March 24 2016

Title: Biobehavioral Intervention for Smokers Living With HIV (Human Immunodeficiency Virus)

Phase 4 Clinical Trial of the FDA approved Nicotine Replacement Therapy with over the counter medications (Nicorette gums and Nicotine Patch 1 and 2

NCT: 02982772

STATISTICAL ANALYSES:

Sample Size and Power Calculation: We plan to recruit a total of 600 participants (300 in each arm), and allow an attrition rate to be 15%, so we will have at least 500 subjects (250 in each arm) at the end of study. Statistical power is based on the primary endpoint - expected outcomes per treatment arm at the 6 month follow-up. We assume a two-tailed test for differences between independent proportions, with alpha set to .05. Power was computed with the G*Power program. Based on our prior studies, we assumed a 10% abstinence rate in the standard care arm with NRT, and we adjusted the sample size to yield 80% power for at least a doubling of this effect, which is deemed to be of minimal clinical significance. As seen in the Figure, we have ample power to detect a 10% ≥ 19% difference in cessation outcomes.

Hypothesis 1: The tailored NRT condition will produce superior abstinence outcomes at 6 and 12 months compared to standard care on the following.

Primary Outcome: Abstinence at 6-and 12 months. The binary response variable, 7 day point prevalence abstinence at 6 months, will be compared between the ESC and Tailored arms via logistic regression, where the estimated coefficient for the treatment effect in the log odds scale is expressed as an odds ratio. The model will also be estimated including covariates to rule out possible confounding effects. These will include gender, race, age, nicotine dependence, HIV stage of disease, other drug abuse, and others, as deemed appropriate.

Other outcomes, including continuous and 30-day point prevalence abstinence, will be analyzed in a similar fashion. To take advantage of the longitudinal design, repeated binary point prevalence outcomes will be analyzed via mixed effects generalized linear mixed effects models implemented in SAS PROC GLIMMIX, in which the response and random effects vectors are fully specified, and estimation/inference is likelihood-based. The main effects of treatment condition, time, and their interaction will be modeled to establish durability of treatment effects over time. Effect modification will be tested by introducing higher order interaction terms, e.g., three-way interactions among treatment, time, and select covariates (gender, race, age, grade of dependence).

Throughout these analyses, special attention will be paid to missing data. Mixed model analysis using maximum likelihood estimation provides valid statistical inferences in the presence of either “missing completely at random” (MCAR: missingness can depend on model covariates) or “missing at random” (MAR: missingness can depend on model covariates or observed values of the dependent variable) mechanisms. We will examine whether attrition is related to any potential covariates (e.g., age, ethnicity, dependence, BMI) or prior values of the dependent variable (e.g., subjects who are heavy smokers drop out of the study), and augment our longitudinal models accordingly to provide valid tests in the presence of these types of missing data mechanisms. It should be noted that although the observed data can help distinguish MCAR from MAR, if one suspects that missingness is related to the dependent variable value that would have been observed, then the mechanism is said to be missing not at random (MNAR) and “non-ignorable.” In this situation, one can do sensitivity analyses to examine the degree to which conclusions vary as a function of the assumed missing data mechanism. In particular, two classes of models are useful in this endeavor: selection and pattern mixture models.

Mediators to explore include improved knowledge, greater self-efficacy to resist temptations to smoke, as well as fewer cravings which we hypothesize will be better controlled in the tailored arm (ESC) by

providing adequate doses of nicotine. It also includes moods, and BDNF. Mediation analysis conducted on the data from a randomized experiment enables the examination of the mediated effects of the intervention as a whole as well as the examination of the mediated effects of each treatment arm. The analyses will consist of the following steps: 1) modeling the treatment effect on the behavioral outcome, which will have been conducted previously; 2) fitting the same model for each of the mediators but with the addition of the mediators as covariates; 3) differences between the main effect and interaction estimates in Steps 1 and 2 provide estimates of the mediation effects. If an effect that was significant in Step 1 is reduced to non-significance when the mediator is introduced into the regression equation, this is evidence for complete mediation of that effect. If an effect that was significant in Step 1 is reduced by introduction of the mediator but remains significant, this is evidence for partial mediation. We will test the mediation effects for significance using the general approach described in MacKinnon.

The full models included age, sex, socioeconomic status, and nicotine dependence at baseline in the first step, treatment group (tailor patch, standard patch) and genotype (slow yes/no) in the second step, and interaction terms for treatment × genotype, in the third step.

Confounders: We are cognizant that gender, race, age, HIV stage of the disease, consumption of certain foods and certain medication, can confound our analyses so we have selected statistical models that will permit controlling their effects.

Modeling the confounders: We will formally model their status, for example, using a principle components analysis. In general, even with numerous factors in the matrix, the first several principal components will explain a high percentage of the variability of the overall matrix of confounders. The next step of the procedure will involve post-hoc examination of each variable in the matrix of confounders, to ascertain the individual effect on the model.