PROTOCOL

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"P01 Cessation Screening Study"

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Study Overview

Smoking causes almost 30% of cancer-related deaths[1] and continues to be the leading preventable cause of death and disease in the US[2]. While effective smoking treatments exist[3-6], their effectiveness in clinical contexts is likely limited because: 1) most treatments have been evaluated under tightly controlled research conditions (i.e., efficacy trials) using highly screened samples recruited via advertisement; and 2) virtually no treatments have been developed via careful evaluation of the individual and joint effects of the intervention components[7,8] (e.g., intervention components may not work well together thereby reducing overall effectiveness, some components may be ineffective but increase cost and patient burden[9-14]). Thus, we have not yet identified optimized strategies for using the two most effective smoking cessation medications (combination nicotine replacement therapy [C-NRT] and varenicline) in primary care so that each is especially effective and cost-effective.

This study will use the Multiphase Optimization Strategy (MOST)[8,15,16] 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 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 effects 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) the main and interactive effects of the cessation interventions on cost-effectiveness.

This proposed research builds on our expertise and prior research findings, using an efficient and innovative methodology (e.g., MOST) to identify cessation treatment components that

produce especially high levels of abstinence in primary care patients who want to quit smoking. Optimization methods will yield two smoking cessation treatments that are especially effective and affordable when used in healthcare settings. The development of two different, highly effective smoking cessation treatments has the potential to increase treatment reach and substantially reduce smoking prevalence in healthcare populations.

It should be noted that 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. When this occurred, we paused all study enrollment. To ensure participant safety, but continue to obtain data, we will resume study recruitment but not randomize anyone to any of the 8 varenicline conditions until we can get varenicline that Pfizer can verify does not have elevated levels of nitrosamine. When we can get safe medication, we will petition the IRB to resume recruitment into all 16 treatment conditions.

On 8/11/2021, the FDA approved a generic version of varenicline. The generic varenicline was found to be bioequivalent and therapeutically equivalent to the Pfizer version of varenicline, with levels of novel nitrosamine well below the acceptable daily intake (ADI) set forth by the FDA. The study will resume providing the generic version of varenicline to participants according to study protocol. The study will not resume providing Pfizer varenicline (Chantix) to study participants until new laboratory information has been released proving it's safety.

Recruitment & Study Entry

Participants will be patients from 12 large primary care clinics in two Wisconsin healthcare systems that treat diverse populations of patients with a large percentage of smokers. UW Health is the integrated health system of the University of Wisconsin-Madison serving more than 600,000 patients each year in the Upper Midwest and beyond at six hospitals and more than 80 outpatient sites. Aurora Health Care (Aurora) is the largest healthcare delivery system in Wisconsin and serves ~1 million Wisconsin residents including Medicaid-eligible, commercially insured, and indigent patients in urban (e.g., Milwaukee) and suburban areas in eastern Wisconsin.

All EHR-identified smokers in a clinic will receive an invitation in the mail and, if they are active on MyChart, via a MyChart message, to find out more about smoking treatment by calling a Care Manager (CM) within the health system. In addition, Medical Assistants (MAs), using an EHR-guided prompt, will refer patients seen at in-person or tele-health visits who report smoking to a CM using an opt-out strategy. The CM will call and tell patients about the smoking cessation options available for them including the availability of this smoking cessation study.

As part of a sister study (IRB # 2022-0973), all patients automatically enrolled in 2022-0973 will receive information on the Cessation study. In addition, all patients automatically enrolled in sister study 2022-0973 who are on the smoking registry at our active recruitment clinics and are not currently enrolled in the Cessation Study will receive a second outreach mailing letting them know about the Cessation Study, along with their standard care options (care from the Wisconsin Tobacco Quitline or from their primary care team). Patients in all clinics will be directed to call their Tobacco Care Manager for more information about this P01 Cessation Screening Project. Patients at a sub-set of clinics will receive additional, quarterly communications regarding these and additional smoking cessation options available as part of this sister study (IRB # 2022-0973). This quarterly outreach will occur via mailed letter and applicable patient-preferred modalities including e-mail (if participant consents to e-mail communication with the TCM) and text messages (if participant consents to text message communication with the TCM). Patients in the clinics receiving quarterly outreach will have the

option to contact their Tobacco Care Manager by phone, or by filling out a brief webform to request the Tobacco Care Manager call them to talk about this study. Thus, there will be additional outreach to patients about this treatment study (in addition to alternative treatment options) as part of this sister study (IRB # 2022-0973).

