Adolescent Interventions to Manage Self-Regulation of T1D (AIMS^{T1D}) Protocol

Full NIH Study Title: Targeting self-regulation to promote adherence and health behaviors in children

Protocol and Statistical Analysis Plan

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The goal of this study, called the UH3 phase, is to take lessons learned in our previous study, referred to as the UH2 (ABC Brain Games; HUM00104622), and test whether self-regulation (SR) assays and interventions can be delivered and change SR in a new sample, and test in a small RCT whether SR interventions lead to change in medication adherence. We have designed our UH3 phase based on lessons learned in the UH2 phase, and detail below our Aims and Approach for UH3. Of note, after observing how our UH2 interventions performed with younger children and extensive discussion with our research team, particularly Dr. Fredericks (Co-I for UH2, MPI for UH3), an expert in medication adherence, and Drs. Hunter (NIH Project Scientist) and Dr. Lee (new Co-I for UH3 phase), experts in Type 1 Diabetes (T1D), we propose to focus the UH3 study on adolescents with T1D. These youth have clear medication adherence goals, yet are often nonadherent and at great health risk during this developmental period.[1-3] As responsibility for diabetes management shifts from parent to youth during this time,[4,5] intervening with adolescents directly is vital for prevention.[6-8] The adolescent T1D population therefore represents an ideal focus for our UH3 study for several reasons.

Urgent need to improve medication adherence in adolescents. To achieve and maintain optimal glycemic control, adolescents with T1D must adhere to a complex self-care regimen including monitoring blood glucose, administering insulin via daily injections or a pump, regulating carbohydrate intake, physical activity, and minimizing hyper- or hypoglycemia.[9,10] Adherence to recommended treatment regimen is critical in determining health outcomes among pediatric T1D patients.[11,12] Yet, poor adherence is common during the transition into adolescence.[2-4] Only 21% of adolescents meet the American Diabetes Association guidelines for hemoglobin A1c (HbA1c) target level of 7.5%.[1,12] Moreover, treatment adherence and glycemic control decline across adolescence.[13] Achieving target HbA1c may prevent long-term complications and enhancing adherence should improve health outcomes for adolescents with T1D.[14] Yet, strict adherence to T1D regimens is challenging. While some intervention approaches have empirical support for improving adherence (e.g. family systems therapy), they can be costly and time intensive. There remains an urgent need to identify effective treatment strategies to improve medication adherence in this population and create lasting behavior change.

Self-regulation (SR) deficits may drive poor adherence. Poor SR has been identified in youth with T1D[15-19] and is proposed as a central mechanism contributing to nonadherence.[10,20-23] Promising interventions suggest that in addition to targeting diabetes-specific adherence behaviors, addressing SR skills is vital.[6,10,24,25] Yet, SR targets have not been tested as mechanisms of behavior change to improve adherence to T1D regimens in youth. Specific aspects of SR that are particularly important for youth with T1D include executive functioning (e.g., working memory, inhibitory control); emotion regulation (e.g., capacity to manage stress and worries), and future orientation and motivation to stay focused on long term goals.[10] In our UH2 study, we developed interventions that successfully engaged these SR targets. Thus, in the UH3 phase we propose a small RCT to deliver our SR interventions and test their impact on three identified SR targets from the UH2 (Executive Function [EF], Emotion Regulation [ER], Future Orientation [FO]), medical regimen adherence, and diabetes-related health outcomes (quality of life; HbA1C) in youth with T1D.

