Study Statistical Analytic Plan

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“P01 Cessation Screening Study”

Principal Investigator: Megan E. Piper, Ph.D. (608) 265-5472
Coordinating Center: UW-Center for Tobacco Research and Intervention (UW-CTRI)
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Study Overview

This study will use the Multiphase Optimization Strategy (MOST) to guide the development of optimized treatment strategies for the two most effective smoking cessation medications (C-NRT and varenicline). We will recruit daily smokers from primary care to participate in a fully crossed, 2x2x2x2 factorial experiment (*N*=608) that evaluates 4 different factors: 1) Medication Type (Varenicline vs. C-NRT), 2) Preparation Medication (4 Weeks vs. Standard), 3) Medication Duration (Extended [24 weeks] vs. Standard [12 weeks]); and 4) Counseling (Intensive vs. Minimal). We will examine main and interactive effects of these four factors (including Medication Type) to identify especially effective components and determine which components significantly enhance or reduce the effectiveness of other components due to synergistic or subtractive interactions. These results will be used to identify optimized treatments for both varenicline and C-NRT, providing new options for a precision medicine approach to smoking treatment (e.g., smokers may have contraindications for one medication, one medication may perform better for a group of smokers). In this factorial experiment, we will also examine potential moderators of intervention component effectiveness including sex, tobacco dependence, and psychiatric history, and examine potential mediators (e.g., withdrawal suppression, enhanced self-efficacy). In sum, this study is designed to produce data on four different smoking treatment factors, allowing us to achieve the following aims:

Primary Aim 1: To determine which smoking cessation intervention components, and combinations of components, significantly improve smoking abstinence and cost-effectiveness based on main and interactive effects on 12-month biochemically confirmed abstinence. This aim addresses the vital question of which individual intervention components are significantly beneficial and which significantly enhance or degrade the effectiveness of other components.

Primary Aim 2: To identify two optimized smoking cessation treatments: one for varenicline and one for C-NRT. Data on both the 12-month abstinence effect sizes and costs of the different intervention components and combinations of components will be examined and multiple criteria decision analysis will be used to determine how to use each medication so that it is highly effective and but low in cost.

Secondary Aims: To determine: 1) whether person factors (e.g., sex, dependence, psychiatric history) moderate response to different treatment strategies; and 2) which proximal effects of each treatment factor mediate its long-term benefits; and 3) the main and interactive effects of the cessation interventions on cost-effectiveness and the cost-effectiveness of the optimal combinations of components for each medication type.

Implementation Challenges: Pandemic and Varenicline

Study recruitment began in November 2020.

In June 2021 Pfizer found that some lots of varenicline contained elevated levels of a novel nitrosamine that exceeded the level thought to be safe by the FDA for traditional nitrosamines. Therefore, we briefly paused recruitment. When we resumed recruitment, all participants were randomized to the C-NRT level of the Medication Type factor until November 2021 when we received IRB approval to use FDA-approved generic varenicline. When we were able to procure FDA approved varenicline, we changed our randomization ratio on this factor to 2:1 varenicline to C-NRT. When FDA initiated the varenicline recall, there were 42 participants actively taking

varenicline; 26 participants opted to switch to C-NRT and 16 stopped all medication. These 42 participants will not be included in the main outcome analyses.

We experienced significant implementation challenges with collecting in-person breath samples for biochemical verification of abstinence. In September 2023 we transitioned from using exhaled CO to verify abstinence (CO < 6ppm) to using cotinine assays on mailed saliva samples to verify abstinence (cotinine ≤10ng/mL).

Due to delays in implementing the study, and subsequent costs, caused by the global COVID pandemic, we were not able to reach our target sample size of 608. Preliminary data analyses conducted with data collected through December 7, 2023 indicated that there was only one factor that appeared to have a strong main effect for 6-month (n=432) and 12-month abstinence (n=334). The difference in abstinence rates for the two levels of each of the other 3 factors ranged from 0.0 to 4.9 percentage points. Given the lack of financial resources and the limited signal for additional main effects, we opted to close study recruitment at 538 (88.5% of the sample).

