PROTOCOL

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"Quitting Using Intensive Treatment Study (QUITS)"

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Study Overview

Current smoking cessation pharmacotherapies are effective but most smokers fail to quit with even the best medications. This may occur because medication use strategies have not been developed in a methodologically principled manner, which had kept clinicians from using available medications most effectively. Some evidence suggests that innovative medication use strategies such as combining varenicline and nicotine replacement therapy may boost medication effectiveness markedly; however, because of a lack of systematic research, we do not know which innovative strategies are optimal.

Building on our recent NHLBI-funded publication in *JAMA*[7] that described the modest effectiveness of varenicline pharmacotherapy, the proposed research will use a factorial design to evaluate two different medication use strategies on their ability to markedly enhance varenicline effectiveness in a large cohort of current smokers. Smokers (N=1250) will be randomly assigned to one of two levels for each of two factors: 1) an Adjuvant factor (varenicline + placebo patch versus varenicline + nicotine patch), and 2) a Duration factor (12 versus 24 weeks of active medication). Thus, this factorial design yields a "standard" varenicline treatment (12 weeks of active varenicline and 12 weeks of placebo varenicline + 24 weeks of placebo patch), and 3 *enhanced* treatments: 1) 12 weeks of active varenicline and 12 weeks of placebo varenicline + 24 weeks of active patch, 2) 24-weeks of active varenicline + 24 weeks of placebo patch, and 3) 24 weeks of active varenicline + 24 weeks of active patch. Both treatment modifications, longer duration therapy and use of a nicotine replacement therapy (NRT) adjuvant, have produced some quite promising effects. However, in both cases these modifications have been little researched, their effects are not *consistently* positive, and they have not been implemented in a potentially optimal manner. We will implement each modification in an innovative manner designed to enhance its effectiveness. In addition, all participants will be given counseling that supports adherent medication use and that is readily translatable to healthcare settings. The scientific rigor of this work will be enhanced by the use of placebo medication, a large sample, and a factorial design. The latter will allow us to test both the main and interaction effects of the experimental factors. We will also be able to compare each enhanced treatment with standard 12-week varenicline-only therapy to determine whether any of these medication use strategies significantly enhances treatment effectiveness. Outcomes will include long-term smoking abstinence (52 weeks), cost-effectiveness, adverse events, and withdrawal severity. This design will allow us to evaluate two major pharmacotherapy strategies (an NRT adjuvant, extended duration) that yield four distinct varenicline-based treatments. Specific aims of this research are:

Specific Aim 1: To determine whether varenicline pharmacotherapy is enhanced by either a nicotine replacement adjuvant (i.e., patch NRT) or extended medication duration (i.e., 24 vs. 12 weeks postquit). The effects of these pharmacotherapy strategies will be reflected in main effects for both experimental factors, and in direct comparisons of the enhanced varenicline conditions with standard 12-week varenicline-only. The primary outcome will be 52-week biochemically confirmed smoking abstinence (7-day point-prevalence).

Specific Aim 2: To determine the effects of the varenicline conditions on additional critical outcomes such as 23-week point prevalence and prolonged abstinence, smoking cessation milestones (abstinence, latency to lapse, and lapse-relapse latency), cost-effectiveness, withdrawal severity, and adverse events. The variables that mediate and moderate (e.g., genotype) the effects of the different pharmacotherapies will also be identified.

This research will determine whether two highly promising modifications to varenicline treatment, use of a nicotine patch adjuvant and extended 24-week duration, produce superior smoking outcomes when they are used either individually or together. Despite their promise, the tested modifications have never been experimentally evaluated relative to standard varenicline pharmacotherapy. Thus, this innovative research will produce novel evidence regarding how best to help smokers quit, and thereby address the leading cause of preventable mortality and morbidity related to cardiovascular and pulmonary diseases.

Recruitment & Study Entry

We will recruit participants via multi-media methods (i.e., TV, radio, newspapers and newsletters and other print media, flyers, referral cards, minority outreach, emails to UW employees, social media such as Facebook, and earned media), which we have previously used very successfully[30,47,82]. Within 1 week, respondents will be called, screened, and potentially eligible smokers will be scheduled to attend a group orientation session. At the Orientation session, interested individuals will be introduced to the study, have a chance to ask questions and provide written informed consent. Participants will complete a final inclusion/exclusion assessment and complete the baseline assessments. Randomization to a treatment condition will also occur at the Orientation (see Table 2), with stratification on sex, site, dependence, and race.

Inclusion/Exclusion

Participants must: plan to stay in the area for the next 12 months, ability to read and write in English, smoke on average ≥5 cigarettes per day over the last 6 months, be ≥18 years old, desire to quit smoking but not be engaged currently in cessation treatment, report no use of pipe tobacco, cigars, snuff, e-cigarettes or chew in the last 30 days, have reliable phone access, willing and able to use both nicotine patch and varenicline, access to transportation to come to our clinic and, if female, not be pregnant and be using an acceptable birth control method/ method to prevent pregnancy. Smoking will be biochemically confirmed via a carbon monoxide breath test at the first visit. Preparticipants must blow a CO of ≥5ppm to continue. Exclusion criteria include: current treatment for schizophrenia or a psychotic disorder; suicidal ideation in the past 12 months; history of suicidal attempts within the last 10 years; on dialysis or being told you have severe kidney disease; hospitalization for a stroke, heart attack, congestive heart failure, uncontrolled diabetes mellitus within the past year; history of seizure within the last year, currently taking Wellbutrin, Zyban, or Buproprion (Contrave is a weight-loss drug that has Wellbutrin in it) for reasons other than to quit smoking or taking to help quit smoking and not willing to stop for duration of the study; currently using any form of nicotine replacement (e.g., nicotine patch, nicotine gum, nicotine lozenge) or using Chantix or varenicline and not willing to stop for duration of the study; had a reaction to the nicotine patch that prevented them from continuing to use it; or currently participating in another smoking cessation study.