Specific SR targets identified in the UH2 Phase (EF, ER, FO) are relevant for T1D regimen adherence. Executive Function (EF). EF deficits are documented in youth with T1D across numerous studies.[15-17] It has been proposed that impairments in EF in youth with T1D interfere with treatment adherence[17,20,22] and extant work finds associations of EF, treatment adherence, and glycemic control in adolescents.[17] In youth ages 13-17 years, parent-rated EF deficits in working memory and attention were associated with poorer adherence;[16] in other work the association between EF and glycemic control was mediated through treatment adherence.[20]

Emotion Regulation (ER). Adherence requires ER skills (e.g., taking medications even if stressed, depressed or anxious).[10,26] Adolescents with diabetes experience high levels of stress,[18,19] which is associated with less adherent behavior, poorer perceived competence, and poorer metabolic control.[27-29] Relatedly, adolescents with poorer ER skills have been found to have higher HbA1c levels.[30,31] Relaxation interventions may improve metabolic control by promoting better regulation of stress hormones, reducing stress and increasing capacity to focus on regimen adherence.[19,29] In prior work, biofeedback and relaxation exercises similar to our UH2 phase intervention were associated with reductions in blood glucose levels in adults with type 2 diabetes.[32,33] Recent

pilot studies with adolescents with T1D suggest that motivational techniques to encourage positive affect are associated with better adherence.[24,25] Thus, improving adolescents' capacity for ER through relaxation and self-calming may reduce the likelihood that distress interferes with adherence.

Future Orientation/Motivation (FO). Adhering to T1D regimens requires planning to understand and achieve goals (e.g., blood glucose monitoring), and motivation to remain engaged (e.g., maintaining optimal HbA1c levels to avoid long term complications). Future orientation (FO) has received significant attention from multiple SOBC projects, including our own, and is associated with health behaviors that promote long-term goals,[34,35] particularly in adolescents.[36] FO has been indexed as future time perspective[37,38] and as capacity for episodic future thinking (EFT), or projecting to "make the future become the present".[34,35] Individuals who can concretely describe and visualize their future may be more willing to invest energy in behaviors leading to long-term health outcomes, such as medication adherence. Research has shown associations between FO and better diabetes management behaviors.[39,40] Yet, few studies examine such associations in adolescents. The period of adolescence is characterized by increased capacity to envision the future due to neurological, psychological and social changes,[41,42] and this capacity is viewed as underlying adolescents' and adults motivation to engage in positive health and other behaviors.[37,43,44] Indeed, motivational interviewing is in part based on these concepts, and motivational interviewing around diabetes-specific goals shows promise in enhancing adherence among adolescents with T1D.[6,45,46] Improving FO capacity may thus enhance the power of this approach to motivate behavior change in adolescents.[47,48] In our UH2 study we used an EFT task based on SOBC Network Member Epstein's prior work[49,50] as our FO intervention. Using this task with adolescents who have T1D, for whom FO is a critically important developmental skill and who have specific goals to achieve with regard to adherence may therefore have important implications for later health.[51]

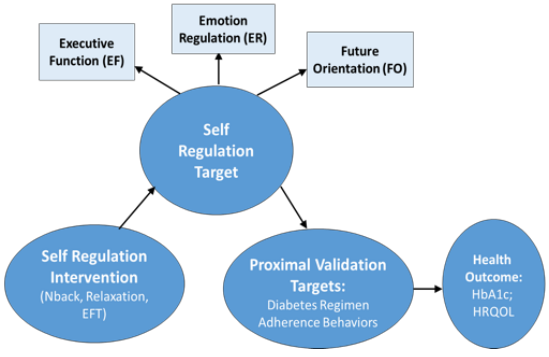
Adolescence is a critical period for SR development. Developmental neuroscience suggests that adolescents' SR skills are increasing, yet still emerging.[52] Associations between SR capacities and medication adherence have been found in prior work with youth.[7,53,54] Medical adherence typically shifts from parent to adolescent self-management across this period.[4,5,8,55] Therefore, supporting adolescents in developing SR skills to manage these tasks is essential[6,7] and may have implications for successful health care transitions across the lifespan.[56] In our UH2 study, we found positive impact of our bundled intervention (Nback, relaxation, EFT) on the self-regulation targets EF, FO, and ER. The UH3 phase will therefore employ this bundled intervention, with developmental adaptations appropriate for adolescents, and content adaptations appropriate for youth with T1D and accompanying medical regimen adherence requirements.

