Epilepsy Adherence in Children and Technology (eACT): Fostering Medication Adherence in Children With Epilepsy Using mHealth Technology

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Power and Sample Size Estimation

Sample size estimation was informed by results of previous studies of adherence interventions. Effect sizes for education-focused adherence interventions with reminders in other chronic conditions relative to controls (e.g., treatment as usual, pre-post) range from 0.08-0.20 [42, 43], while those with adherence feedback range from 0.78-1.03 [44, 45]. Specifically, an HIV study found that individualized adherence feedback demonstrated a large, standardized effect size (Cohen's d=0.78) [44]. Similar and higher effect sizes have been found for mHealth interventions that include education, automated digital reminders, or individualized feedback in adult samples including asthma, diabetes, and heart disease (Cohen's d=0.70-2.51) [46-48].

Given the range of observed effect sizes and taking into account the size of clinically meaningful changes in adherence, sample size was determined to detect a small-to-moderate standardized effect size (Cohen's d=0.36) for the primary analysis of SMART Stage 1 comparing intervention to control with 80% power with significance level 0.05. Assuming 2:1 randomization to intervention vs control yields a conservative total sample size estimate of 270, with ~180 participants randomized to intervention and ~90 to control. This sample size leads to 97% power to detect a moderate standardized effect size (Cohen's d=0.50).

Power for the secondary analysis involving pairwise comparison of the intervention strategies embedded in the SMART is informed by effect sizes for our face-to-face problem-solving adherence intervention, which incorporates individualized adherence feedback relative to treatment as usual. These effect sizes ranged from from 0.95 (1st problem-solving session) to 1.59 (2nd problem-solving session). Power analyses for comparison of intervention strategies require additional unknown assumptions, such as the anticipated response rate to intervention at the end of Stage 1. Assuming a 50% response rate to SMART Stage 1 intervention and a Bonferroni multiplicity adjustment, the proposed sample size provides 80% power with significance level 0.05 to detect a standardized effect size of d=0.69 between any pair of the embedded intervention strategies #1 - #3.

To achieve the propose sample size, the planned study sample was 600 participants across sites, with the goal of approximately 330 of the 600 being randomized (i.e., 10% attrition during the baseline phase, and 45% would be > 95% adherent, completing the study before randomization) [5]. Following initial randomization, these ~300 participants were to be assigned in a 2:1 ratio to intervention (n=200) and control (*n*=100). Making a conservative assumption of 10% attrition of participants in each initial SMART intervention arm results in anticipated *n*=180 randomized to intervention and *n*=90 randomized to control at the end of Stage 1. However, per federal and institution specific guidelines, recruitment was suspended during the COVID-19 pandemic, and the study team determined that 450 participants would need to be enrolled for *n*=180 to be randomized to the intervention arm and n=90 randomized to the control arm.

Statistical Analysis Plan

Primary Analysis Plan:

An intent to treat approach will be undertaken for all analyses, and a significance level of 0.05 will be used. The primary analysis examines the efficacy of the mHealth adherence intervention in caregivers of youth (ages 2-12) with newly diagnosed epilepsy (< 2 years) on electronically monitored adherence relative to control on the basis of the primary outcome of change in electronically monitored adherence from baseline, calculated using the baseline and final 30-day adherence. The primary hypothesis is that participants initially randomized to intervention will exhibit significantly greater improvements in adherence compared to those randomized to control from baseline to end of Stage 1. Although sample size was calculated conservatively based on use of a two-sided, two-sample *t*-test with unequal sample sizes, to achieve a more efficient analysis with enhanced power, the primary analysis will be based on a standard analysis of covariance with adherence at the end of Stage 1 as the dependent variable and baseline adherence as the covariate.

Secondary Analysis Plan:

Secondary analyses will compare the mean outcomes associated with each of intervention strategies #1 - #3 embedded in the SMART on the basis of the outcomes adherence, seizure severity/frequency, HRQOL, and healthcare utilization at 1-, 6-, and 12-months post-intervention**.** Strategies #1 and #2 are non-adaptive intervention strategies in that intervention is not modified in accordance with Stage 1 adherence status (or any other participant characteristics), while #3 is an adaptive intervention strategy in that intervention is augmented by problem-solving in Stage 2 only under non-adherence in Stage 1. The pairwise comparison of the non-adaptive strategy #1 to the adaptive strategy #3 represents comparison of the least resource-intensive strategy (control) to the most resource-intensive strategy. Comparison of strategies #1, #2, and #3 will be carried out using specialized methods for SMART analysis based on inverse probability weighting for estimation of the mean outcome associated with a strategy that account for the fact that actual experiences of participants may be consistent with more than one strategy; for example, a participant who is randomized to intervention in Stage 1, is adherent in Stage 1 (i.e., is a responder to intervention), and continues to receive intervention in Stage 2 is consistent with having followed either embedded strategy #2 or #3. In this case, a participant's data contributes to assessment of improvement in outcome for both strategies. For each strategy, the inverse probability weighting is by the reciprocal of the estimated probability that a participant's experience is consistent with the strategy. We will conduct pairwise comparisons of the three embedded strategies using these methods based on adherence, seizure severity/frequency, HRQOL, and healthcare utilization at 1, 6-, and 12-months post-intervention. We will also conduct a global test of the null hypothesis that the mean outcomes associated with the three strategies are the same versus the alternative that at least one mean differs from the others.

Exploratory Analysis Plan:

The data collected will provide a rich resource for exploratory analyses investigating participant baseline characteristics and post-randomization characteristics ascertained prior to assessment of Stage 1 adherence status that can inform tailored selection of initial intervention (intervention or control) and of subsequent intervention for non-adherent individuals receiving initial intervention (continue intervention or augment intervention with problem solving). We will use standard methods to evaluate whether baseline characteristics moderate participants' adherence status following initial intervention, including tests for qualitative interactions. Evaluation of moderators of outcomes at Stage 2 and at 1-, 6-, and 12-months post-intervention is complicated by the sequential nature of the interventions, requiring the use of specialized statistical methods, such as Q-learning and value-search estimation. We will also use these methods to estimate an optimal adaptive intervention strategy for individualizing selection of initial intervention and intervention in the case of non-adherence based on baseline and evolving child/family characteristics, informing strategies for future study.

Handling of Missing Data:

Missing change in adherence outcomes in the primary analysis will be addressed in several ways. Under the assumption that the adherence outcomes are exactly normally distributed and linearly related, the analysis of covariance based on the complete cases will yield valid inferences under the assumption of missing at random (MAR). To evaluate the evidence in the data under MAR without making the restrictive assumptions of normality and linearity, we will conduct the complete case analysis if missingness is nondifferential by Stage 1 assignment and less than 10% in each assignment group. To assess sensitivity of this analysis to missingness, under the assumption of MAR, we will also conduct an inverse probability weighted complete case analysis of covariance in which outcomes are weighted by the reciprocal of the estimated probability not dropping out of the study in Stage 1 based on a

logistic regression model that incorporates baseline variables associated with with failure to complete Stage 1.

For the secondary analyses, Stage 2 and later outcomes will be assumed to be missing according to a MAR mechanism. If the extent of missingness is less than 10% for each strategy, we will conduct complete case analyses comparing the embedded intervention strategies. To assess sensitivity of these analyses to missingness and to obtain a definitive analysis if the extent of missingness is greater than 10%, under the MAR assumption, we will use inverse probability weighting of complete cases in estimation of the mean outcomes associated with each strategy, where the outcomes are weighted by the reciprocal of the estimated probability not dropping out of the study/having the outcome observed as a function of baseline and previously observed variables based on logistic regression.