Even though we screen out participants who are pregnant, plan to become pregnant, nursing, or are unwilling to take steps to avoid pregnancy, there is a chance that a participant eligible at consent could become pregnant later. She would then be considered part of a vulnerable group. Given the longitudinal nature of the research, a participant who becomes pregnant after enrolling will be given the choice of whether to 1) continue in the study (for counseling and other assessments) and agree to immediately stop taking study meds for the remaining duration of the study and return any unused medications, OR 2) withdraw. No further

medications will be given to this study participant while in the study.

Incarcerated individuals will not be enrolled in this study. However, given the longitudinal nature of the research, participants could be incarcerated for periods during their participation. If study staff learn that a participant is incarcerated at a time point before or at their Week 8 phone call, the participant will be withdrawn from the study. If study staff learn that a participant is incarcerated subsequent to Week 8, the participant will not be withdrawn unless that incarceration will take them beyond the study period. In that case, staff will not contact the participant while incarcerated and will not provide any treatment (counseling or medication) nor conduct any assessments during the period of incarceration. Services and assessments will be re-initiated if the participant is released at a later study time point.

Study Design

All participants (N=1250) will receive at least 12 weeks of V plus counseling that emphasizes adherent medication use. Participants will also be randomized to one level of each of the two factors: 1) an Adjuvant factor: active P vs. placebo P; and 2) a Duration factor: 24 vs. 12 weeks of active medication.

Assessments

Baseline: These will constitute covariates for analyses (e.g., smoking dependence, heaviness, history), characterize the cohort, and capture baseline levels of potential mediators of treatment effects. They also will permit assessment of constructs that will be used to develop an optimal, patient-centered treatment algorithm. The surveys (gathered at Visit 1: Table 2; associated references provide psychometric data) will include: (1) The Smoking History Questionnaire[30], which provides accurate information about lifetime smoking cessation treatment history, family smoking, environmental exposure, and psychiatric history; (2) The Brief Wisconsin Smoking Dependence Motives questionnaire (Brief WISDM)[83]; (3) The Fagerstrom Test for Cigarette Dependence (FTCD)[84]; (4) Alcohol use and problems assessed with a quantity-frequency measure for the past week[86-88]; (5) The Wisconsin Predicting Patients' Relapse questionnaire (WI-PREPARE) which may inform algorithm development[90]; (6) The 5-trial Adjusting Delay Task to assess ability to delay reward; (7) interview about changes to make to quit successfully; and (8) the Depression, Anxiety and Stress Scales (DASS-21) to assess current symptoms of depression, anxiety and stress. In addition, a psychiatric history will be gathered that assesses prior diagnoses and treatment for psychiatric disorders including substance use (as per[78]). Blood will be drawn (about 2 tablespoons) for DNA extraction and genotyping as in prior UW-CTRI RCTs and for serum cotinine analysis. Breath carbon monoxide will be assessed.

DNA assessments. Samples for DNA analysis will only be taken from those providing consent for this. As outlined in the Biological Samples protocol supplement, blood will be drawn for samples of DNA for genetics, DNA for methylation (Madison site only), and RNA(Madison site only). DNA for genetics will be extracted by the UW Biotechnology Center. All three samples will be relabeled at the UW Biotechnology Center with DNA IDs/ barcodes, which allows connecting additional data secured from participants at later visits but does not contain HIPAA identifiers that can be connected back to the study. Samples will be stored at both the UW Biotech Center (DNA for genetics @-80^{o}C) and CTRI Madison (DNA for methylation and RNA @-20^{o}C) until shipped in batches to Washington University. Banking will occur at Washington University in St.

Louis within a genetics research facility. In this facility samples will remain labeled with only DNA IDs. All study information is stored in secure computer databases at that location.

In addition, we plan that DNA data and associated phenotype information from study participants will be sent to an NIH GWAS center, where stringent controls are in place for security of genomic information and any study information related to the samples. GWAS will utilize these samples, combined with others submitted to the repository, for additional research questions

Note: Participants can withdraw their DNA consent by request to the study PI

IVR Assessments: To enhance scientific rigor, participants will provide nightly data (via phone keypad responses to voice prompts or complete an on-line survey) for a total of 31 days (3 days prior to starting treatment, 14 days during pre-cessation treatment, 14 days post-target quit day; see Table 2). Each report will take about 3-4 minutes to complete. Reports will assess mood, anhedonia, withdrawal[85], cessation fatigue (post-quit), cue exposure and reactivity, and tobacco and medication use with brief items used in our prior successful research[19,49,50,82,101]. Medication effects and reasons for not using medications will also be assessed. All reports will end with a reminder of the number participants can call to discuss any concerns they have about study medications. Nightly IVR data collection reduces error that might arise from memory decay and recall biases[97]. This time frame should capture key pharmacotherapy effects, the peak of withdrawal[98,99], and most lapse occurrences[100]. These assessments will capture potential treatment mechanisms/mediators, treatment effects, and variables related to safety/side effects. Our procedures entail minimal burden (~3-4 min/day) and yield high (~80%) completion rates[31]. Those who report having difficulty maintaining a stable phone/email service will be provided phones to take IVR phone calls.