Scientific Premise and Impact. The Scientific Premise of this proposal is that poor SR underlies poor medical regimen adherence in youth with T1D. We further posit that improving SR targets relevant for adherence in these youth may yield a novel approach to health behavior change that may apply to youth with other chronic illnesses who are becoming independent managers of medical regimens. Findings will therefore not only inform our understanding of SR as a mechanism of behavior change and develop interventions to engage SR targets in youth with T1D, but also have transdiagnostic implications and thus broad impact. As well, the bundled interventions to be delivered in the UH3 phase are designed to be light-touch and scalable, thus may yield useful tools and resources to use in future studies of behavior change mechanisms in new populations. The **Specific Aims** are as follows:

Aim 1. Test the hypothesis that interventions developed in the UH2 phase enhance relevant identified self-regulation targets (EF, ER, FO) in a new population (adolescents with T1D).

Aim 2. Test whether interventions improve medical regimen adherence behaviors and T1D health outcomes.

Figure 2. UH3 Phase Conceptual Model: Self Regulation as Mechanism of Behavior Change



Approach

Conceptual Model. The model to be tested using an RCT design in the UH3 phase is presented in Figure 2. We will assess the self-regulation targets of EF, ER, and FO and the proximal validation target of medical regimen adherence

using multiple methods (see Tables 6 and 7). Diabetes related health outcomes include HbA1c level and quality of life.

Participants. 94 youth between 13.0 and 17.99 years of age will be invited to participate. Inclusion criteria are: 1) youth must have been diagnosed with T1D for at least 6 months; 2) reside with a parent; 3) have HbA1c≥7.0 4) regular access to WiFi; and 5) feel comfortable speaking English enough to complete study activities. Exclusion criteria include: 1) non-fluency in English in parent or youth; and 2) psychiatric or cognitive conditions that would impede ability to participate.

Recruitment. There are two recruitment streams for this project. The first and primary source will be patients from UM. The second source of recruitment will be non-Michigan Medicine patients with T1D living in Michigan and northeast Ohio (e.g. Toledo).

The UM Diabetes clinic serves 1300 children with diabetes, primarily T1D. Co-I Lee runs these clinics and has successfully used the below strategies to recruit youth with T1D for multiple studies. The clinic participates in a hospital-wide registry of patients with diabetes and the T1D Exchange. The University of Michigan is one of the leading sites in the T1D Exchange Registry; Co-I Lee's team enrolled 1009 participants this way (nearly 500 participants were < 18 years old at enrollment). Participants will be recruited from the UM Pediatrics Diabetes Clinic Research Registry and the T1D Exchange T1D Registry.

Targeted recruitment outreach of all eligible potential participants will be conducted through phone calls, mailings, and emails as well as in-person outreach for UM patients at routine endocrinology appointments and in-person recruitment at fairs, camps and/or community events for any eligible youth with T1D. Electronic advertisements will also be posted on UMHealthResearch.org and clinic website umpedsdiabetes.com. The study team will inform the staff and providers within Pediatric Endocrinology of the study and its requirements and request referrals. Paper advertisements will be distributed in Pediatric Endocrinology clinic rooms at C.S. Mott Children's Hospital and e-newsletter. The team has extensive experience utilizing hospital electronic medical records to screen participants for eligibility.

In addition, the team will utilize listservs and other points of contact (e.g. Facebook groups) of T1D-focused groups in Southeast Michigan. For example, after gaining permission from colleagues at the local chapter of the Juvenile Diabetes Research Foundation (JDRF), the approved study email, flyer, text, and/or umhealthresearch.org link could be sent to members of their listserv or posted to their Facebook group. Project clinicians will also work with outside endocrinologists to have them share the study with their patients. If interested, patients will initiate contact with the study team since the investigators will not have access to other clinic's patient names, addresses or phone numbers. Current families enrolled in the study will also be able to share the study with their T1D network or community via word-of-mouth or by sharing approved recruitment materials; anyone interested would then initiate contact with the study team.

Interested families will complete eligibility screening through an intake call or in person, based on their preferred method. During the intake, informed consent/assent, study activities and random assignment will be detailed. Participants will be randomly assigned to intervention group at enrollment using a random number generator. We will employ a block randomization scheme stratified for youth sex and age (+/- 1 year), to ensure equal allocation to control and intervention groups.

