indicate that we will have access to a pool of 1256 YAs with T1D who meet study eligibility criteria. Based on our past recruitment rates, greater than one-half of YAs in this pool are likely to enroll, which would enable us to easily meet the study recruitment goal of 210 individuals. If for some reason we are unable to achieve this expectation, we will have access to a variety of additional clinical sites, and/or can make increased use of social media outreach, as a means of obtaining the stipulated sample size.

Strategies to Enhance Retention. To maximize retention, consistent with the successful strategies used in our previous research and as reflected by research on retention of YAs in longitudinal studies,[109] we will: (a) employ consistent study staff with flexible working hours and strong interpersonal skills; (b) maintain regular points of contact throughout the intervention and follow-up period (using websites, social media presence, phone numbers, and email addresses); (c) collect multiple forms of contact information for each participant and update this information at each data collection point; (d) provide participants with choices as appropriate (e.g., completing surveys on paper or electronically); (e) track participants' whereabouts through the Postal Service (Forwarding Address requests), web search engines, and medical record numbers; (f) offer adequate stipends to show our appreciation for participants' time and effort in completing study activities; and (g) convey our respect and gratitude for participants at each point of contact.

Randomization. Participants will be computer randomized using random block sizes. The statistician will securely maintain the randomization list on her network drive and upload to REDCap to automatically assign participants to a treatment condition after they complete baseline testing.

Intervention. The REAL-T intervention will be delivered as outlined above. Participants in both the REAL-T intervention and usual care control condition will continue to have access to routine diabetes care from the provider of their choosing, and their care will not be disrupted in any way due to their study participation.

Measures and Data Collection. A trained research assistant, blind to condition assignment, will administer the assessments outlined in Table 5. All self-report measures have been validated in this age group. All diabetes-related measures are appropriate for use in T1D. We will assess A1c with a CLIA-waived point-of-care device (DCA Vantage) which collects capillary blood using a standard finger-prick procedure. If traditional in-person testing for A1c is not feasible, we will offer one of the following sample collection methods: (1) an in-person appointment on campus or in the community using socially-distanced methods such as contactless transfer of supplies and demonstration of sample collection from a safe distance; (b) contactless drop off and pick up of supplies in the community, or (c) mailing participants provide participants with a mail-in A1c kit. We will collect CGM data using Abbot's Freestyle Libre Pro blinded CGM, which will be placed by the research team at the assessment session and worn by participants on their upper arm for 14 days. If the research team is unable to apply the CGM in-person through traditional means, we will offer one of the following application methods: (1) an in-person appointment on campus or in the community using socially-distanced methods such as contactless transfer of supplies and demonstration of self-application from a safe distance; (b) contactless drop off and pick up of supplies in the community, or (c) mailing participants the CGM application kit with instructions along with a prepaid postage box to be mailed back. After completing the CGM data collection period, participants will remove the device and mail it to the study site in a postage-paid envelope for data download by the research team. The Libre Pro CGM was chosen because it requires no calibration, manipulation, or restriction of activities on the part of the participant, and does not interfere with a patient's use of a personal CGM or closed loop CGM-pump system. As noted in Figure 2, we will conduct the full assessment battery at baseline, 6 months (immediately after the intervention), and 12 months (long-term follow-up), and a slightly abbreviated assessment battery at 3 months (midway through the intervention), and 9 months. The 3-month and 9-month assessments serve several critical functions. These assessments will be conducted in-person through the REDCap mobile app on the study's iPads, via surveys through REDCap's secured electronic system, or mailed out to the participants' homes for completion and mailed back in prepaid postage envelope. If participants prefer, they can also complete surveys over the phone with a trained research assistant. First, collecting data on key outcomes midway through the intervention will contribute to our understanding of how changes unfold over time, and in relation to each other, during the intervention, facilitating future refinements to intervention dose and timing. Second, the resulting information will permit longitudinal modeling of changes in A1c and other key variables at quarterly intervals over the full study period. Finally, quarterly assessments will provide additional contact with participants in the usual care condition, increasing retention. As the standard of care for diabetes dictates quarterly assessment of A1c, self-care (e.g., meter downloads), and psychosocial well-being (e.g., depression screening), this measurement strategy reflects typical clinical care.[110] Monthly surveys sent through a secured electronic system will be conducted to gather healthcare utilization data, which will facilitate more accurate recall of healthcare utilization, to supplement data from medical chart reviews.