Phone Follow-Up Assessments: These person-to-person phone assessments will occur at 4, 8, 11, 17, 23, 39, and 52 weeks post-TQD (Table 2). Data will be gathered on daily smoking, new quit attempts, use of other cessation medication, potential mediators (e.g., withdrawal, affect, cigarette liking/effects, stressors, cue exposure, motivation), use of any nicotine product, medication use, and adverse events. Participants claiming abstinence at the 6- and 12-month calls will be invited to a visit for biochemical testing and short questionnaire on CO exposure to confirm abstinence self-report via exhaled CO. If participants claim abstinence from cigarettes but blow a 6 or greater on the CO breath test at the Week 52 Follow-Up Visit, we will ask the participant if they will give us a saliva sample to test for cotinine. This will allow us to be more certain that these participants have not been smoking cigarettes (as evidenced by cotinine-free saliva or saliva with low levels of cotinine). At the 12-month call all participants will be asked to estimate the likelihood that their pill and their lozenge contained active medication.

Smoking Outcome Measures: As per Society for Research on Nicotine and Tobacco recommendations[102], we will analyze abstinence at 52 weeks (primary) and 23 weeks using two abstinence measures to enhance scientific rigor: (1) 7-day point-prevalence (CO-confirmed self-report of abstinence from smoking for 7 days before and including the follow-up day: CO cutoff ≤ 5ppm)[103] and (2) prolonged (a continuous abstinence measure that ignores smoking in the first

Table 2. Schedule of Study Activities

	Pre-Cessation	Treatment Phase						Phone Follow-up				
	Orientation	V1	C1	V2	V3	C2	C3	C4	C5	C6[1]	C7	C8[1]
Week	Orientation	Wk -2	-1	TQD	2	4	8	11	17	23	39	52
Screening & Informed consent	X											
Randomization	X											
Pre-cessation counseling		X	X									
Cessation counseling				X	X	X	X					
Exhaled CO	X	X		X	X					X[1]		X[1]
Short questionnaire on CO exposure	X	X		X	X					X[1]		X[1]
Smoking status	X	X	X	X	X	X	X	X	X	X	X	X
Blood sample for DNA/RNA and cotinine		X										
Non-cigarette nicotine use	X	X		X		X	X			X		X
Baseline questionnaires	X	X										
IVR assessments	X	X	X	X	X							
Treatment mechanisms assessment[2]		X	X	X	X	X	X	X	X	X	X	X
Medication provision		X		X			X					
Medication use assessment			X	X	X	X	X	X	X	X[3]		
Adverse events			X	X	X	X	X	X	X	X	X	

[1]If participants claim abstinence during this assessment call, they will be invited to an in-person visit to provide biochemical verification of abstinence (CO assessment).
[2]Treatment mechanisms include withdrawal, affect, fatigue, cigarette liking/effects, stressors, cue exposure, motivation, and self-efficacy.
[3]Timeline follow back only

week post-quit). Per our intention-to-treat data analysis plan, any randomized smoker who does not provide biochemically confirmed evidence of abstinence will be counted as a smoker; multiple imputation also will be performed in secondary analyses to further enhance scientific rigor. A daily smoking calendar will permit determination of lapse/relapse latencies for survival and milestones analyses[104,105]. In order to enhance *scientific transparency*, we will post all assessment instruments and, ultimately, de-identified data, online (e.g., the UW-CTRI website; average of 7,000 hits/month over last year from 17,387 visitors), so that other researchers can use our de-identified data and instruments (see detail in Data Sharing Plan).

Interventions

Pharmacotherapy: Pharmacotherapies will be V-only (with placebo Patch) and V+P. As in the successful Koegelenberg trial[14], we will start NRT therapy (for both placebo and active P) 2 weeks prior to the target quit date (TQD). The V lead-in will start 1 week prior to the TQD. Table 3 displays the dosing information for the relevant experimental conditions. To enhance scientific rigor, placebo medication will be used to double-blind medication assignment. Thus, V-only condition participants will be given placebo patch. Also, 12 week duration condition participants will receive placebo medication week 13 through 23 (pill) /24 (patch) to match the 24 week duration condition participants' active medication regimen. Therefore, each participant will be given both medications for 6 months so that the number of medications provided and medication duration will not signal assignment; use instructions will be the same for placebo products as for the respective active medication (see Table 3 note).

Table 3. Medication Dosing Regimens for the Factorial Experiment

	Pre-Cessation Meds	Cessation Meds: 12 Weeks Duration	Cessation Meds: 24 Weeks Duration
Varenicline Pills	Days -7 to -5: 0.5 mg pill QD Days -4 to -1: 0.5 mg pill BID	Days 1 to Week 11: 1 mg pill BID Weeks 12-23: placebo pill BID	Weeks 1 to 23: 1 mg pill BID
Active Patch	Days -14 to TQD: 14 mg patch 14 mg patch	Weeks 1 to 12: 14 mg patch Week 13-24: placebo patch	Weeks 1 to 24: 14 mg patch

Note: The timing and dose adjustments for active nicotine patch shown above will be matched with the placebo patch given to the V-only condition. Also, medications may be discontinued or doses may be reduced in the case of adverse events.

Participants will receive medications and use instructions at Visit 1 and 2 and following the Week 8 call (via the mail: Table 2). Participants will be given an information sheet with medication instructions and a number to call with questions or to report concerning side effects or toxicity. Adverse events will be assessed at each person-to-person study contact during the treatment phase. Medication use will be assessed during each study contact during the treatment phase.

