Statistical Analysis Plan

Diabetes Journey: An Adolescent Adherence Barriers Intervention Study Protocol

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Introduction

Type 1 diabetes (T1D) treatment adherence is complex and involves glucose monitoring, counting carbohydrates, and intensive insulin delivery via injections or insulin pump in response to food intake, exercise, and illness to achieve near-normal blood glucose. Overwhelming evidence demonstrates that T1D treatment adherence is challenging, especially during adolescence, which can lead to suboptimal glycemia (e.g., HbA1c) that severely compromises health, including acute (e.g., diabetic ketoacidosis) and long-term complications (e.g., kidney failure), and in some cases, premature death. While several interventions have been developed for adolescents with T1D, none have focused on adherence barriers, a novel patient-reported outcome (PRO). The Barriers to Diabetes Adherence questionnaire, assesses these important targets for tailored adherence interventions, including stress/burnout and time pressure/planning (executive dysfunction). These adherence barriers are significantly associated with non-adherence, higher HbA1c, and lower health-related quality of life (HRQOL); however, no interventions have targeted stress/burnout and time pressure/planning in research or clinical practice. The overall objective of this study was to use PROs (e.g., adherence barriers) to identify patient-centered intervention targets that will guide the integration of a novel tailored intervention into clinical care to improve adherence, HbA1c, and HRQOL.

We conducted a pilot randomized controlled clinical trial (RCT) of the *Diabetes Journey* intervention that was developed iteratively using feedback from user-centered experiences and experts in T1D. Our goal was to evaluate the initial efficacy, feasibility, and acceptability of *Diabetes Journey* targeting adherence barriers (stress/burnout, time pressure/planning) in adolescents with T1D. Secondary outcomes include adherence, HbA1c, and HRQOL.

In March 2022, due to the COVID-19 pandemic and slow recruitment, we made a number of changes, approved by NIDDK, to our protocol. For Aim 3, these included lowering our age eligibility to 12 years old, making the age range 12-17 years. We also eliminated our exclusion criteria regarding use of metformin and asthma medications as these had no impact on the science of our study. We also reduced the sample size from N=256 to N=190 based on our preliminary data and considered the study a pilot trial. We eliminated the final follow-up assessment from required to optional, and reverted to 1:1 randomization for the treatment and control group allocation. Finally, to minimize missing data, we modified procedures to ensure our primary outcome was captured at our primary endpoint (Follow-up 1) at a minimum to ensure we could make valid causal inferences. Thus, we made the Barriers to Diabetes Adherence questionnaire the only required measure for completion prior to randomization or moving to subsequent timepoints. Because HbA1c could be collected from chart reviews, we were confident about obtaining these data, as well as basic measures of adherence from the medical chart.

Study Hypotheses

Primary Aim: Examine feasibility, acceptability, and preliminary efficacy of *Diabetes Journey* to reduce adherence barriers (PRO) in adolescents with T1D over time.

Hypothesis: The treatment group will find the treatment acceptable and feasible and demonstrate significant improvements in barriers, adherence, HbA1c, and HRQOL.

Study Design

This study was a multi-site RCT designed to evaluate the efficacy of the *Diabetes Journey* mHealth intervention aimed at reducing barriers to T1D self-management among adolescents. These barriers include stress/burnout, executive dysfunction, and time management challenges. Participants were randomized into two groups: *Diabetes Journey* intervention or Enhanced Standard of Care, using stratified block randomization. The study was conducted across multiple sites and followed participants at baseline, post-treatment, and follow-ups at 6 and 12 months.

Adolescents endorsing clinically elevated adherence barriers during routine clinical care (primary outcome and intervention target-Barriers to Adherence scale) were randomized to: 1) *Diabetes Journey* or 2) Enhanced Standard of Care. For *Diabetes Journey*, each mHealth module accompanied a telemedicine session to review skills and problem-solve adolescent-identified goals with a therapist. For Enhanced Standard of Care, adolescents received handouts and phone calls from a certified diabetes educator.

