DOCUMENT: Statistical Design and Power

PROTOCOL TITLE: Complimentary Electronic Cigarettes for Harm Reduction among Adult Smokers with Asthma

NCT: NCT05278065

DOCUMENT DATE: 06/17/2020

Statistical Design and Power

Statistical Design

Initial data analysis will include descriptive analysis for the sample and within study condition, tests of attrition, missing data analysis, evaluation of distributional properties, and correlations among measures. Potential moderators of treatment outcome (e.g., compliance) will also be examined.

Quantitative Analyses

Aim 1 - Hypothesis 1: At Week 8, ENDS participants will smoke fewer cigarettes/day (CPD) and show reduced cigarette dependence relative to BL. Relative rates of CPD reduction and cessation across study arms will be examined. DVs: cigarettes per day (from TLFB); FTCD and WISDM scores. IVs: time; condition; time by condition interaction.

Aim 2 - Hypothesis 2: ENDS participants will exhibit better asthma control and self-reported respiratory symptoms (wheezing, bronchitis, shortness of breath, mucus production) versus baseline. Changes in lung function will be explored. Primary DVs: *Asthma Control*: ACT scores, *Asthma Symptoms*: ASUI scores, Mini-AQLQ scores; Secondary DVs: *Spirometry:* PEF, FEV_1, FVC, FEV_1/FVC ratio, and FEF_{25-75}. IVs: time; condition; time by condition interaction.

Aim 3 - Hypothesis 3: Biomarkers of exposure, toxicity, and inflammation will be lower in ENDS participants versus BL. DVs: *Inflammatory and Disease Biomarkers*: IL-6, FENO, *Exposure and Toxicity*: NNAL, TNE, TNE/NNAL ratio. IVs: time; condition; time by condition interaction.

Qualitative Analyses

Aim 4 - Hypothesis 4: High willingness to participate, high weekly retention, low attrition, and few reported barriers to engagement will demonstrate feasibility of complimentary ENDS provision for cigarette substitution. Hypothesis 5: Positive responses during qualitative exit interviews will demonstrate acceptability.

Analytic approach:

Multiple approaches will be used to investigate smoking/ENDS use; respiratory function; and inflammatory and disease marker outcomes but will primarily focus on developing a longitudinal model based on intent-to-treat principles. Initially, *t*-tests (paired and independent samples) will quantify differences in outcomes across groups or time, and ANOVA will be used to investigate within, between, and within-between interactions. We will leverage the robustness of linear mixed effects models (LMEM) or generalized estimating equations (GEE) to examine outcomes within a longitudinal framework. Intraclass correlations (ICCs) of outcome variables within participant classes will be investigated. Model terms will include time, condition, and their interaction, and covary for potentially unbalanced baseline demographic and behavioral (e.g., smoking) factors across conditions. LMEM models will include random intercepts to account for subject-level differences in outcomes and investigate fixed linear, quadratic, and subject-level random effects of time. Appropriate LMEMs will be selected based on the distributional properties of the DV. We will investigate logarithmic transformations of the outcome where necessary. DVs with high resolution data (e.g., measure of cigarettes per day available weekly), will be modeled at the weekly level. All analyses will be conducted in R version 3.6.0, using the geepack package for GEE and lme4 package for LMEMs.

Missing data:

Systematic missing data due to attrition or other factors will be examined. We will first conduct Little's MCAR test on a dataset including all participant characteristics, covariates, primary, and secondary outcomes to evaluate whether missing data patterns are consistent with the Missing Completely at Random (MCAR) assumption. As data in longitudinal studies is rarely MCAR, we will initially use the VIM package in R to identify patterns of systematic missingness across time. We will also use *t*-tests and χ^2 tests to examine whether covariates and outcomes at week 8 vary as a factor of attrition at subsequent time points. Multiple-imputation will be used for sensitivity analyses of all primary and secondary outcome models following identification of predictors of missingness to help sustain the missing-at-random (MAR) assumption. Multiple imputation will be conducted in the *mice* package for R.

Power Analysis and Sample Size

Tobacco use outcomes: Power and sample size calculations were conducted in GPower 3.1 based on between- and within-subjects analyses. Dr. Tidey's pilot trial examining 6 weeks of complimentary ENDS provision on tobacco use behaviors and nicotine dependence at weeks 6 and 10 (i.e., 4 weeks after final ENDS provision) found significant reductions between baseline and both time points in average cigarettes per day (baseline=19.6(8.2); week 6=6.7(7.9), *d*=1.64; week 10=8.8(8.3), *d*=1.12) and cigarette dependence (baseline=5.94(1.96); week 6=3.89(2.78), *d*=.88; week 10=3.50(3.08), *d*=1.03); all with large effects. However, given the unknown effect of providing free ENDS to adult smokers with asthma and the limited interpretability of effect sizes from pilot trials we chose to use a more conservative medium-large (*d*=0.65*)* effect size. With our planned enrollment (*N*=30), anticipated 10% dropout, and target power (1-β=.8), sample size was adequate to detect within-subject repeated measures (Aim 1) differences in the intervention (ENDS) group but was inadequate to detect between-subjects effects (i.e., group differences). Although power is below .80 to detect group differences, this pilot proposal will help determine the magnitude of these effects and inform the design of future research.

Respiratory outcomes: Investigations of respiratory symptoms and lung function change in 'healthy' smokers switching to ENDS have found very large (*h*=1.94) within-subjects effects for cough, very large (*h*=1.50) within-subjects effects for shortness of breath, and large (*d*=.998) within-subjects effects for FEF_{25-75}; also found were large (*d*=.921) between-subjects effects comparing successful to failed switchers. As these improvements may be even more pronounced for adults with asthma, the current planned enrollment achieves adequate power to examine these within-subjects (but not between-subjects) outcomes within the ENDS condition per the power and sample size analyses outlined above (Aim 3). However, analysis of spirometry are limited by the short follow-up period for the proposed pilot within-which changes in these metrics are not anticipated. As with the tobacco use outcomes, although power is below .80 to detect group differences, this pilot proposal will help determine the magnitude of these effects and inform the design of future research.

Biomarker: The effect of complimentary ENDS provision on biomarkers of exposure, toxicity, and inflammation in adults with asthma in real-world use conditions should be considered exploratory and preparatory for future intervention design.