Procedures. The adolescent and their parent will be scheduled to visit our research offices at the Center for Human Growth and Development (CHGD), which are set up for family-friendly visits. A parking pass will be provided. Pre-test and post-test assessments will be completed at CHGD (see **Intervention and Attention Control Protocols**). The pre-test visit will consist of completing SR behavioral assessments (youth) and questionnaires (youth and parent), medication adherence questionnaires (youth and parent), and introduction of intervention (for the intervention group) or control activities (for the control group; youth and parent). We will also show youth and parents the umpedsdiabetes.com website as a source of information on medication adherence, stress relief, and managing medications.

We will provide all parents with contact information for resources for themselves and their adolescent in the community to access mental health care, as well as social services and resources as needed. During the consenting process we will highlight the referral resource list, noting that it includes referrals for a range of services that families might find useful, including community-based behavioral health resources for parents and children. If a parent specifically requests assistance with finding an appropriate referral, PI Fredericks or Co-I Albright will contact the parent to identify an appropriate referral based on individual concerns.

We have balanced feasibility with rigorous measurement; the Pre-test visit is anticipated to take up to two and a half hours to complete all study activities. The post-test visit will be nearly identical to the pre-test with the exception of the intervention or control activities, and is anticipated to take 1.5 hours. Participants can complete post-test surveys remotely by receiving links to the surveys stored in the project's secure electronic database (REDCap). Patient diabetes devices (glucometer, insulin pump, and/or continuous glucose monitor (CGM)) will be downloaded at pre-test and post-test visits in adjacent clinic space to obtain these clinical data as a measure of adherence. For the post-test visit, devices may also be downloaded remotely and securely. The family will be escorted to co-located UM-lab sites or instructed to visit any UM-lab site on their own within 7 days of pre-test to have blood drawn to assess for HbA1c. A review of the electronic medical record will be conducted after the family has completed the post-test to assess number and purpose of clinic visits and any health events (e.g., DKA). We will inform the families that we may look at the teen's medical record up to 1 year after the 2nd study visit in order to review T1D health events. Youth will be offered up to $175 and parents up to $100 using a pro-rated incentive structure designed to enhance retention. For completing their home practice, youth in the intervention group will offered up to $80 more and will be entered into a lottery to win a gift card.

Measures. We will use multi-method assessment. Post-test assessments will be conducted 8-10 weeks after pre-test, based on anticipated changes in self-regulation, medication adherence, and HbA1c across this period of time, and the optimal timing of intervention delivery as determined during the UH2 phase. Table 6 outlines self-regulation assessments; Table 7 outlines medical regimen adherence and T1D assessments.

Self-regulation. SR will be assessed using the multi-method assays developed in our UH2 study. Adolescents in the UH3 phase will complete SOBC Network-developed measures that are hypothesized to change as a result of our intervention but that we were not able to use in the UH2 due to the younger age of our sample (e.g., CFC; 5-trial Delay Discounting). All assays were shown to be psychometrically reliable in our own and/or other SOBC Network work, or with adolescents in prior research. EF will be assessed using objective tasks and parent-reports to evaluate working memory (Backward Digit Span; BRIEF); inhibitory control (Go-no-go task; BRIEF); organization/planning (BRIEF). Parents will also complete a digit span and Go-no-go task to assess EF. ER will be assessed using youth self-report and parent-report to evaluate affect dysregulation (SIDES) and perceived stress (NIH PSS) and youth self-report of anxiety (GAD-7) and positive and negative affect (PANAS). FO will be assessed using youth self-report and objective tasks to evaluate self-efficacy (NIH Self-Efficacy), consideration of future consequences of actions (CFC); and delay discounting (5-trial task). We also seek to identify potential mechanisms of association between parent SR capacity and youth T1D outcomes, including diabetes-relevant family processes that have been identified as important in shaping health outcomes for youth with T1D (Table 8).