Counseling: Participants will receive counseling based on our recent factorial research[42,56] and on Guideline recommendations[2]. *Pre-cessation* counseling will occur at Visit 1 and Call 1 (3- and 1-week pre-TQD: Table 2). Counseling in these sessions will include instructions for using the medications with a special focus on smoking reduction, clear smoking reduction goals, and behavioral training to facilitate smoking reduction[56]. Recent research suggests the value of combining precessation medication and reduction counseling[78]. *Cessation* counseling will occur during Visits 3 & 4 and Calls 2 & 3 (Table 2) and will provide support, inculcate coping skills, promote motivation for quitting, and provide clear instructions regarding proper medication use[2,56]. The medication adherence training will include elements that yielded promising effects in our prior research (e.g., data-based feedback on medication use, problem solving regarding adherence challenges, and motivational intervention to support medication

use[42]). All counseling sessions will last about 15 min. Most counseling will occur close to the target quit day since some research suggests that such early counseling may be especially effective[106], and because most relapse occurs early in a quit attempt[100]. We have a long history of successfully conducting such interventions and have existing counseling manuals that will require only modest adaptations for this work[42,56]. Counselors will be bachelor-level health educators supervised by licensed psychologists. To support the scientific rigor of the work, quality/fidelity assurance strategies developed in our prior work[30,33] will include intensive training in counseling techniques and ethical conduct (20 hours over 2 weeks), practice sessions, regular supervision using audio recordings of session, and quarterly team meetings to discuss safety, confidentiality, and counseling fidelity. Participants will be paired with a single counselor for all treatment contacts. The timeline for the conduct of the experiment is depicted in Figure 1.

Promoting Continued Experimental Participation

We will utilize participant retention strategies that were effective in our prior research, including strategies such as scheduling flexibility, calling participants' cell phones if they request that, continued interaction with the same health counselor, and providing medication contingent upon visit attendance/call completion. If participants appear to have dropped out of the study (they miss appointments and do not reschedule, or they do not answer our phone calls, but they have not formally withdrawn from the study), we may write them (via standard mail or email) to encourage their renewed participation. Finally, consented participants who we are not able to reach using contact information obtained at the baseline and subsequent visits, we will call and/or send a letter to the alternate contacts provided by the participant, designated as a contact for this specific situation.

Compensation: Participants will be paid for: attending the Orientation Visit) and Visit 1 ($20/visit), completing the follow-up calls for Weeks 4, 8, 11, 17, and 39 ($10/call) and Weeks 23 & 52 ($20 at Wk23, $60 at Wk52), and for attending the two in-person follow-up visits for biochemical confirmation of abstinence, if needed ($40 at Wk23; $200 at Wk 52). If participants are unable to be reached for their follow-up calls at Weeks 23 and 52, they will be mailed a questionnaire that assesses their current smoking status and asked to complete and return it. Those who return the Week 23 mailed questionnaire will receive $20 and those who return the Week 52 mailed questionnaire will receive $40. All participants will receive $50 if they complete at least 80% (26) of the nightly IVR assessments (this means answering at least 1 question) or $25 if they answer between 60 and 79% of assessments (20-25 assessments). This would result in a total potential compensation of $460. Checks will be issued after Visit 1 (up to $40), after Week 4 (up to $60), after Week 23 (up to $50), after Week 52 (up to $70) and at the Week 23 and Week 52 visits, if they are invited ($40 at Wk23; $200 at Wk52).

Update: Due to COVID-19 pandemic, participants will not be brought in for Week 52 in-person visits for biochemical confirmation of abstinence. Regardless, participants eligible for that visit will receive the full $200 payment, as described above.

Analytic Approach

Cessation: The primary outcome (biochemically confirmed, self-reported point-prevalence abstinence at 52 weeks post-TQD) will be analyzed via two strategies. First, we will conduct factorial design analyses using logistic regression with dummy coding that examines

the main and interactive effects of the two factors. Importantly, main effects obtained with dummy coding in 2-factor designs are directly interpretable even in the presence of a significant interaction as long as the interaction effect is included in the model. Thus, main effects will reflect the effects of V+P vs. V-alone, and the effects of 24- vs. 12-week treatment duration. Interaction effects would reveal whether the magnitude of differences in effects of the levels of V treatment varies in a multiplicative manner depending on duration. While we hypothesize that we will see only main effects in this research, interactions would be interpreted via visual inspection (the highest and lowest scores for the interacting treatment combinations should be readily apparent) and via simple effects tests[107-109]. Second, we will conduct analyses typical of an RCT, which use logistic regression models with dummy coding to contrast each of the three enhanced varenicline treatments (12-week V+P, 24-week V-only and 24-week V+P) with the standard V-based treatment (12-week V-only). The V-only condition will serve as the reference condition because the intent is to determine if any of the enhanced V-based treatments is superior to that condition. Covariates will include sex, race, treatment site, and level of tobacco dependence (FTND item 1). Results will be reported with and without covariate adjustment and the specific effects of sex and race on each outcome will be explored. The same analytic approach will be used for secondary abstinence analyses (e.g., point-prevalence at 6-months and prolonged abstinence[47]). The intent-to-treat principle with the assumption of missing=smoking will be used for abstinence analyses but will be supplemented with sensitivity analyses and multiple imputation for missing data to support scientific rigor [47,110]. The latter models will assume that 80% of dropouts return to smoking and that abstinence likelihood is related to baseline smoker covariates[42,47,56]. Analyses of secondary abstinence outcomes will support scientific rigor by controlling for experiment-wise error in families of related tests[111,112]. Milestones analyses will be conducted as in our prior research[104,105]. For instance, latency between initial abstinence and lapsing, and latency between lapsing and relapse, will be computed with Cox proportional hazards regression/survival models.

Mediation and Moderation: Candidate mediators of cessation treatment effects, gathered from IVR and follow-up phone assessments will be: medication use and side effects, withdrawal symptoms (e.g., craving, negative affect, anhedonia[19]), anticipatory pleasure from smoking, adverse events, nicotine reward, nicotine anticipation, and reports of cue-elicited urges. Treatment will be modeled both as main effects and as contrasts of particular Adjuvant X Duration combinations that differ significantly in abstinence rate from the standard V treatment condition at follow-up. Mediation will be tested using multiple indices including the joint significance test[49,50]. Care will be taken to preserve mediator/outcome temporal priority and the occurrence of smoking during the quit attempt will be statistically controlled[49,50]. Mediation models including multiple mediators[49] will use methods developed for use with dynamic mediator assessments (maximum likelihood estimation using hierarchical linear modeling: HLM 5.04101). Both 23- and 52-week abstinence will be used as outcomes, which will be modeled via a weighted least squares approach in Mplus. The 23-week outcome may be more sensitive to treatment mediation than the 52-week outcome[75]. We will attempt to characterize orthogonal routes to outcome change via use of multiple covariates and models of multiple mediation. In these models, the individual mediators revealed as strongest in univariable analyses will be included in multi-mediator models as per our prior research[49].