If patients are interested in participating in this study, the CM will obtain oral assent for screening and sharing contact information, primary care team, and screening data with the UW research team before screening patients for eligibility in a UW REDCap database. Eligible patients will learn more about the study and have a chance to ask questions and provide verbal informed consent. Finally, participants will complete a brief series of questions and then the CM will schedule a call with the study staff (i.e., a Health Counselor) in the REDCap database to initiate treatment and complete study assessments. Participants interested in quitting but not eligible for this study will be electronically referred to the Wisconsin Tobacco Quit Line and/or told to make an appointment with their primary care provider (PCP) by the CM.

After providing consent at Call 1, the Health Counselor (HC) will ask if the participant gives the study permission to stay in touch with them and send them reminders about upcoming study contacts and to remind them that it is time for a refill on their study medication during the study via email and/or text message. The HC will remind them that email and text messaging are generally not a secure way to communicate about their health as there are many ways for unauthorized users to access email and text messages. The HC will also inform them that they do not have to provide their email address or text message number to participate in this study.

Inclusion/Exclusion

To ensure the generalizability of these findings, we kept our inclusion criteria as broad as possible, focusing on ensuring that participants were medically appropriate to use the study medications. Therefore, inclusion criteria will be: age >17 years; smoking >4 cigarettes/day for the previous 6 months; able to read, write, and speak English; not currently taking bupropion or varenicline; if currently using NRT, agreeing to use only study medication for the duration of the study; medically eligible to use study medications (e.g., no severe renal disease, no allergic reactions to tested agents); and, for women of childbearing potential, using an approved method of birth control during treatment. Patients will be excluded if they report suicidal ideation within the last 12 months or any suicide attempts in the past 10 years.

Those who agree to and pass the screening for the inclusion/exclusion criteria for study participation will be asked to complete an oral consent and HIPAA authorization process next. During this process, participants will be read a consent script that conveys the key points regarding study procedures; risks; and participant rights, protections, and benefits in accessible, lay language. Prospective participants will be given an opportunity to ask questions and raise concerns during this process, which will be addressed prior to assessing participant consent to participate in the study. Informed consent for study participation will be formally documented electronically in a REDCap database. Following consent, study staff will send the participant the Study Information Sheet that will remind the participant of study procedures and will include detailed information including all required elements of informed consent and HIPAA authorization. Those who decline the screening invitation, do not meet eligibility criteria, or do not provide oral consent for study participation will be advised to quit smoking and offered standard smoking cessation treatment (told to make an appointment with their primary care provider and/or referral to the Wisconsin Tobacco Quit Line or other tobacco quit line, as appropriate given state of residence).

After the patient provides oral consent, the CM will notify the patient's PCP via EHR that the patient has volunteered for a study with C-NRT or varenicline. The PCP will notify the CM via the EHR that the patient is medically eligible to receive *either* agent, as required by the collaborating healthcare systems. This will occur within 5 business days. To enhance external validity, we will not exclude participants based on their prior use of cessation medication, psychiatric diagnoses, or their use of multiple tobacco products including e-cigarettes (these will be statistically controlled in analyses). We will encourage participants to discontinue use of all tobacco products on their target quit date (TQD). The PCP will be notified via EHR of the patient's treatment assignment and of study-related serious adverse events or adverse events that prompt medication discontinuation that may occur. Care coordination with the PCP will occur via Tobacco Care Manager entry of data in the patient EHR.

While this study does not target incarcerated individuals, some participants may be incarcerated during the period of study involvement. All study outreach, treatment provision, and assessment will be suspended during a participant's period of incarceration.

Study Design

The Cessation Screening Project is a 4-factor, fully crossed, factorial screening experiment (i.e., 2x2x2x2 = 16 experimental conditions) designed to identify the most promising intervention components that are especially effective and cost-effective with regard to their main and interactive effects on 12-month abstinence (see Table 2). This **scientifically rigorous** design will allow us to: 1) detect main effects and interactions within the factorial experiment and identify especially effective medication regimens for varenicline and for C-NRT; 2) compare the relative effectiveness of varenicline and C-NRT; and 3) identify the most effective and cost-effective counseling modality to use with the optimized medication regimens. This will allow us to identify two optimized treatment packages for use with primary care smokers interested in quitting: packages that include both counseling and pharmacotherapies optimized on the bases of effectiveness and cost.