Table 6	Specific Construct	Measure Details	Who / Data Source
Intake			
	Regimen (Parent and Child), Parent Depression, Family Chaos, Family Composition and Income, Demographics	29 min	Parent for all; Child self-report on Regimen
Executive Function			
Forward & Backwards Digit span	Working memory	7 min (online)	Parent and child complete task
Go No Go task	Inhibitory control	7 min (online)	Parent and child each complete task
Behavior Rating Inventory of Executive Function – A	EF broad	15 min (75 items)	Parent self-report
Behavior Rating Inventory of Executive Function (BRIEF-2)[57]	EF (inhibit, shift, emotional control, initiate, working memory, organize, monitor)	10 min; 63 items (parent), 55 items (child)	Parent report on child Child-self-report

Emotion Regulation			
NIH Perceived Stress Scale (PSS)[58]	Youth stress (parent- and youth-perceived)	4 min; 10 items	Parent report on child
NIH Perceived Stress Scale (PSS)[58]	Youth stress (parent- and youth-perceived)	4 min; 10 items	Child self-report
NIH Perceived Stress Scale (PSS)[58]	Parent stress	4 min; 10 items	Parent self-report
Difficulties in Emotional Regulation Scale (DERS)[59]	Parent emotion regulation	9 min; 36 items	Parent self-report
Affect Dysregulation Scale (SIDES)[60]	Stress reactivity and emotion dysregulation	2 min; 6 items	Child self-report
Positive and Negative Affect Schedule (PANAS)	Youth affect	5 min; 20 items	Child self-report
GAD-7 (screener)	Youth anxiety	7 items; 5 min	Child self-report
Future Orientation			
NIH Self-Efficacy[58]	Belief in capacity to manage, control life events	4 min; 10 items	Parent report on child
NIH Self-Efficacy [58]	Belief in capacity to manage, control life events	4 min; 10 items	Child self-report
NIH Self-Efficacy[58]	Belief in capacity to manage, control life events	4 min; 10 items	Parent self-report
Consideration of Future Consequences (CFC)[61]	Thinks about long term consequences of actions	10 min; 14 items (break out)	Child self-report
5-trial Adjusting Delay Discounting Task[62]	Valuing rewards less as time until reward increases	1 min	Parent and child each complete task

Medical Regimen Adherence. We will obtain clinical measures and parent/youth report of T1D adherence behaviors (see Table 7). We will analyze adherence on a continuous basis as well as classify youth as "adherent" vs. "nonadherent" based on clinical criteria.[63] Clinical Adherence is defined with respect to regimen and includes blood glucose monitoring (BGM) frequency and insulin administration. BGM frequency will be assessed by downloading data from the prior two weeks from the adolescent's diabetes devices. Youth may be adherent to BGM, insulin administration, or both. Adherence to BGM is defined as an average of 4 blood glucose measurements/day and/or wearing a CGM 6 out of 7 days vs. not; insulin administration adherence is defined as at least 3 short acting insulin boluses/day vs not. We will assess regimen-specific adherence (BGM; insulin administration) at pre-test and assess again at post-test as a dichotomous and continuous variable.[63] The division of Pediatric Endocrinology has access to the latest tools for T1D treatment and monitoring including an account with Glooko/diasend, a cloud-based, secure platform for uploading data from over 150 diabetes devices and consolidating data into a single dashboard; Dexcom Clarity, a system for downloading and viewing continuous glucose monitoring data; and Tidepool.org (nonprofit, HIPAA-compliant platform for downloading diabetes meter, pump, CGM data). BGM and insulin administration frequency for youth on a CGM pump can be measured using the software. For youth on injections, the number of short-acting insulin boluses will be measured by self-report. The Self-Care Inventory (SCI-R)[64] is a 15-item youth- and parent-report measure of multiple T1D self-care adherence behaviors. Versions are available for adolescents and parents (identical item content) and shown to be reliable in comparable samples.[64] Items reflect main aspects of the T1D regimen, including: monitoring and recording glucose, administering and adjusting insulin, regulating meals and exercise, and keeping appointments. Respondents report on adherence behaviors on a 5-point scale (1=*"never do it"; 5="always do this as recommended without fail";* or N/A.