Power and Sample Size Estimates

Initially, sample size estimates were based on the Epilepsy Journey study, which found moderate to large effect sizes from baseline to 6-month follow-up, ranging from d = 0.55 to d = 0.93 for the Global Executive Composite Score of the Behavior Rating Inventory of Executive Function. We also used Barriers to Diabetes Adherence questionnaire data collected as part of routine care from adolescents who attended T1D medical appointments at Cincinnati Children's Hospital Medical Center (CCHMC) from 2016-2017, which showed improvement across one year on Stress/Burnout and Time Pressure/Planning subscales (d = 0.19). A Monte Carlo simulation in Mplus with n = 5,000 replications was conducted assuming: 1) proper handling of missing data; 2) 25% attrition; 3) standardization of all analysis variables; 4) >30% of the error variance in our primary outcome ($R^2 = 0.30$) explained by baseline Barriers to Diabetes Adherence questionnaire scores and covariates; 5) smallest effect size from our preliminary work in the treatment group (i.e., d = 0.55); and 6) small improvement in Enhanced Standard of Care (d = 0.19). Our analysis indicated >80% power to detect a follow-up group difference effect size of $\Delta d = 0.36$ (where $\Delta d = 0.55 - 0.19$) with a total sample size of N = 256, with n = 100 in Enhanced Standard of Care and n = 156 in *Diabetes Journey*.

Given recruitment challenges and the resulting changes to eligibility and randomization, we decided to focus on the overall *Diabetes Journey* versus Enhanced Standard of Care difference at our primary endpoint, instead of powering for treatment subgroup comparisons. Using the same effect size estimates and assumptions in the original power analyses, but assuming a 1:1 randomization to only two groups, we determined that reducing the sample size from N = 256 to N = 190 ensured >80% power to detect a follow-up group difference effect size of $\Delta d = 0.36$, resulting in final group sizes of n = 110 in *Diabetes Journey* and n = 80 in Enhanced Standard of Care.

Randomization

At baseline, all participants who met inclusion/exclusion criteria (e.g., elevations on the Stress/Burnout and/or Time Pressure/Planning subscales of the Barriers to Diabetes Adherence questionnaire) were randomized to either the control group (i.e., Enhanced Standard of Care) or treatment group (i.e., *Diabetes Journey*). We used stratified block randomization with two strata and blocks of size 2 or 4 chosen randomly within each stratum. Stratification was based on baseline HbA1c (i.e., >9% or <9%), site (i.e., CCHMC or University of Florida/University of

Colorado's Barbara Davis Center for Diabetes), and Barriers to Diabetes Adherence elevation type within the treatment arm (i.e., elevated on one or both of the subscales). The HbA1c criterion was selected because the average HbA1c in 13-17 year olds with T1D in the US is 9%, which resulted in comparable sample sizes above and below 9%. In addition, although the American Diabetes Association recommends an HbA1c <7%, very few adolescents achieve this. Site was chosen to ensure balance for any site-related differences. The randomization list was held by an individual independent of the study to reduce any potential biases. Those who were randomized were notified of their randomization status after completion of the baseline questionnaires so intervention materials could be provided immediately.

Measures

Definitions and Derivations (numbers at the end of variable names represent timepoint: 0=baseline; 1=post-treatment, 2=follow-up1 and 3=follow-up2)

Barriers to Diabetes Adherence (BDA) (Mulveany et al., 2011)				
Subscale	**Descriptor**	**Items**	**Range**	**Interpretation**
bdastress	**BDA Stress and Burnout Subscale**	4	1-5	↑ scores ↑ stress and burnout
bdatime	**BDA Time Pressure and Planning Subscale**	5	1-5	↑ scores ↑ planning barriers

bdastress0, bdastress1, bdastress2, bdastress3, bdatime0, bdatime1, bdatime2, bdatime3

Type 1 Diabetes and Life (T1DAL) Adolescent 12-17 (Hilliard et al., 2019)				
Subscale	**Descriptor**	**# of items**	**Range**	**Interpretation**
t1dalttotal	**T1DAL Adolescent Total Score**	23	0-100	↑ scores ↑ HRQOL
t1daltemotion	**T1DAL emotional experiences and daily activities**	11	0-100	↑ scores ↑ HRQOL
t1dalthandlingt1d	**T1DAL Handling Diabetes**	6	0-100	↑ scores ↑ HRQOL
t1daltpeer	**T1DAL Peer Relationships**	3	0-100	↑ scores ↑ HRQOL

t1daltfamily	**T1DAL Family Relationships**	3	0-100	↑ scores ↑ HRQOL

t1dalthandlingt1d0, t1dalthandlingt1d1, t1dalthandlingt1d2, t1dalthandlingt1d3, t1daltpeer0, t1daltpeer1, t1daltpeer2, t1daltpeer3, t1daltfamily0, t1daltfamily1, t1daltfamily2, t1daltfamily3, t1dalemotionr0, t1dalemotionr1, t1dalemotionr2, t1dalemotionr3, t1daltotalr0, t1daltotalr1, t1daltotalr2, t1daltotalr3