At the second study call, participants (*N*=608) will be randomized to one level of each of 4 factors (see Table 2): 1) Medication Type (Varenicline vs. C-NRT), 2) Preparation Medication (4 weeks vs. Standard), 3) Medication Duration (Extended vs. Standard), and 4) Counseling (Intensive vs. Minimal). Participants will complete phone assessments one week pre-quit, during the first week post-target quit date (TQD) and at Weeks 2, 4, 12, 20, 26, and 52 post-TQD.

Assessments

Call 1. At Call 1, participants will complete the phone screen, complete the oral consent and HIPAA authorization process, and complete a brief demographics assessment. After this call, participants will be mailed a Study Information Sheet that contains all of the information related to the study. They will also be sent information on how to use WebEx so they can have video visits if they so choose.

Call 2. Participants will answer questions about their smoking and other tobacco use history, their self-efficacy and motivation, their physical and emotional health, the impact of Covid-19 on their life and their beliefs about Covid-19 and smoking, and their satisfaction with their health care and they will complete the Fagerström Test of Cigarette Dependence[117] (see Table 1). Participants will be randomized to their treatment condition, set a target quit date, and be educated about their assigned medication (including how and when to request refills).

Calls 3-6. Participants will receive a call one week pre-quit, during the first week post-target quit date (TQD) and at Weeks 2 and 4 from their Health Counselor. This research staff member will assess: a daily smoking calendar using timeline follow-back[118], medication use (as appropriate

based on study condition), use of alternative nicotine products (e.g., e-cigarettes), withdrawal, self-efficacy, and adverse events. We will recommend dosage/use alterations as per good clinical practice if participants experience adverse events. Participants will be referred to their primary care physician should they require medical consultation. Participants will also receive smoking cessation counseling as appropriate, based on their assigned treatment condition. If the call does not include treatment it will not be conducted by the participant's health counselor (i.e., Calls 5 and 6 for those in the Minimal Counseling condition).

Calls 7-10. All participants will get calls at Weeks 12, 20, 26 and 52 from research personnel who did not provide treatment to determine: smoking status (7-day point prevalence and daily calendar using timeline follow-back); use of alternative nicotine products (e.g., e-cigarettes); study medication use in the last 7 days; and withdrawal, self-efficacy, and adverse events (if using study medication). Calls 7, 9, and 10 will also assess the impact of Covid-19 on their life and their beliefs about Covid-19 and smoking. These assessment calls will not include counseling. If participants do not complete the 26 or 52-week assessment calls, we will send a brief assessment to them in the mail with a return envelope for them, and/or via text/email if the participant has consented to text/email communications, to report their smoking status. If participants report a serious adverse event or if they discontinue their study medication due to an adverse event, that information will be emailed to their primary care provider in the EHR by the Care Manager to enhance clinical care.

Table 1. Schedule of Cessation Screening Project Assessments and Interventions

Assessments			**Wk -1**	**Day 2**	**Wk 2**	**Wk 4**	**Wk 12**	**Wk 20**	**Wk 26**	**Wk 52**
	C1*	C2	C3	C4	C5	C6	C7	C8	C9	C10
Eligibility screening	X									
Verbal consent and info sheet mailed	X									
Demographics	X									
Smoking history		X								
Covid-19 questions		X					X		X	X
Self-efficacy/ motivation		X	X	X	X	X	X	X	X	X
Random assignment to treatment		X								
Tobacco dependence		X								
Health, alcohol use		X								
Withdrawal		X	X	X	X	X	X	X	X	X
Smoking status		X	X	X	X	X	X	X	X	X
Use of other tobacco products		X	X	X	X	X	X	X	X	X
Cannabis use		X				X	X		X	
Medication use†			X	X	X	X	X	X	X	
Adverse events†			X	X	X	X	X	X	X	
Patient satisfaction		X					X		X	
Medication education and mailing		X								
Set target quit day**		X								
Intensive counseling (phone/video)			X	X	X	X				
Minimal counseling (phone/video)			X	X						
Cotinine/anabasine									X[a]	X[a]

*C1 will be conducted by the healthcare system Care Manager. All other calls will be conducted by research Health Counselors or other research staff

**The TQD will be set either 5 weeks from C2 to allow a week for medication to be delivered and 4 weeks for prequit medication use for those in the prequit medication condition, or 2 weeks from the C2 to allow a week for medication to be delivered and 1 week for prequit medication if the participant is in the

varenicline no-pre-quit medication condition
†Medication use and adverse events will be assessed for participants currently receiving study medication (this will vary by treatment condition)
[a]All participants who report 7-day point-prevalence abstinence will be asked to provide a saliva sample to biochemically confirm abstinence.