Sample Description

Participants' demographic and baseline smoking characteristics will be summarized using the appropriate descriptive statistics. The 42 people who were assigned varenicline and then discontinued varenicline and were switched to NRT after the FDA recalled Pfizer's varenicline will not be included in the main outcome analyses. We will conduct descriptive analyses to examine the differences between those in the varenicline condition who completed the treatment vs. those who switched to NRT during the FDA recall.

Outcome Analyses

Primary Aim 1: Identifying Main and Interactive Effects on Abstinence*.* The primary outcome is biochemically confirmed, point-prevalence abstinence (PPA) at 12-months post-TQD (based on CO <6 ppm for those assessed prior to September 2023 or salivary cotinine ≤10ng/mL for those assessed from September 2023 onward). We will conduct logistic regression analyses with predictors corresponding to the four factors using effect coding. The logistic regression models will include main and all interactive effects. Main effects will reflect the degree to which participants in the "ON" condition of a factor have significantly higher 1-year point-prevalence abstinence, relative to participants in the "OFF" condition for each factor, averaged across the other factors. These analyses will allow us to identify optimized treatments based upon main effects and interactions as they provide effect sizes (standardized regression coefficients) for the various intervention components and their combinations. We will conduct sensitivity analyses that compute abstinence means for those with CO vs. cotinine bio-verification. Due to the small sample sizes we will not do inferential testing on these comparisons.

The question of primary interest is how treatments affect abstinence amongst diverse smokers amidst the variety of other factors that also influence smokers' ability to maintain abstinence, not whether such effects occur in a statistically adjusted sample. Therefore, the primary analyses will first be conducted without covariate adjustment, to ensure that covariate adjustment does not cloud interpretation or reduce external validity for various reasons. In secondary analyses, we will statistically control for covariates including: living with a smoker, biological sex, age, clinic, health system, use of other tobacco products at baseline, cigarettes per day at baseline,

and education. In addition, primary analyses will exclude participants who were switched to cNRT from varenicline or stopped using any medication during the FDA varenicline recall.

Self-reported point-prevalence abstinence at Weeks 12 and 26 and biochemically confirmed abstinence at Week 26 will be analyzed as secondary outcomes using methods similar to those used for the primary outcome. These analyses will allow us to examine the stability or robustness of the intervention component effects.

We will also examine the main and interactive effects on cost-effectiveness in which the costs of implementing each intervention (minus research-related costs) will be computed from a societal perspective using data from publicly available Medicare and Medicaid reimbursement rates. Costs will be combined with the intent-to-treat biochemically verified 7-day point-prevalence abstinence at 12 months post-TQD to determine the cost per quit. Cost-effectiveness analyses will focus on the intervention components and combinations of components and on the entire program costs more globally, including implementation costs related to recruitment, medication, screening, and CM time. We will use methods recommended by the US Panel on Cost-Effectiveness in Health and Medicine, consistent with our prior research. Cost estimates will be converted to a common year and QALYs will be computed, using a rate of 3% to discount future outcomes and costs to present value. We will determine net monetary benefit (NMB), cost per quit, and incremental cost-effectiveness ratios (ICERs). The components of NMB will be the added costs of the treatments and the monetized value of the QALYs added by the treatments. We will convert the increased effectiveness of the treatments from quits to added QALYs, as per Stapleton and West (2012). Total program costs will be compared to program costs of the usual care approach to tobacco (MA offer, fax-to-quit referral) in place prior to the research implementation. These cost-effectiveness outcomes will be computed for all intervention conditions for all projects. To generate stable estimates of short and longer-term costs and savings, we will extract data on healthcare utilization from 1 year pre-enrollment to up to 4 years post-enrollment (maximum of 5 years total). We will also conduct probabilistic sensitivity analyses to account for uncertainty.