Additional Variables

- a1c0, a1c1, a1c2, a1c3 (Hemoglobin A1C value)
- Condition (0=ESC, 1=Diabetes Journey)
- site (1=CCHMC; 2=UF, 3=BDC)
- age (continuous variable from 12-17 years old)
- sex (0=male; 1=female)
- insur (0=public; 1=private, 2=both, 3=uninsured)
- cgm (0=No CGM device, 1=Yes CGM device)
- timedx (continuous variable - T1d duration)
- race (0=Native American/Alaskan; 1=Asian, 2=Native Hawaiian/Pacific Islander; 3=Black, 4=White, 5=More than one race, 6=Other)
- ethn (0=Non-Hispanic; 1=Hispanic)
- rel (0=Mothers/StepMothers; 1=Fathers/Stepfathers, 2=Legal Guardian, 3=Grandmother, 4=Grandfather, 5=Other)
- mstatus (0=Single, 1=Married, 2=Separated, 3=Living with Someone, 4=Divorced, 5=Widowed)
- edu (0=6th grade or less, 1=7-8th grade, 2=9-11th grade, 3=High school graduate, 4=Some college or certificate course, 5=College Graduate, 6=Graduate or Professional degree)
- meth (0=Premixed/conventional insulin, 1=Multiple Daily injections, 2=Insulin Pump)

Subscale	Descriptor	Items	Range	Interpretation
cefisaya_distress	**COVID-19 distress score**	1	1.0-10.0	↑ scores ↑ distress

cefisaya_impact

Statistical Analyses

Primary Aim Analysis Plan:

An intent to treat approach will be undertaken for all analyses. We will examine the data for intervention group comparability using chi-square tests for categorical variables (e.g., biological sex, insurance status, technology use) and t-tests for continuous variables (e.g., age, T1D duration) prior to analysis of the primary outcomes. Should we observe intervention group

differences at baseline on any variables, these variables will be added to the outcome models as covariates.

Our primary hypothesis examines group differences at the 6-month follow-up (i.e., primary end point) given that we expect participants to have made the most significant gains from the intervention after implementing the acquired skills for some time. Two separate Analysis of Covariance models (one for each barrier subscale) will be used to test the primary hypothesis that the *Diabetes Journey* intervention group will demonstrate significantly lower barriers compared to the Enhanced Standard of Care group at 6-month follow-up, after controlling for baseline barriers. For secondary outcomes (i.e., HRQOL, T1D self-management behaviors, HbA1c), the same analytical approach will be used, with baseline values of the respective outcome included as a covariate. To evaluate the treatment effect on our primary and secondary outcomes across time, we will employ Generalized Estimating Equations (GEE), while controlling for baseline covariates.

Handling Missing Data

Missing data will be addressed using full information maximum likelihood (FIML) under the assumption of data missing at random (MAR) in the ANCOVA models. For the longitudinal GEE models, we will use multiple imputation to address missing data under the assumption that the data are Missing at Random (MAR). The imputation will use chained equations (`mi impute chained`) with relevant predictors to generate 100 imputed datasets.

Variables:

Outcome variables:

- Primary: BDA subscale scores for stress and time pressure (bdastress, bdatime)
- Secondary: a1c, T1DAL subscales and total score (t1dalthandlingt1d, t1daltpeer, t1daltfamily, t1dalemotionr, t1daltotalr)

- **Group (independent variable)**:
  - condition (0 = ESC, 1 = DJ)
- **Timepoints**:
  - time (post-treatment = 1, follow-up 1 = 2, follow-up 2 = 3)
- **Covariates**:
  - age (continuous)
  - sex (categorical, 0 = male, 1 = female)
  - insurance (insur, 0=public, 1=private)
  - time since dx (timedx, continuous)
  - use of technology (cgm yes = 1, cgm no = 0)
  - adolescent reported COVID impact scores at baseline (cefisaya_impact; continuous)
  - baseline outcome scores (outcome scores measured at time 0; continuous)
  - site (dummy coded as s1, s2; UF, BDC, CCHMC)

- **Correlation Structure (for GEE model)**: Exchangeable correlation structure (to account for correlations within participants over time).