Clinical Trials Title: Behavioral Economics and Adherence in Teens (BEAT!)

NCT03958331

Date Created: 2/27/2018

NIH Grant Title: Improving Drug Adherence Using mHealth and Behavioral Economics in Adolescents with Epilepsy (R21NR017633)

4.4 Statistical Design and Power

Aim 1: Examine the feasibility, accessibility, acceptability, and responsiveness of a mHealth social norms intervention to improve AED adherence for adolescents with epilepsy. H1: Adolescents with epilepsy will rate the intervention as highly feasible, easy to use, acceptable, and responsive to their needs.

Analyses Aim 1: We will examine means and standard deviations of ratings completed by adolescents on the Adapted Feasibility and Acceptability Questionnaire, Revised Website/mHealth tool Evaluation Questionnaire (WEQ), and System Usability Scale. For the Adapted Feasibility and Acceptability Questionnaire, ratings of 3-4 are considered good. The WEQ is primarily qualitative in nature and will be used during Phase 1b modifications, as well as the RCT to obtain qualitative data on the use of the social norms mHealth tool. Finally, scores on the System Usability Scale[85] ranging from 80-100 range indicate good to excellent usability.

Aim 2: Examine the preliminary efficacy of the mHealth social norms intervention on AED adherence, seizure severity, and HRQOL in adolescents with epilepsy. H2a: Participants in the treatment group will demonstrate statistically significant *improvements* in adherence with corresponding medium/large effect sizes compared to the control group at post-treatment. H2b: Greater improvements in seizure severity, HRQOL, and adherence are expected at 3-month follow-up for the treatment versus control group.

Analyses Aim 2: For the pilot RCT, adherence will be calculated using daily adherence data and collapsed for the one-month prior to treatment (baseline adherence) and the one-month following treatment (post adherence). For example, if a patient is prescribed their AED twice a day and takes 50 of their 60 doses in the month, their adherence rate would be 83.3% (total doses taken/total doses prescribed x 100%). For the follow-up period, three-month adherence will be calculated to assess sustainability of treatment effects. All analyses will be carried out with missing data assumed to be missing at random and handled via maximum likelihood estimation with auxiliary correlates[113] within Mplus (Version 8) on the full randomized sample (N=80). An ANCOVA model will be used to test the primary hypothesis that the mHealth social norms group will demonstrate significantly higher adherence rates compared to the control group at post-treatment (one-month of adherence following intervention), after controlling for baseline adherence (1-month of adherence prior to intervention), age, sex, SES, seizure type, side effects, and cognitive/executive functioning[114] (Aim 2, H2a). When examining our secondary outcomes (i.e., seizure severity, HRQOL) and adherence at 3-month follow-up (Aim 2, H2b), the same statistical model and covariate logic employed for our primary hypothesis will be used in a longitudinal mixed model.

Missing Data: *Strategies to minimize loss to follow-up are outlined in Form E: Section 2.5 Recruitment and Retention Plan. Data that remain missing despite our retention efforts will be accommodated in our analyses and their impact evaluated through sensitivity analyses. The models we propose can be estimated without bias under the missing at random (MAR) assumption[115] and provide valid analysis as long as auxiliary covariates associated with missingness (if any) are included in the analysis model. To determine which covariates are associated with the missing data, we will create binary indicators of whether an observation was missing or not on each of the outcome variables, then use logistic regression to determine which covariates (if any) predict the "missingness" we observe on each of the outcomes. We can also examine whether those with complete data versus those with missing data differ on any of the outcomes.*

Power: *For the focus group and extended formative usage evaluation (ORBIT Phase 1a and 1b), we will use qualitative data analysis to modify the mHealth tools. A sample size of 10 for usability is sufficient to detect 95% of usability problems when pilot testing an mHealth tool.[88]*

Given timeline and resources proposed for this pilot RCT (ORBIT Phase II), we anticipate recruiting N=138 participants. We expect that 58% will have adherence $\leq$95%, leaving N=80 to be randomized. We conducted a Monte Carlo simulation in Mplus with N = 5000 replications, assuming a total randomized sample of N=80, 25% attrition, proper handling of missing data, standardization of all analysis variables, and that baseline adherence, age, sex, side effects, cognitive/executive functioning, seizure type, and SES (covariates) will explain at least 40% of the post-treatment adherence error variance (based on our pilot data and previous studies[1]) Our analysis indicates that we will have at least 80% power to detect a post-treatment group difference effect size of d > 0.62 in adherence rates (i.e., approximately 15% difference in group adherence

rates at post-treatment). Effect sizes for recently published social norms interventions have ranged from 0.41[24] to 0.85[58] when compared to those without social norms comparisons, and we have sufficient power to detect effects within the range of those published. The estimates of preliminary efficacy and variability of our social norms intervention that we obtain will be used to power for a future larger trial.

Exploratory Analysis: *In this pilot trial, we plan to explore potential differences in treatment efficacy based on subgroups and other covariates. For example, we will examine whether our preliminary estimates of* ***efficacy vary as a function of sex, side effects, seizure type, cognitive/executive functioning, or age.*** *In* ***our*** *analyses, should we observe differences, we can use these variables as covariates in order to obtain unbiased and efficient estimates of our treatment effect. This information will also guide statistical power calculations and possible block randomization schemes for a future large-scale trial. We also plan to* ***explore potential mediators*** *of adherence change, including peer influence and adherence barriers, to better understand the full conceptual model that can be used to guide the design of a future full-scale trial. Finally, given that minimal clinically important differences in change for pediatric adherence have not been established, we will instead explore the clinical impact of our intervention by examining the* ***proportion of patients within each of our treatment groups who reach ≥ 95% adherence*** *at post-test and follow-up.*