Statistical Analysis Plan

TITLE: Cessation in Non-Daily Smokers: A RCT of NRT With Ecological Momentary Assessment
NCT Protocol #: NCT02168855
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Outcomes

Outcomes are assessed and analyzed in three ways:

The primary outcome is 6-month continuous abstinence, allowing for a 2-week 'grace period' following the start of treatment and quit date.[1,2] Participants are considered to meet the criterion if they claim abstinence throughout the period, demonstrate CO levels ≤3 ppm each time they are tested, and further demonstrate urinary cotinine levels ≤25 ng/ml when tested at 3 and/or 6 months. For the primary analysis, participants who are lost to follow-up will be considered to be smoking, consistent with the common standard for assessing smoking cessation outcomes. However, Hedeker, Mermelstein & Demitras[3] have shown that imposing this very strong assumption is not necessarily conservative. Following procedures recommended by those authors, sensitivity analyses will consider a range of assumptions about the relationship between loss to follow-up and smoking.

Complementing the assessment of continuous abstinence, we will also assess 14-day point-prevalence abstinence at each time-point throughout the study, specifically at 2, 4, 6, 12, and 24 weeks. (Analysis of ad libitum smoking patterns among ITS[4] indicates that 7 day periods of abstinence are relatively common, whereas 14-day periods are not.) Subjects will be considered abstinent if they report no smoking for 14 days, and demonstrate exhaled CO levels ≤3 ppm. No imputation is made for missing data.

Finally, Shiffman et al.[5] have proposed an assessment paradigm that separately examines key behavioral milestones in trajectories of smoking cessation success or failure, namely achievement of abstinence, lapsing after achieving abstinence, and relapsing following a lapse. Subjects will be considered to have achieved abstinence if they have 7 consecutive days of abstinence. A lapse is defined as any occasion of smoking after abstinence is achieved, and a relapse is defined as reaching a rate of cigarette consumption ≥50% of the subject's baseline level. (Previous definitions of relapse[6] have been based on consecutive days smoking, but such definitions are unsuitable for ITS, who might not meet such criteria even when smoking ad libitum at baseline.)

Moderators

Three individual difference variables are hypothesized to potentially moderate the treatment effects: Degree of dependence will be expressed as a dichotomy, distinguishing subjects with an FTND[7] score of 0 from those with higher scores. Previous research has indicated that this distinction is behaviorally relevant among ITS.[8] Self-reported history of previous daily smoking (for at least 6 months) has previously been shown to help predict ITS behavior[9] and smoking cessation outcome.[10] The amount of gum used has previously been shown to influence outcomes in smoking cessation studies with nicotine gum.[11,12] Because gum use can change over time, sometimes in response to relapse, we focus on gum use

in the first week of treatment. Whereas daily smokers are directed to use at least 9 pieces per day initially,[13] the ITS in this study were not given a target number of pieces, but were instead instructed to use gum when they felt they needed it. Thus, there is no absolute standard against which to assess the amount of gum use; we instead capture gum use in strata based on the observed range of gum use in the study (strata: 0 pieces per day, <0.5/day, 0.5-1.0/day, >1/day).

Nollen et al.[14] are conducting a trial of nicotine replacement focused exclusively on African-American individuals. Anticipating the value of comparing outcomes across studies, an exploratory analysis will examine outcomes among African-American participants in the present study, also examining whether race moderates outcomes.

Analysis

Continuous abstinence will be assessed by logistic regression, with treatment as the primary predictor. Moderation will be tested by interactions between treatment and each of the three moderators: dependence, history of daily smoking, and gum use. Sensitivity analyses will test a range of hypothesized relationships between missing data and smoking,[3] expressed as odds ratios of 1, 2, and 5. If analyses detect baseline differences between treatment groups in variables that also correlate with outcomes, these will be included as covariates.

Point-prevalence abstinence over multiple time-points will be tested using multi-level generalized mixed models, with random effects (SAS PROC GLIMMIX), which allow for multiple correlated dependent variables per subject. Abstinence at 2, 4, 6, 12 and 24 weeks will be entered; parameters will include assessment time (with both linear and quadratic expressions) and treatment assignment and their interaction. The resulting analysis essentially considers the 'area under the curve' for abstinence-by-time. Missing assessments will not be imputed; GLIMMIX allows for incomplete data across time and uses full maximum likelihood estimation. This allows for missing at random (MAR) in which the missingness can be related to model covariates as well as observed values of the dependent variable.[15] The three pre-specified moderators and their interaction with treatment and time will also be considered, and baseline differences will be included as covariates.

Achievement of cessation milestones (abstinence, lapsing, and relapsing) during the primary treatment period of 6 weeks will be analyzed using event-history ('survival') analyses using Cox proportional hazards models. (If the assumption of proportionality is untenable, other survival analysis models will be applied.) Time to achieve cessation will be assessed from the first treatment day; time to lapse is assessed from the first day of abstinence, among those who achieve abstinence; time to relapse is assessed from the day of first lapse, among those who lapse. For subjects who are not observed to reach a milestone (e.g., subjects who do not achieve abstinence by end of study or when they drop out), time will be censored as of the last day of observation. Moderators and potential group-assignment confounds will be considered as above.

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