Analysis of moderators of abstinence outcomes will use both logistic regression with model-fitting techniques[113] and regression tree analyses that reflect differential treatment responses[71,114] in 23- and 52-week abstinence. The logistic regression and regression tree approaches are complementary since the former fits interactions in the entire sample whereas

the latter identifies the most robust interactions amongst subpopulations of a sample (groups of participants nested within levels of another predictor, which could include either a covariate or treatment condition[71,114]. Candidate moderators of treatment effects on abstinence will include tobacco dependence, contextual factors such as household smoking, and biological variables such as sex and genotype. In the logistic regression analyses moderators will be evaluated with regards to their interactions with treatment main effects and interactions.

Cost-Effectiveness: Cost-effectiveness of key comparison treatments will be evaluated using methods recommended by the United States Panel on Cost-Effectiveness in Health and Medicine and consistent with our prior research in this area[72-74]. We will: (1) measure all costs from the societal perspective; (2) convert cost estimates to a common year; (3) use a rate of 3% to discount future outcomes and costs to present value; (4) use QALYs as the outcome metric; and (5) conduct Monte Carlo sensitivity analyses[115]. The proposed research will cost out all intervention component combinations that reflect significant main and synergistic interaction effects. We will determine net monetary benefit (NMB), cost per quit, and incremental cost-effectiveness ratios (ICERs)[116]. The components of NMB will be the added costs of the treatments and the monetized value of the QALYs added by the treatments. Using methods described by Stapleton, we will convert the increased effectiveness of the treatments from quits to added QALYs[117].

Statistical Power for Primary Outcome: Power was determined for effects that we prognosticated based upon prior data[2,3,14,23,24]. Table 4 depicts predicted 52-week abstinence outcomes. We propose an abstinence rate for 12-week V treatment of 25%. This is comparable to that found in Koegelenberg for 12-week V-only treatment (28.8% at 24 weeks follow-up; abstinence rates tend to fall about 5 percentage points from 24 to 52 weeks post-TQD[118,119]). This abstinence rate is higher than that produced by V-only in our recent clinical trial (19% abstinent at 52 weeks), but somewhat lower than the rates reported in the initial studies on V (52-week rates of about 30%[118,119]; thus, we set the expected abstinence rate for 12 weeks of V at a mid-point (25%). Table 4 shows that we predict an increase in 52-week abstinence from 12 weeks of V alone (25%) to 34% for 12 weeks of V+P. We believe this increase of 9 percentage points is reasonable and somewhat conservative. It is midway between increases seen by Koegelenberg[14] (15%) and Ramon et al.,[22] (5%, in 24-week *continuous* abstinence). Also, a 9 percentage point increase is somewhat less than the boost in abstinence seen with combination NRT vs. NRT monotherapy (36.5% vs. 23.4% at 5+ months as per the PHS Clinical Practice Guideline meta-analyses[2]). In sum, we believe the estimated effect of the P adjuvant at 12-weeks duration seems reasonable and somewhat conservative.

Table 4. Predicted Biochemically Confirmed Abstinence Rates at 52-Weeks After the Target Quit Date

	V-only	V+ML	Marginals
12 Weeks of Medication	25.0% (78/312)	34.0% (106/312)	29.5% (184/624)
24 Weeks of Medication	32.0% (100/312)	44.9% (140/312)	38.5% (240/624)
Marginals	28.5% (178/624)	39.4% (246/624)	

Note: Koegelenberg et al.,[14] found abstinence rates of 65.1% (with multiple imputation) and 44% (with intent-to-treat) at 6-month follow-up with 12-weeks of V+P treatment. Thus, our predicted rates for V+ML may be conservative. Also, note that the new enrollment goal of 1250 does not divide evenly by 4=312.5, so we rounded down to 312 for the purposes of this chart.

In terms of the effects of increased duration of medication use, Schnoll et al.,[44] found that 24 versus 8 weeks of nicotine patch increased abstinence rates by only about 5 percentage points at 52-week follow-up. However, extended V treatment (24 weeks total) increased abstinence rates at 52 weeks post-TQD by about 10 percentage points in one study just among patients who were abstinent early in treatment[38], and by about 40 percentage points in another, smaller study[39]. We believe that extended medication will increase abstinence rates by 7-11 percentage points (with regard to the V-only and V+P conditions, respectively) because research shows that extended pharmacotherapy both reduces relapse in those who are abstinent[39,119] and increases the likelihood of cessation amongst those who have lapsed[35,40,45]. Moreover, both NRT and V produce such effects, thus, these actions could be additive in those using both active agents. Because of the possibility of an additive effect, we posit slightly higher increases in Duration-related abstinence rates for the V+P condition than for the V-only condition. However, the uncertainty about the effect of Duration highlights the innovativeness of this work; we know very little about the effects of extended V treatment and nothing about the effects of extended V+NRT treatment. While the abstinence rates forecast may seem high, we believe they are reasonable given that they reflect the effects of 3 pharmacotherapy elements or dimensions (vareniciline therapy, 24 week duration, and an NRT adjuvant) all supported by evidence of efficacy. The predicted outcomes result from the reasonable assumption that these 3 components will produce at least additive effects.