Table 7	**Specific Construct**	**Measure Details**	**Who / Data Source**
Medical Regimen Adherence			
Adherence to BGM; Insulin Administration	Clinical Adherence (objective)	N/A (2nd RA should be able to do)	Diabetes devices
Adherence BGM; Insulin Administration	Self-reported adherence	N/A (only if meter fails)	Self-report
T1D Adherence Self-care Inventory (SCI)-Revised	Multiple T1D regimen adherence behaviors	15 items (7 min)	Parent report on child Child-self-report
Health Outcome			
HbA1c	Glycemic control	N/A	Clinic

T1D Events	Health events (e.g., DKA)	N/A	Chart Review
PROMIS (Short Form v2.0 Pain Interference 8a)	Pain Interference	8 items (3 min)	Parent report on child Child-self-report

T1D-related health outcomes. Glycemic control will be measured by HbA1c, a measure of glycosylated hemoglobin in the blood representing glycemic control over the prior 2-3 months that is often used in behavioral interventions with youth.[46] HbA1c will be collected at MLabs, methods used by Co-I Lee. Guided by Co-I Lee, chart reviews will be conducted to assess number and reason for clinic visits and T1D-related health events (DKA; Hospitalizations).

Pain Interference will be measured using the Patient-Reported Outcomes Measurement Information System (PROMIS) Pediatric Short Form v2.0 - Pain Interference survey, which is an 8-item measure of the impact pain has on engagement with social, physical, cognitive, and emotional activities. Both child-self-report and parent-report of child's pain interference will provide information about how the child's experience of pain impairs overall functioning and quality of life.

Diabetes-Relevant Family Processes. We will measure *Diabetes-relevant Family Processes* via parent completion of several questionnaires (Table 8) and teen completion of one questionnaire. Specifically, *Diabetes-relevant Family Functioning* will be measured by the Revised Diabetes Family Conflict Scale caregiver form[65] The Revised Diabetes Family Conflict Scale is a 19-item measure of diabetes-specific family conflict around diabetes management tasks that are direct (e.g., checking blood glucose) and indirect (e.g., identifying what to eat when away from home).

Table 8	Specific Construct	Measure Details	Who / Data Source
Diabetes-Relevant Family Processes			
Revised Diabetes Family Conflict Scale	Diabetes-relevant family functioning	19 items (5 min)	All Parent Report, except PAID-T
Identifying Problem Areas in Diabetes – Parents of Teen (P-PAID-T) and Teen version (PAID-T)	Perceived family burden	15 items (5 min) 14 items (5 min)	
Diabetes Family Responsibility Questionnaire	Parent involvement in diabetes management	17 items (5 min)	

Perceived Family Burden will be measured with the short forms of the Identifying Problem Areas in Diabetes Survey – Parent Of Teen Version (P-PAID-T) and Teen Version (PAID-T).[66] The P-PAID-T is an 15-item measure while the PAID-T has 14 items. Both are valid, reliable, and clinically useful instruments for identifying diabetes-related distress among teenagers with T1D and their parents.

Parent Involvement in Diabetes Management will be measured using the Diabetes Family Responsibility Questionnaire, a 17-item scale that describes diabetes-specific and general health situations or tasks that youth with diabetes commonly engage in.[67] Parents report who, if anyone, in their family takes responsibility for these situations and tasks, including whether the parent and youth share responsibility.

Covariates. As in the UH2 phase, demographics and covariates will be assessed in order to include in analyses as needed. These include family income, composition, and medical history; parent depression symptoms (Center for Epidemiologic Studies Depression Scale[68]), youth anxiety, and household stress (CHAOS Scale[69]).

Intervention and Attention Control Protocols

All youth in the intervention condition will receive the bundled intervention, which focuses on EF, ER, and FO. The intervention will occur mostly through home practice and be supplemented by engaging youth remotely using approaches that PI Fredericks has used in her work with teens managing chronic illness and in other studies with this population (e.g., text based reminders and mobile apps to practice techniques[70]). Intervention activities will be introduced after evaluation activities are completed for the pre-test and we will monitor home practice to assess dosage as in the UH2 phase (e.g., number of NBack sessions; relaxation practice; EFT cues played).