Primary Aim 2: Comprehensive Optimization of Treatment. The results of the analyses for Primary Aim 1 will allow us to identify optimized treatments based upon main effects and interactions as they provide effect sizes (standardized regression coefficients) for the various intervention components and their combinations. Interactions between Medication Type and other factors could potentially yield distinct optimized treatment regimens for C-NRT and varenicline, especially given the frequency of meaningful interactions amongst smoking intervention components. *A priori* we have decided to identify two optimized treatments to allow for patient choice, provide flexibility for patients who may have contraindications, and provide an opportunity for strategic assignment depending on smoker characteristics (algorithm-based personalized medicine).

An optimization criterion is a benchmark upon which intervention components will be selected for ultimate inclusion in the optimized packages of components. The primary criteria we will use for this project are abstinence at 12 months post-TQD and cost. We will attempt to balance cost and effectiveness in this effort, so that the selected components hit a “sweet spot” on a synthesis of the two criteria. We will work with investigators from the Optimization and Analysis Cores to use multiple criteria decision analysis (MCDA) to select component packages that are especially effective and low in cost, to constitute optimized treatments. MCDA focuses on how to weight and combine criteria (i.e., effectiveness and cost) to support meaningful decisions and to decide on the optimal treatment packages. Following the recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Best Practices

Task Force (e.g., use of the value measurement approach, criteria weighting, sensitivity analyses), we will synthesize cost and effectiveness scores for groupings of intervention components via an additive model with weights for the scores being derived from data generated by assessments of key healthcare system and clinical stakeholders (e.g., physicians, healthcare system administrators; see Implementation Project). The optimized packages will be those that perform best with regard to stakeholder-based preference weightings. These packages will ultimately be compared to Standard Care in the Optimized Care Project RCT on the bases of effectiveness and cost-effectiveness in primary care.

The robustness of the optimized treatments will then be evaluated with regard to other factors such as patient preference and implementation/burden data (e.g., required clinician/staff time). We will conduct sensitivity analyses that vary both the criteria and weightings (derived from stakeholder data) to examine the robustness of the identified optimized care packages.

Secondary Aims Analyses. Analysis of moderators of abstinence outcomes will use regression tree analyses that can identify differential treatment responses in 6- and 12-month abstinence. Candidate moderators of treatment effects on abstinence will include: living with a smoker, biological sex, age, use of other tobacco products at baseline, cigarettes per day at baseline, and education, and psychiatric history. Candidate mediators of cessation treatment effects will be: medication use and side effects, attendance at counseling sessions, withdrawal symptoms (e.g., craving, negative affect, anhedonia), and cessation self-efficacy. Treatment effects will be modeled as main effects and 2-way interactions with the outcomes being 6- and 12-month biochemically confirmed 7-day point-prevalence abstinence. Mediation analyses will use bootstrapped confidence intervals of the mediated effect. Care will be taken to preserve mediator/outcome temporal priority and the occurrence of smoking during the quit attempt will be statistically controlled. Mediation models will include multiple mediators and will use methods developed for use with dynamic mediator assessments (maximum likelihood estimation using hierarchical linear modeling: HLM 5.04).

Additional Analyses. We will examine the main and interactive effects of the 4 factors on the occurrence of adverse events and treatment engagement (count and proportion of counseling sessions completed [1 session for Minimal vs. 4 sessions for Intensive], counseling modality [video vs. phone] chosen for remote protocol participants, count and proportion of medication refills requested [1 for Standard Duration vs. 3 for Extended duration]). Logistic and linear regression will be used for categorical and continuous variables, respectively, with appropriate transformations of continuous variables and/or adoption of generalized regression modeling techniques as necessary. The primary analyses will be unadjusted and then we will statistically control for covariates including: living with a smoker, biological sex, age, clinic, health system, use of other tobacco products at baseline, cigarettes per day at baseline, and education. Analyses of these exploratory outcomes will achieve scientific rigor by controlling for experiment-wise error in families of related tests using the Benjamini-Hochberg approach.