***Month 6 and 12 Biochemical Confirmation*.** Participants who report 7-day point-prevalence abstinence at the Month 6 and 12 follow-up call will be mailed a saliva collection kit with instructions on how to collect a saliva sample and mail it back to the Center. These saliva samples will be sent to a lab to assess the level of cotinine (a metabolite of nicotine and biomarker for smoking and other sources of nicotine). Please note, if participants have a detectable level of anabasine (a biomarker specific for combustible tobacco), we will also collect those results. Participants who report abstinence in the last 7 days at this visit but have a cotinine level >10ng/mL or who do not have provide a cotinine result will be considered to be smoking. When a participant demonstrates biochemically confirmed abstinence, that information will be conveyed to the primary care provider by the Care Manager via either email in the electronic health record or by changing the electronic health record smoking status.

***Satisfaction Assessments*.** All participants will evaluate their treatment in terms of burden, acceptability, and perceptions of the healthcare system, using measures based on previous research on patient satisfaction assessments. At Weeks 12 and 26 we will assess satisfaction with research staff, clinic staff for referring the smoker to the study, and the healthcare system for providing the treatment. Up to 110 participants will also be offered up to an additional $20 ($10 for Call 2 assessment and $10 for Call 7 assessment) for completing a brief (5 minute) interview related to burden, acceptability, and perceptions of telehealth modality (i.e., Webex versus telephone). This additional interview is supplementary, will occur at Call 2 and Call 7 with the first 110 smokers in the study who agree to participate, and will not affect their eligibility in the study or care provided. These interviews will be recorded and transcribed.

Healthcare Utilization. Data on health status and healthcare utilization for participants who do and do not quit smoking will be extracted from the EHR for up to 1 year pre-enrollment, and 4 years post-enrollment to inform economic analyses for the Secondary Aims.

Interventions

Participants will be told their treatment condition at Call 2, set a target quit date (TQD), and instructed how to use their study medications. Medications will be mailed following this call, along with a handout that describes: 1) when to begin taking study medication; 2) the type and doses involved; 3) how and when to obtain the next month's medication; and 4) complete instructions on proper medication use, including information from the package insert and contact information if they have questions regarding their medication and/or symptoms they experience. Participants will be mailed all Preparation Medication as well as one month of post-quit study medication after Call 2. They will need to call in to a study line to request that more medication be mailed to them (Standard Duration participants will call one time to receive their final 2 months of medication; Extended Duration participants will call once to get 2 additional months of medication and again to get the remaining 3 months of study medication). Participants will also receive a counseling handout with their medications; those randomized to intensive counseling will receive a Quit Plan listing their target quit day and when they start the medications and those randomized to minimal counseling will receive the mHealth handout.

Medication Type: Varenicline vs. C-NRT. Half of participants will be assigned to receive varenicline and half to receive nicotine patch + mini-lozenge (C-NRT). Unless participants are assigned to Preparation or Extended Duration, they will receive the standard dosing and duration of pharmacotherapy (e.g., 12 weeks of varenicline starting 1 week prequit or 12 weeks of C-NRT starting on the TQD; see Table 2).

Preparation Medication: 4 weeks vs. Standard. Half of participants will be assigned to receive the Preparation Medication ("ON" condition); they will be instructed to use their assigned medication type (varenicline or nicotine patch) for 4 weeks prior to their TQD (see Table 2). Participants will use a lower dose of NRT (14-mg patches) while they are still smoking to reduce the risk of adverse events. Our prior research found no significant increases in adverse events among smokers who used NRT prior to the TQD and prior research has shown that use of varenicline up to 35 days prior to the quit day is safe and effective. Participants assigned to the "OFF" level start their C-NRT use on their TQD or the standard Preparation varenicline, which starts 1-week pre-TQD (see Table 2).