The predicted data would strongly implicate the additive effects of both 24-week duration and the P adjuvant as being necessary to achieve a marked increase in abstinence over standard V-based therapy. Of course, we might discover instead that a single treatment modification or enhancement confers as much benefit as the combination of the two components (e.g., 24-week V-only produces as much benefit as 24-week V+P). This finding would be welcome to the extent that it means that exceptionally strong results are obtained with the use of only one treatment enhancement, which would save money and perhaps reduce adverse events and burden.

Statistical Power: We computed power (via SAS PROC POWER) for the abstinence outcomes in Table 4, assuming $p < .05$ and two-tailed tests. Power is .88 for the main effect for Duration (n's=625), and .97 for the main effect of Varenicline (V+P vs. V: n's=625). Moreover, power is > .99 for the key hypothesis that the 24-week V+P combination will be superior to 12-weeks of V-only (n's=312). The N used clearly provides some room for error if the predicted outcomes are too sanguine. For instance, we noted above that some data suggest that the increase in abstinence seen with extended medication might be as small as 7%. The proposed N (1250) would permit detection of a 7 point difference with power = .80. Thus, the N proposed would provide good power to detect the proposed effects, and even effects that are modestly weaker, but still of public health significance.

Protection of Human Subjects

Risks to the Participants

Human Subjects Involvement and Characteristics: Up to 1100 adult smokers will be consented from the community in order to enroll (randomize) at least 1250 participants (up to 1300). Participants must: plan to stay in the area for the next 12 months, ability to read and write in English, smoke ≥10 cigarettes per day, be ≥18 years old, desire to quit smoking but not be

engaged currently in cessation treatment, report no use of pipe tobacco, cigars, snuff, e-cigarettes or chew in the last 30 days, have reliable phone access, and, if female, not be pregnant and be using an acceptable birth control method. Exclusion criteria include: current treatment for schizophrenia or a psychotic disorder; suicidal ideation in the past 12 months; history of suicidal behavior within the last 10 years; on dialysis or being told you have severe kidney disease; hospitalization for a stroke, heart attack, congestive heart failure or uncontrolled diabetes mellitus within the past year; or currently participating in a smoking cessation study.

Sources of Materials: Participants will provide data for the express purpose of research. Data will consist of answers to questionnaires and interviews assessing smoking history, demographics, nicotine dependence, personality, affect and psychiatric history, disease status and health history. In addition, certain physiologic and medical tests will be done that assess disease status or biomarkers thought to index disease risk. These will include provision of blood samples that will later be used for nicotine/cotinine tests and genetic assays. Breath tests and a brief questionnaire will be used to assess exhaled carbon monoxide.

Potential Risks: Risks associated with this research are judged to be minimal. None of the medical, physiologic, self-report, or behavioral assessments constitute a significant risk. The use of cessation medications poses a risk of side-effects. Varenicline is approved by the FDA for smoking cessation and is medically safe for most smokers to take except for individuals with severe (end-stage) kidney failure or hypersensitivity to varenicline. Current labeling for varenicline (FDA, 2009[1]) recommends monitoring for serious neuropsychiatric symptoms including changes in behavior, agitation, depressed mood, suicidal ideation, and suicidal behavior although no causal relationship has been established. Varenicline labeling also notes that some individuals with pre-existing psychiatric conditions may experience worsening of their conditions. Labeling of Varenicline also indicates increased risk of certain heart problems in people with heart and blood vessel disease. Finally, labeling of Varenicline also indicates risk of new or worsening seizures. These seizure findings are from infrequent post-marketing observations that are similar to the frequency of epilepsy found in the general population and are not formal contraindications. We ask that participants notify study staff immediately and stop taking the study medication and notify study staff immediately if you experience any significant emotional or heart-related symptoms, or a seizure. In such cases, it is expected that the study medication will be stopped and the participant will remain on study but off study medication. NRT risks are well-documented, given their wide-scale use and over-the-counter availability; the nicotine patches are available over the counter. According to the package insert, the most likely side effects associated with the nicotine lozenge are heartburn, hiccup, nausea, upper respiratory tract infections, coughing and sore throat. It is important to note that all studies evaluating the combination of varenicline and nicotine patch have found it safe[2-5]; therefore, there are no data suggesting any additional risk of combining varenicline and NRT. Blood draws can be painful and very rarely can lead to infection. There is always a remote, but existing, possibility that sensitive or personal information about a participant could be divulged as a function of his/her research participation. Finally, smoking withdrawal is associated with a number of unpleasant symptoms, such as sleep disturbance, hunger, craving, and negative mood. Most smokers have tried to quit before and are familiar with these phenomena. Though unpleasant, smoking withdrawal symptoms pose minimal health risk. Participants will be informed about the likely effects of smoking withdrawal. Individuals who elect not to participate in this research, or are eliminated due to screening failure, will be given a list of alternative smoking cessation programs at any point during the pre-consent process.

Adequacy of Protection Against Risks

Recruitment and Informed Consent: As in our previous research, participants will be recruited via TV, print, flyers, referral cards, social media such as Facebook, and earned media (e.g., press releases and conferences).

Participants will be recruited in the Milwaukee and Madison metro areas. Advertisements and publicity will contain a phone number for interested individuals to call to contact study personnel. Study staff will call potential participants and conduct an initial phone screening to rule out those with clear contraindications. The study will be briefly described, questions answered, and potentially qualifying individuals will be invited to attend an Orientation Session. At the Orientation Session the general requirements for participation will be reviewed (e.g., session attendance, need for follow-up, participation in assessments). In addition, participants will be informed of the nature of the interventions involved. They will be told about the pharmacotherapy and counseling interventions that will be studied. Everyone will be told that that they will receive counseling designed to aid them in their cessation attempt. The risks of taking varenicline will be described including the possibility of changes in behavior, agitation, depressed mood, suicidal ideation, and suicidal behavior. Participants will also be told that varenicline may worsen pre-existing psychiatric illness. All participants will be informed as to the various parts of the study and what will be entailed in each part. Individuals will then be screened for any remaining exclusion factors. After answering any participant questions about research participation and intervention, screened and eligible participants will be given a combined HIPAA/consent form to review and take home. At their first treatment visit (V1) potential participants will be allowed to ask questions about the consent form. Interested participants will then sign the consent form at the beginning of that visit before they participate in any further assessments or research activities. Should eligible smokers decide not to participate in the research at V1, the personally identifying information collected at the Orientation session and the screening phone call will be destroyed at the point that data for a study consort diagram have been cleaned and analyzed. Participants will be encouraged to ask any further questions about the study protocol throughout the study.