Table 5. Demographic, Clinical, and Psychosocial Assessments									
General Construct	**Variable**	**Instrument**	**Description**	**Time Point**				
				0	**3**	**6**	**9**	**12**
Demographic/ background		Study-specific survey; medical record reviews	Age; gender; race/ethnicity; education; employment; country of origin; duration of diagnosis; treatment regimen; comorbidities	X				
Treatment satisfaction		Patient Satisfaction Survey	14 items; adapted from physical therapy satisfaction survey; α=0.99.[112]			X		
Glycemic control	A1c	Axis-Shield Afinion point-of-care assay	CLIA-waived; meets NGSP certification criteria; correlation with laboratory A1c measure=0.991.[113]	X	X	X	X	X
	% TIR, % hyper, % hypo	Abbot Freestyle Libre Pro CGM	14-day factory-calibrated blinded CGM; MARD of 11.4% compared to capillary blood glucose reference values[114, 115]	X		X		X
Psycho-social well-being	Diabetes quality-of-life	Audit of Diabetes-Dependent Quality of Life (ADD-QoL)	19 items; α=0.85; assesses impact of diabetes on social, physical, and emotional functioning.[118]	X		X		X
	Diabetes distress	Diabetes Distress Scale (DDS)	28 items; 7 subscales. Total scale α=0.91, subscale range α=0.76-.89;[119] r=0.56 correlation with CES-D[120]	X		X		X
	Health-related quality-of-life	MOS SF-12v2	12 items; evaluates global physical and mental well-being; subscale α in patients with diabetes=0.83-0.85; r=0.40-0.43 concurrent validity with self-reported physical/mental health[121]	X		X		X
Self-care behaviors	Medication adherence	• Medication adherence self-rating	• 3 items; quantitative self-rating of adherence over 30 days; 0.55 correlation with MEMS[122]	X	X	X	X	X
	SMBG	• 14-day meter data	• Number of BG checks completed over 14 days.	X	X	X	X	X
	Global self-management	Diabetes Self-Management Questionnaire (DSMQ)	16 items, 5 subscales; subscale α range=0.72-0.83; r=-0.53 correlation with A1c in adults with T1D[124]	X	X	X	X	X
Habit strength		Self-Report Behavioral Automaticity Index (SRBAI)	8 items, 4 for each target behavior (SMBG and taking insulin/medication); assesses habit strength; correlation to corresponding behaviors ranges from 0.42-0.86.[125]	X	X	X	X	X
Self-efficacy		Diabetes Empowerment Scale-Short Form (DES-SF)	8 items; α=0.84; self-efficacy for performing diabetes self-management[126]	X	X	X	X	X
Healthcare utilization		Study-specific survey; medical record reviews	Incidence of diabetes-related outpatient medical visits, ED visits, urgent care visits, hospitalizations	Monthly				

Data Management and Analysis. The study's analytic plan is outlined in brief in this section; for further details, please refer to the "Statistical Design and Power" attachment in the PHS Human Subjects and Clinical Trials Information section. *Data Management:* Data will be uploaded and stored in a REDCap database management system.[111] REDCap is a secure, web-based application designed to support data capture for research studies, providing an intuitive interface for validated data entry. It also includes audit trails for tracking data manipulation and export procedures; automated export procedures for seamless data downloads to common statistical packages; and procedures for importing data from external sources. The REDCap website is password-protected and restricted to authorized users (See Data and Safety Monitoring Plan). Research assistants will enter and reconcile all data, with further data quality checks performed by the biostatistician. Prior to conducting hypothesis tests, baseline participant characteristics will be described using frequency distributions, histograms, and summary statistics. Sparse data may be recoded to dichotomous or ordinal data.

Power and Sample Size: The study is powered for an intention-to-treat analysis of our primary outcome, change in A1c over the intervention period (including 3 and 6-month data). Other analyses are designated as secondary, to control the type 1 error rate in identifying statistically significant changes in the primary outcome. Power analyses were conducted using proc glmpower in SAS using a 2-sided alpha of 0.05. As described comprehensively in the "Statistical Design and Power" attachment, we calculated power for a range of

Table 6. Power, given 210 participants, for testing intervention effects on A1c over 6 months (Aim 1), 9 and 12 months (Aim 2), and mediators/secondary outcomes (Aim 3).

A1c 0-6 months (Aim 1)				**A1c 0-9 or 0-12 months (Aim 2)**				**SEM/mediation analysis (Aim 3)**		
% Δ	Effect size	6-month attrition		**% Δ**	Effect size	Annual attrition		Effect size	6-month attrition	
		7.4%	10%			14.3%	20%	*(path a/path b)*	7.4%	10%
0.81	0.55	>.99	>.99	0.81	0.55	>.99	>.99	.26/.36	.95	.95
0.59	0.40	.93	.92	0.59	0.40	.97	.96	.36/.26	.92	.92
0.50	0.34	.82	.81	0.50	0.34	.89	.86	.26/.26	.89	.88

Finally, power for analyses of mediators and secondary outcomes using structural equation modeling (SEM) is excellent for effect sizes of at least .26 for the direct effects of intervention on the mediator (path a) and of the

mediator on the outcome (path b), which are reasonable to anticipate given effect sizes derived from previous literature (see “Statistical Design and Power” for additional details).