Table 2. Medication Dosing

		Cessation Medication: Standard Duration (12 Weeks)	Cessation Medication: Extended Duration (24 Weeks)
Varenicline		No Preparation Meds: ▪ Days 1-3: 0.5 mg pill QD ▪ Days 4-7: 0.5 mg pill BID ▪ Day 8 (TQD)-Week 11: 1 mg pill BID Preparation Meds: ▪ Days 1-3: 0.5 mg pill QD ▪ Days 4-7: 0.5 mg pill BID ▪ Day 8-Week 16: 1 mg pill BID (TQD in Week 4)	No Preparation Meds: ▪ Days 1-3: 0.5 mg pill QD ▪ Days 4-7: 0.5 mg pill BID ▪ Day 8 (TQD)-Week 23: 1 mg pill BID Preparation Meds ▪ Days 1-3: 0.5 mg pill QD ▪ Days 4-7: 0.5 mg pill BID ▪ Day 8-Week 28: 1 mg pill BID (TQD in Week 4)
Combination NRT*	Nicotine Patch	Smoke ≥10 cigs/day: ▪ Weeks 1-8: 21 mg ▪ Weeks 9-10: 14 mg ▪ Weeks 11-12: 7 mg Smoke 5-9 cigs/day: ▪ Weeks 1-10: 14 mg ▪ Weeks 11-12: 7 mg	Smoke ≥10 cigs/day: ▪ Weeks 1-20: 21 mg ▪ Weeks 21-22: 14 mg ▪ Weeks 23-24: 7 mg Smoke 5-9 cigs/day: ▪ Weeks 1-22: 14 mg ▪ Weeks 23-24: 7 mg
	Nicotine Mini-lozenges	▪ 2 mg ▪ Weeks 1-6: 1 ML/1-2 hrs ▪ Weeks 7-9: 1 ML/2-4 hrs ▪ Weeks 10-12: 1 ML/4-8 hrs	▪ 2 mg ▪ Weeks 1-20: 1 ML/1-2 hrs ▪ Weeks 21-22: 1 ML/2-4 hrs ▪ Weeks 23-24: 1 ML/4-8 hrs

*Participants randomized to Preparation C-NRT will receive 14-mg patches for the 4 weeks prior to the TQD. QD = daily, BID = twice a day, ML = mini-lozenge

Medication Duration: Extended vs. Standard*.* After Call 2, all participants will be mailed enough medication to get through the first month post-TQD and instructed to call a toll-free study number to have their refills mailed to them. Half of participants will be assigned to the Extended Duration (i.e., the "ON" condition); these participants will be able to use varenicline for 23 weeks post-TQD (24 weeks post-TQD if also randomized to preparation meds) or use C-NRT for 24 weeks post-TQD (see Table 2). The other half of participants will have varenicline for 11 weeks post-TQD (12 weeks post-TQD if also randomized to preparation meds) or C-NRT for 12 weeks post-TQD. We will urge all participants to use all of their study medication, regardless of whether they are abstinent or not.

Counseling: Intensive vs. Minimal. Half of the participants will be assigned to the Intensive Counseling condition and will receive four 15-20-minute counseling sessions occurring 1 week prequit, during the first week post-TQD and during Weeks 2 and 4 (see Table 1). During the first counseling call, the HC and participant will create a quit plan that the HC will then mail to the participant following the call. The counseling will be provided either via HIPAA-secure WebEx

video conference or phone, depending on the participant's preference. A web link for the video conferences will be sent to participants via Outlook email to the participant's email address they have provided the HC. The counseling sessions will be designed to produce intra-treatment support and skill training and problem-solving.

The other half of the participants receive a brief (15-30 minute) phone/video counseling session 1 week prior to the TQD to promote engagement with free mobile health (mHealth) resources: smokefree.gov and/or the Wisconsin Tobacco Quit Line, mHealth resources developed and maintained by the National Cancer Institute and the Wisconsin Department of Health Services. This will include a fax referral to the Wisconsin Tobacco Quit Line, which will then fax back to the research office what services the participant received (i.e., did they complete the counseling call, were they sent any smoking cessation medications). Smokefree.gov allows participants to develop a quit plan and access different quit smoking resources. The Quit Line is an interactive program that involves one-on-one telephone coaching sessions with a trained Quit Line coach to encourage smoking cessation, offer personalized advice on how to quit, information on medications, and assistance with choosing a quit date and creating a plan. This counseling will include informing participants about the features of the resources and encouraging them to sign up during their counseling session and a mailing that describes the mHealth resources. Participants will then receive a brief (10-20 minute) follow-up phone/video session during the first week post-TQD to mimic a nurse or clinician follow-up after a quit attempt and to provide additional mentoring around the use of the mHealth resources (e.g., has the participant signed up/used these resources, recommendation for specific pages that would be appropriate).