Protection Against Risk: As noted above, participants will be screened to ensure that they are medically and psychiatrically fit to use varenicline or nicotine patches. Study participants will be closely monitored in accordance with current FDA recommendations (last update March 2015[1]) as well as the consensus recommendations of the 2008 Guideline Panel[6], which provides additional, detailed instructions for clinicians regarding all FDA-approved cessation medications. In addition, we will make appropriate changes in study procedures if the FDA issues updates on varenicline or nicotine patches. We will recommend dosage/use alterations including stopping medication treatment as per good clinical practice if the participant experiences troublesome side effects once they begin medication treatment. Thus, we will take extraordinary care to ensure the safety of study participants.

Study participants will be carefully monitored for side effects including changes in mood, agitation, or distress and suicidal ideation, . Monitoring for these and other symptoms or conditions will be accomplished though assessment of adverse events (AEs) and serious adverse events (SAEs) at each study visit and follow-up contact during which the participants are receiving study medication. For all AEs and SAEs, study staff will take appropriate action to ensure the safety of the participant as follows: 1) Nonurgent AEs will be reported in a timely

manner to study clinical staff (MDs); and 2) SAEs or AEs that raise concerns (e.g., allergic reaction; severe, unresolved changes in mood or any suicidal ideation) will be immediately reported to the study physician who will determine an appropriate course of action. In addition, participants will be given a telephone number to contact study staff in the event that participants have questions or concerns about study medication or medical/psychiatric reactions that may be related to study medication or participation, as well as instructions on when to seek emergency medical assistance. Individuals who report any significant mood change or suicidal ideation will be contacted immediately by a licensed staff psychologist or physician who will assess the level of risk and provide referrals as needed.

Confidentiality of participant data and information will be accomplished by using participant numbers as unique identifiers, allowing us to keep participant data separate from identifying information. Data generated through study participant and data obtained on medical history from participants will be stored in secure databases under protections and procedures consistent with the guidelines and regulations of the UW School of Medicine and Public Health (UW-SMPH). Outside access is available only via an encrypted connection to the Department of Medicine Citrix server located at the UW Clinical Science Center in Madison. The servers at the University of Wisconsin Center for Tobacco Research and Intervention (UW-CTRI) Madison office are physically secured in a locked room. Data backups are created nightly and stored in a locked safe. Significant safeguards have been implemented to protect data including virus and adware protection, firewall, access controls and encryption when appropriate such as wireless and remote access. All UW-CTRI staff members have completed HIPAA/human subjects training and are aware of the sensitivity of study-related data. The UW SMPH has developed school-wide data security policies and procedures. UW-CTRI data security policies and procedures conform to those of the SMPH. UW-CTRI will use an enterprise-level database that supports audit trails such as access, change logging, and more sophisticated access control for managing and tracking user access privileges. In addition, this project will request a Certificate of Confidentiality, related to the collection of genetic material, information on substance abuse, and information on sexual orientation. No publications or presentations resulting from this research program will contain any identifying information about individual participants.

Potential Benefits of the Proposed Research to the Participants and Others

The potential benefits for smokers participating in this study include the chance to receive free smoking cessation counseling and FDA-approved pharmacotherapy, both of which double a smoker's odds of quitting. The risks of this research are chiefly associated with the provision of varenicline as one of the pharmacotherapies. These risks are reasonable because this medication has been shown to be safe in numerous large clinical trials, and we are exercising additional caution by using varenicline in accordance with FDA recommendations as well as the consensus recommendations of the 2008 Guideline Panel[6]. Because the health risks associated with continued smoking dramatically outweigh those associated with varenicline use (and NRT as well), and because it is likely that many participants will successfully quit smoking as a result of their participation in this research, the potential risks to participants are acceptable compared to the potential benefits. The availability of consultation with the research program, including physician consultation, also decreases the likelihood of adverse consequences from varenicline or patch use. In addition, this research has the potential to provide improved treatment strategies for clinicians trying to help patients quit smoking. This could result in more efficient provision of maximally efficacious intervention for smokers.

Importance of the Knowledge to be Gained

The results from this study will allow researchers to determine which medication regimen is more effective for smoking cessation and which works better for which type of smoker. Also, this research will produce valuable new information on the mechanisms via which these medication regimen's aid smokers in quitting. This information will be gathered in a contemporary population of smokers so the results will be highly relevant to today's smokers and clinicians, and can be used to motivate clinicians to intervene and to motivate smokers to use evidence-based treatments to stop smoking.

Summary

Given the limited risks of varenicline and nicotine patch, the rigorous pre-treatment screening, and the availability of both physicians and psychologists to address any adverse effects, we believe that the potential risks involved in participating in the study are outweighed by the benefits to both the individual study participant and society.

Data Safety Monitoring Plan

The Data Safety and Monitoring Plan (DSMP) for this research comprises not only the research conducted directly by the University of Wisconsin Center for Tobacco Research and Intervention (UW-CTRI) researchers, but also research conducted by other investigators collaborating with UW-CTRI-funded projects. All investigators must agree to comply with the procedures outlined in this DSMP. This DSMP does not reduce any investigator's obligation to comply with the requirements of the Institutional Review Board (IRB) at his/her home institution or the IRB of any collaborating organizations.