Aim 1: Evaluate the efficacy of REAL-T in improving glycemic control and psychosocial well-being. Our primary analysis will evaluate efficacy for changes in A1c on an intention-to-treat basis, assessing between-group differences using mixed effects regression models. Nonparametric or other robust statistical methods will be used to evaluate the effect of deviations from normality including outliers and truncated data (e.g. eligibility criteria of >7.5% A1c) on results. An advantage to mixed effects regression models is that they incorporate all available data even when data are incomplete, providing robust effect estimates and high statistical power, as well as easy comparisons of the treatment groups. We will also conduct sensitivity analyses to evaluate whether outliers or missing data are driving the observed effects, and moderation analyses to examine whether baseline clinical or demographic characteristics (e.g., age, gender, ethnicity, SES, treatment regimen, duration of diagnosis) modify any observed effects of the intervention. Secondary analyses: We will evaluate the impact of the intervention on psychosocial well-being and CGM-derived measures of blood glucose control. Analysis of secondary outcomes will assess between-group differences in signed change scores on measures of % time in range (the proportion of all time measured by the CGM when blood glucose is between 70 and 180 mg/dl), % time in hypoglycemia (the proportion of time blood glucose is below 70 mg/dl), % time in hyperglycemia (the proportion of time blood glucose is above 180 mg/dl), depressive symptoms, DQoL, and diabetes distress.

Aim 2: Assess the post-intervention durability (3- and 6-months post-intervention) of REAL-T’s effects on glycemic control and psychosocial well-being. Data analysis will be similar to that outlined in Aim 1, using mixed effects regression models, and will examine changes from baseline to 9 and to 12 months (i.e., 3 and 6 months post-intervention). In addition, we will explore the pattern of changes in A1c and other outcomes across the 4 study subintervals, stratified by treatment group. We will fit linear trends to the subintervals and test if model fit is improved significantly compared to models using fewer linear subintervals. Although analyses can be completed incorporating data from all time points in one model, the potential for varying effects over time has led us to frame our primary endpoints in terms of changes over specific shorter periods; exploratory analyses will consider possible longer-term patterns of change.

Aim 3: Examine mediating mechanisms of REAL-T’s observed effects through structural equation modeling. In Aim 3, we propose to test mediation of: (a) intervention effects by self-care behaviors on A1c and psychosocial well-being (Aim 3, Hypothesis 1); (b) self-care behaviors as well as psychosocial well-being by self-efficacy (Hypothesis 2); and (c) self-care behaviors by habit strength (Hypothesis 3). These potential mechanisms will be assessed via structural equation models which include both direct and indirect effects of intervention. The indirect effects will be estimated as the multiplicative effect of direct paths between intervention and the mediator and between the mediator and the outcomes.

Cost Analyses: We will evaluate the cost-effectiveness, cost impact, and change in quality-adjusted life years (QALYs) associated with REAL-T relative to usual care. We will calculate incremental cost-effectiveness ratios (ICERs) divided by the average difference in QALYs; if preliminary analyses demonstrate that REAL-T is both cost-saving and net health beneficial (which would render the ICERs moot), we will instead calculate the projected total net health benefits for REAL-T relative to usual care. ICERs will be calculated according to generally recognized best practices, using two different timeframes and scopes. The first will be a simple Cost Utility Analysis (CUA) over a 12-month timeframe, using cost and QALY inputs derived directly from observed data, adopting a “Payer” perspective (direct medical costs only). This CUA estimate will likely represent a conservative lower bound, given the short follow-up period, as the greatest intervention costs are incurred up-front, while some medical cost savings may take longer to realize. The second CUA will employ modeling to project longer-term costs and health benefits, using parameter estimates derived from the literature, from both a “Payer” perspective and a “Social Planner” perspective (direct and indirect medical costs). The mathematical approach will employ Markov modeling, but may also incorporate microsimulation, decision trees, or Monte Carlo methods. Non-parametric bootstrapping methods will be used to bound the ICER estimates by deriving confidence intervals around the cost-effectiveness ratios for the 12-month timeframe CUA. For the longer-term CUA, we will conduct univariate and multivariate sensitivity analyses to further bound the ICER estimates.