All participants will receive the medication conditions as outlined above, regardless of their counseling condition. Regular team meetings will discuss safety, confidentiality, and fidelity to the counseling manual. Health counselors (HCs) will also meet for 2 hours/month for clinical supervision with the Project Leader, Dr. Piper, a licensed clinical psychologist, to review the study protocol and address treatment issues.

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, and continued interaction with the same health counselor. In addition, consented participants who we are not able to reach using contact information obtained at the baseline and subsequent calls, the CM will check in the EHR for updated contact information. If there is no updated information, 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 compensated for completing assessments: $20 for Call 2; $10/assessment for Calls 3-8 (1 week pre-quit, Weeks 1, 2, 4, 12, and 20); $20/assessment call at Weeks 26 and 52; and $50/Month 6 and 12 returning the saliva sample for cotinine analysis. This would result in a total potential compensation of $220. If participants are unable to complete the assessment calls at Weeks 26 and 52, return the assessment letter or complete it online, they will receive $15. Up to 110 participants will also be offered an additional $10 for completing a brief (5 minute) interview related to of burden, acceptability, and perceptions of telehealth modality (i.e., Webex versus telephone) at Calls 2 and 7 (total of $20).

Analytic Approach

Primary Aim 1: Identifying Main and Interactive Effects*.* The primary outcome is biochemically confirmed, point-prevalence abstinence at 12-months post-TQD. We will also

examine the main and interactive effects on cost-effectiveness. The secondary outcome is cost effectiveness in which the costs of implementing each intervention (minus research-related costs) will be computed from a payer perspective. 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.

Effectiveness. 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. 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). On the other hand, if we obtain a strong main effect for one of the medications (e.g., varenicline), this would be important clinically and would identify one of these agents as the preferred basis for optimized treatment.

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 additional analyses, we will statistically control for covariates such as healthcare system and clinic, and important smoker characteristics known to affect either treatment response or abstinence likelihood (**biological variables**: e.g., sex and age, as well as other key variables such as living with a smoker, educational attainment) to explore how treatment effects are related to such variables.

Cost-effectiveness. Cost-effectiveness analyses will focus on the intervention components and combinations of components per se 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. We will measure costs from a societal perspective using data on smoking cessation benefits from publicly available Medicare and Medicaid reimbursement rates. 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 also conduct probabilistic sensitivity analyses to account for uncertainty. 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. 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).

Primary Aim 2: Comprehensive Optimization of Treatment. The results of the analyses for Primary Aim 1 will be used to optimize two treatment packages: varenicline-based treatment

and C-NRT-based treatment. We will select component packages that are especially effective and low in cost, to constitute optimized treatments. 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 use multiple criteria decision analysis (MCDA), which focuses on how to weight and combine such criteria to support meaningful decisions and to decide on the optimal treatment packages. We will follow recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Best Practices Task Force[139,140] with respect to problem definition, criteria selection, use of the value measurement approach, criteria weighting, sensitivity analyses, and so on. 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.

***Secondary Aims Analyses*.** Exploratory analysis of *moderators* of abstinence outcomes will use complementary logistic regression analyses with appropriate model-fitting techniques[141] and regression tree analyses that can identify differential treatment responses[142,143] in 6- and 12-month abstinence. Candidate moderators of treatment effects on abstinence will include tobacco dependence and psychiatric history, contextual factors such as household smoking, and **biological variables** such as sex. In the logistic regression analyses, moderators will be evaluated with regard to their interactions with treatment main effects and interactions. With a similar sample size, we were able to detect moderation in our prior factorial research.

***Additional Exploratory Analyses*.** Seven-day point-prevalence abstinence at Weeks 12 and 26 will be analyzed using similar methods to those used for the primary outcome. These analyses will allow us to examine the stability or robustness of the intervention component effects. These findings may also be used in future research to optimize cessation treatments based on longer-term outcomes. In addition, we will examine the occurrence of adverse events and its relation with adherence. 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. 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[148-150].