Monitoring the progress of trials and the safety of participants. The Principal Investigators are responsible for routine monitoring of the trial's progress. This includes scheduled (biweekly during the first few months of the study and monthly thereafter) meetings with study staff and review of written documentation. Data reviewed at these meetings include the number and type of participants enrolled, the number and reasons for exclusions from enrollment, the number treated and the stage of intervention, summary of adverse events (AEs), individual review of serious adverse events (SAEs) and study participation, and outcome data. In addition, as noted above, SAEs or AEs that raise concerns (e.g., allergic reaction, significant change in mood or suicidality) will be immediately reported to the study physician who will determine an appropriate course of action. As data become available, Research Administrator and Principal Investigators will review the data on a regularly scheduled basis (initially biweekly and later monthly) to determine progress.

To facilitate participant safety, study participants must meet study inclusion and exclusion criteria. Once enrolled, study protocols will assess the presence of AEs and SAEs at all study visits and follow-up contacts. Should either excessive risk to study participants and/or convincing evidence of lack of measurable benefit to study participants be determined, the study will be stopped and all participants notified in a manner appropriate to the nature of the risk and/or lack of benefit. When taking that step the investigators will consult with the IRB and NHLBI.

Plans for assuring compliance with requirements regarding the reporting of adverse events. This DSMP requires that investigators notify NIH and the University of Wisconsin IRB in a timely manner (consistent with IRB and NIH policies) of the occurrence of any SAE or any AE which is severe, unexpected, and possibly related to study medication or protocol. All staff will assume that patients are taking active medications unless medical treatment requires unblinding

Because this study involves pharmaceutical agents, if an unexpected SAE might be related to study drug use, both the Food and Drug Administration (FDA) and the manufacturer will also be notified within five days of investigators becoming aware of the event. To be compliant with rules for all studies receiving products from Pfizer, Inc, all SAES that occur during participant medication use or within 28 days after medication use will be reported to Pfizer within 24 hours, along with reports of pregnancy. The PI principal investigator will assist Pfizer in investigating any AE and will provide any follow-up information reasonably requested by Pfizer. Examples of unexpected SAE would be untoward medical or intervention occurrences that result in death, are life-threatening, require hospitalization or prolonging of existing hospitalization, create persistent or significant disability/incapacity, or involve congenital abnormality/birth defects.

Unanticipated AEs, including less serious problems that merit reporting to the DSMC because they are severe, unexpected, and possibly related to study participation. Any SAE will be queried and reported even if it appears that the serious adverse event is unrelated to study participation. The Principal Investigators will also be responsible for the accurate documentation, investigation and follow-up of all study-related adverse events. Adverse event assessment, recording, reporting, and investigation will be accomplished through staff training, structured/standardized assessments of untoward occurrences/events, and regular monitoring by study physicians and other study investigators. The Principal Investigators have ultimate responsibility for ensuring that SAEs are detected and reported in a timely manner. Additionally, the IRB will receive an annual report of all SAEs and AEs meeting the criteria listed above.

Plans for assuring that any action resulting in a temporary or permanent suspension of an NIH-funded clinical trial is reported to the NIH grant program director responsible for the grant. The NIH grant program director will be notified within five days if the Principal Investigators deem it necessary to suspend the clinical trial. In the case of a temporary suspension, the Principal Investigators will develop a plan for continuation of the study and discuss this plan with the NIH grant program director in a reasonable time frame.

Plans for assuring data accuracy and confidentiality and protocol compliance. The UW-CTRI Research Director and Principal Investigators will develop plans for assuring data accuracy and protocol compliance. Such plans will include data verification and protocol compliance checks. The Data Manager and Principal Investigators shall also be responsible for ensuring that the data for the project are securely stored, that storage is in compliance with University and federal regulations and that no unauthorized persons have access (electronic or physical) to any participant-identifiable data. All HIPAA regulations and guidelines will be followed, and all study staff must complete approved human subjects and HIPAA training programs.

<u>Data and Safety Monitoring Committee.</u>

In addition to the protections outlined in the DSMP (above), all research activities

conforming to the NIH definition of a clinical trial will also have an independent Data Safety and Monitoring Committee (DSMC). This application includes a Phase IV clinical trial using FDA-approved medications. The DSMP specifies overall monitoring that will be conducted by Principal Investigators, including timely reporting of AEs and SAEs. Every six months, the DSMC will convene to review the overall safety data, as well as data on safety summarized by treatment condition. As per NIH guidelines, the objective of these reviews will be to determine whether continued conduct of the trial poses any undue risk for participants.

The existing UW-CTRI DSMC is chaired by Dr. James Cleary, leader of the Cancer Control Program of the UW Comprehensive Cancer Center. Dr. Cleary is an experienced physician and clinical trial researcher with no involvement in any of this project's research activities. Dr. Cleary is joined on the DSMC by Dr. Burke Richmond. Dr. Sosman is Associate Professor of Medicine and Medical Director of the HIV/AIDS Comprehensive Care Program at UW Hospital and Clinics who has previously collaborated on a clinical trial of smoking cessation with UW-CTRI. Dr. Richmond is an otolaryngologist who has served on independent DSMBCs for Phase II and III trials involving a nicotine vaccine. Neither has direct involvement with any of the proposed research. The Principal Investigators will report to the DSMC; the three DSMC members will not be unblinded as to treatment conditions and will make the final determinations as to study continuation.

Data Sharing with MiCASA

Limited data will be shared with the MiCASA study team (IRB 2017-1013) for those subjects that enroll in both studies (Madison only). Subjects will consent to this sharing under 2017-1013. The full list of data to be shared is maintained by the 2017-1013 IRB protocol.

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