1. EF Intervention. We will use the NBack intervention[71-73] as in the UH2 phase.[74] Youth will be shown how to play a game wherein they recall which image they saw in prior sequences. As in the UH2, participants will be given a tablet with the game loaded on it to play at home.
2. ER Intervention. In the UH2 phase, participants learned how to engage in relaxation and biofeedback activities during in person visits by completing activities (e.g., modulating breathing to keep heart rate and skin conductance within a certain range) on a computer while wearing sensors.[75] They were told to complete the relaxation activities on their own at home, but were not given access to a computer-based version to practice. In the UH3, we will conduct similar in-person relaxation and biofeedback training but also show participants how to practice these activities at home using commercially available apps that PI Fredericks uses clinically (e.g., Heartmath and Insight Timer). These will be loaded onto the tablets with the Nback task and/or onto the participant's smartphone.
3. FO Intervention. In the UH2 phase, we developed an EFT intervention based on SOBC Network Member Epstein's work.[49,50] The EFT intervention, in which participants generate positive upcoming events and describe these events using prompts to elicit concrete, episodic language, is hypothesized to promote future-oriented thinking because the participant is encouraged to mentally project and pre-experience the future event in the present.[76] Our EFT intervention showed positive impact on the number of episodic, descriptive words our UH2 child participants used when describing future events. For the UH3 phase, as we are working with adolescents who have greater cognitive capacity to engage in such activity, and who are at an age when developing FO is critical,[51,77-79] As in our UH2 phase, participants will be asked to envision and describe future events they are looking forward to, using concrete, vivid descriptive language. The interventionist will transcribe the participant's descriptions, or cues, and concise prompts will be texted to participants at home. The participant will be prompted to look at the cues at home at specified times of day (e.g., 7am and 3:30PM).

Attention Control Protocol. Youth in the control condition will receive care that is already in place. After post-test data collection is complete participants will be asked if they would like to receive a summary of study findings at the completion of the study and if results are favorable, will have the option of learning intervention techniques.

Intervention and Attention Control Fidelity Measures. As in our UH2 phase, we will assess fidelity of delivery for both the intervention as well as the attention control condition by videotaping and coding a subset of sessions.

COVID-19 follow up study. In light of events with the COVID-19 pandemic, we are inviting participants who have finished the post-test visit to complete an online survey to help us understand how families are coping. All data collection will occur remotely. The follow up consists of 12 questionnaires that parents answered before (10 for teens) plus 1 new survey [11 items] about life changes during the COVID-19 pandemic. In addition, we will include the COVID-19 survey in our battery for all pre-test visits going forward.

In the COVID-19 follow-up, parents will be asked to answer the following 12 questionnaires again: Family Chaos, CESD, Difficulties in Emotion Regulation Scale, Perceived Stress (parent report on child), Self-Efficacy (parent report on child), SCI-R, T1D Regimen Survey, Perceived Stress (self-report), Revised Diabetes Family Conflict Scale, Problem Areas in Diabetes Parents of Teens (P-PAID-T), Diabetes Family Responsibility Questionnaire, PROMIS. In addition, parents will be asked the 11-item COVID Family Stress scale. The COVID-19 Family Stress scale measures increased stress for families in light of the pandemic. It consists of 11 items in areas such as child care, job loss, and physical health.

Teens will be asked to answer the following 10 questionnaires again: Perceived Stress (self-report), Affect Dysregulation scale, Self-Efficacy (Self-report), Consideration of Future Consequences, PANAS, GAD7, SCI-R, T1D Regimen Survey, Problem Areas in Diabetes – Teen (PAID-T), PROMIS. As well, teens will be asked to answer an 11-item version of the COVID Family Stress Scale modified for their age group.

Parent and teen participants who choose to participate in the COVID-19 follow up will receive an additional $25 for completing the follow-up.