Sample Size and Power Considerations

This study was designed to have sufficient power to detect a clinically significant (i.e., 10 percentage point increase) difference between the two levels of a factor (i.e., the main effects) in 52-week biochemically confirmed abstinence. In other words, the sample size was chosen to ensure that the Primary Aim comparisons of ON vs OFF levels of a factor would have sufficient power to detect clinically meaningful increases in abstinence. It should also be noted that because this is a balanced factorial design, we will have the same power to detect 2-way interactions that we have to detect main effects. To address the Primary Aim, we assume that the base rate (participants who get Standard Preparation Medication and Standard Duration) of 52-week biochemically confirmed abstinence will be 20%. This is consistent with our prior research that found a self-reported 52-week abstinence rate of 26.8% among primary care smokers who received 8 weeks of C-NRT[13] and our efficacy trial that showed biochemically confirmed 52-week abstinence rates of approximately 20% for smokers who received either 12 weeks of varenicline or 12 weeks of C-NRT[43]. If we assume that abstinence rates among real-world primary care patients might be somewhat lower (e.g., 15%), then with a sample size of

608 (304 in the ON and 304 in the OFF levels of each factor with no missing data because missing=smoking) and α=.05, we are powered at .87 to detect a difference between 15% and 25% in 52-week biochemically confirmed abstinence; we also have sufficient power (.81) to detect a difference between 20% and 30% in 52-week biochemically confirmed abstinence. Treatment optimization will be based on the effect size estimates of the main and interactive effects on 12-month abstinence, rather than statistical significance, consistent with our prior research[15].

Protection of Human Subjects

Human Subjects Involvement and Characteristics. All EHR-identified smokers in a clinic will receive an invitation (in their preferred modality: mail, MyChart messages from the EHR, text) to find out more about smoking treatment by calling a healthcare system Care Manager. In addition, Medical Assistants (MAs), using an EHR-guided prompt, will inform all smokers attending in-person or tele-health visits that they will be getting a call from their clinic's Care Manager, using an opt-out approach. The Care Manager will call the smoker and assess their interest in quitting smoking. Smokers who are interested in quitting in the next 30 days will be offered a variety of cessation treatment options, including the opportunity to participate in this smoking cessation study.

Specific eligibility requirements for this project are: age >17 years; smoking >4 cigarettes/day for the previous 6 months; able to read, write, and speak English; not currently taking bupropion or varenicline; if currently using NRT, agreeing to use only study medication for the duration of the study; medically eligible to use study medications (e.g., no severe renal disease, no allergic reactions to tested agents); and, if the participant is a woman of childbearing potential, using an approved method of birth control during treatment.

Those who agree to and pass the screening for the inclusion/exclusion criteria for study participation will be asked to complete an oral consent and HIPAA authorization process next. During this process, participants will be read a consent script that conveys the key points regarding study procedures; risks; and participant rights, protections, and benefits in accessible, lay language. Prospective participants will be given an opportunity to ask questions and raise concerns during this process, which will be addressed prior to assessing participant consent to participate in the study. Informed consent for study participation will be formally documented electronically in a REDCap database. Following consent, study staff will send the participant the Study Information Sheet that will remind the participant of study procedures and will include detailed information including all required elements of informed consent and HIPAA authorization.

The Care Manager will notify the patient's primary care provider (PCP) that the patient has volunteered for a study with C-NRT or varenicline and that the PCP should notify the Care Manager that the patient is medically eligible to receive *either* agent. The PCP will notify the CM that the patient is medically eligible to receive *either* agent (e.g., no severe renal disease, no psychiatric concerns), as required by the collaborating healthcare systems. This will occur within 5 business days. The PCP will be notified of the patient's treatment assignment, and of study-related serious adverse events or adverse events that prompt medication discontinuation that may occur. Care coordination with the PCP will occur via Tobacco Care Manager entry of data in the patient EHR.

Patients who are eliminated due to screening failure or elect not to participate in this research program will be given a list of alternative smoking cessation programs, including the Wisconsin Tobacco Quit Line (1-877-QUIT-NOW) and told to make an appointment with their PCP to discuss smoking cessation treatment.

A total of 608 participants will be recruited for this project. No special vulnerable populations will be recruited (pregnant women will be specifically screened out due to medication safety concerns and no persons under the age of 18 will be allowed to participate because the medications we are using have not been approved by the FDA for individuals less than 18 years old). Eligible participants will be randomized following provision of oral informed consent and PCP verification of eligibility (stratified by clinic, gender, and race [white vs. non-white]).

Nicotine patch and varenicline dosing will be consistent with the 2008 PHS Guideline[3] and package inserts. All participants in the C-NRT group will receive 2mg mini-lozenges due to the superior palatability of the 2mg lozenges.