Statistical Analysis Plan

We will transform skewed outcome variables as needed, run descriptive statistics, apply transformations to assure normality, and assess potential covariates to include. While maximum effort will be made to retain all subjects and minimize the amount of missing data, we anticipate there will be some data lost-to-follow-up and incomplete measures. Thus as is our practice we will address missing data by applying advanced statistical techniques, such as multiple imputation using PROC MI in SAS and IVEWARE SAS macro. Co-I Kaciroti has extensive experience managing datasets with missing data using both Likelihood and Bayesian methods. Both methods are valid when the missing data mechanism is missing at random, which is less restrictive than data missing completely at random. In addition, as needed we will implement sensitivity analysis to assess the robustness of the results under different missing-data mechanisms including missing data that are potentially missing not at random. Co-I Kaciroti has developed and used Bayesian models for sensitivity analysis for different outcomes using these methods.[80-84] We outline the analytic plan below.

Youth will be randomly assigned to receive intervention or control using a random number assignment protocol we used in the UH2 phase. To test whether the interventions were effective in changing self-regulation targets (**Aim 1**), medical regimen adherence and T1D health outcomes (**Aim 2**), and diabetes relevant family processes (on an exploratory basis), we will use an intent-to-treat analysis (all analyses will use an alpha value of $p<.05$). Baseline comparability of the groups will be assessed for multiple variables using t-tests for continuous variables (e.g., home chaos) and χ^2 tests for categorical variables (e.g., regimen type). We will use generalized linear (for continuous adherence and health outcomes) and logistic regression (for dichotomous adherent/nonadherent outcomes) to compare changes in SR, adherence and health outcomes across the two groups (treatment vs. control; $\alpha= 0.05$). We anticipate that some children will have only partial adherence to the intervention (i.e. attend a subset of sessions), thus we will conduct a dose-response analysis where dose corresponds to number of sessions, controlling for covariates that relate to number of sessions attended and outcome of interest. Sex will be examined as a biological variable as some differences have been identified in SR-adherence associations.[16,31] **Power.** In UH3 we will test the feasibility of assaying SR in a new sample and detecting change in SR targets and medication adherence. We anticipate medium effect sizes of 0.6 with the bundled interventions, so our proposed sample size of 94 (47 per group) should result in sufficient statistical Power of 82% to detect such effects using a two-sided Type I error alpha of 0.05. In addition, controlling for baseline variables that relate to outcome would reduce the residual variance and further increase the statistical Power.

UH3 Study Timeline. Table 9 outlines the timeline for UH3 activities. We include 3 months of "start-up" to refine assays and interventions (which are largely the same as in the UH2 phase), obtain IRB approval, and train staff. We will enroll 2 new participants per week to reach our recruitment goals (n=94), which is feasible. The rhythm of data collection in prior studies is similar to that proposed here, and we are thus confident in the feasibility of the project. Co-I Lee's successful recruitment in the UM Diabetes clinics she runs and the large population of youth with T1D (638 youth per year who met study criteria) from which to recruit will help to ensure success. We had no delays in meeting UH2 milestones, even though we had a limited participant pool as we only included children from an existing cohort. In the UH3, we will recruit new participants so we do not anticipate difficulties. As well, the Clinical and Translational Science Award at UM supports Behavioral Clinical Trial Support Units (CTSUs) that provide pre- and post-award support to investigators running behavioral clinical trials (e.g., grants administration specialists; science coordinator). We will coordinate with our Children's and Behavior, Function and Pain CTSU to ensure that we meet IRB, NIH clinical trial, Clinicaltrials.gov, and other regulatory requirements and deadlines for all UH3 study activities.

Table 9. Study Timeline	Sep-Nov	Dec-Feb	Mar-May	Jun-Aug	Sep-Nov	Dec-Feb	Mar-May	Jun-Aug
Finalize Study Protocols, Train, IRB								
Participant Recruitment, Randomization								
8 week Intervention Period								
Follow-up Assessments								
Data Analysis and Dissemination								
SOBC and Study Team Meetings								

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