- Nicotine patches: ≥10 cigs/day = 8 [or more, depending on treatment condition] weeks of 21 mg, 2 weeks of 14 mg, and 2 weeks of 7 mg nicotine patches; 5-9 cigs/day = 8 [or more, depending on treatment condition] weeks of 14 mg, and 4 weeks of 7 mg nicotine patches;
    - Participants assigned to Preparation NRT will receive 14 mg patches
- Nicotine mini-lozenges: 2mg mini-lozenges;
- Varenicline .5 mg once/day for 3 days, then .5 mg bid for 3 days and then 1 mg bid for the remainder of the regimen.

The study will recommend dosage/use alterations as per good clinical practice if the participant experiences side effects. The Health Counselor will refer participants to their primary care physician should they require medical consultation. Medication is provided to participants in dosage periods defined within each treatment condition (e.g., participants may start their medication 4 weeks prior to the TQD; participants may receive medication for 12 or 24 weeks post-quit).

This project involves collaboration with staff of the two health systems (Aurora Health Care, UW Health). In prior research of similar scope, MAs at referring clinics have been determined to be not involved in research since their role is limited to providing information about the availability of a study and sending contact information to the study to the Care Manager. The Care Manager, who will be a clinic employee but also engaged in research procedures, will complete the necessary Human Subjects training. The only study data shared by the Tobacco Care Managers with clinic teams will be interest in or enrollment in the study, study medications that may be and are given to study participants, study-related serious adverse events or adverse events that prompt medication discontinuation, and changes in smoking status.

Sources of Materials. Contact information on all smokers interested in hearing more about smoking programs will be sent to the clinic Care Manager. The Care Manager will reach out to patients by phone and invite them to learn more about stop-smoking resources, including standard care (fax referral to the Wisconsin Tobacco QuitLine and/or their PCP) and the research study. Those interested in the research study will then be told that this research is being conducted with Dr. Piper at the University of Wisconsin and asked if they would be willing to spend 10 minutes learning about the study and see if they qualify for it. Those who assent to this will then be told how their information will be used and stored, and asked if they would like to continue. If they assent again, and confirm that they smoke cigarettes, then then are read a detailed description of the study and asked if they are interested in participating in the study and if they assent to sharing their contact information and screening responses with the University of Wisconsin research team. If they provide oral assent to this, then the Care Manager completes eligibility screening in a UW instance of REDCap. For those who pass the eligibility screening, Care Managers (CM) will provide more information about the study, allow the patient to ask questions, and then patients will provide verbal consent. Finally, participants will complete a

brief series of questions and then the CM will schedule a call with the study staff (i.e., a Health Counselor) in the REDCap database to initiate treatment and complete study assessments. Care Managers will also contact potentially eligible patients' PCP to finalize eligibility via EHR records and communication. Final PCP approval will be documented and participants' randomized treatment assignment will be conveyed to the PCP as well as study-related serious adverse events or adverse events that prompt medication discontinuation that may occur. Care coordination with the PCP will occur via Tobacco Care Manager entry of data in the patient EHR

Data will be transferred from the EHR to research databases for tracking recruitment, participant healthcare utilization, smoking cessation treatment, and changes in smoking status, insurance type, or health status over the course of the study. Both healthcare systems maintain secure, HIPAA-compliant electronic health records for their operations and have mechanisms and processes in place to extract and encrypt data from the EHR for research purposes. Staff at UW-CTRI will receive data on enrollees who have provided consent for phone screening. The data to be extracted from the EHR for the purposes of assessment are shown in the uploaded List of EHR Data to Be Extracted. The research office will also receive data from the Wisconsin Tobacco Quit Line regarding which services the participants in the Minimal Counseling condition received.

Data collected from participants in this program will primarily be used for research. Data will consist of answers to questionnaires and interviews assessing smoking history, demographics, nicotine dependence, medication usage, medication side effects and satisfaction surveys. A small subset of participants will also complete interviews about telemedicine preferences. Participants will also provide saliva samples for cotinine assays that reflect smoking status. All data are retained in the research database. The research database access is limited to the clinic Care Managers and those staff members and investigators directly involved in the study and all under the supervision of the UW IRB.

Potential Risks. Risks associated with this research are judged to be minimal. 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 in the past and are familiar with these phenomena. Participants will be informed about the likely effects of smoking withdrawal.

With respect to the pharmacotherapies, participants will be made aware of the common side effects before they consent to participate in the study. It should be noted that the nicotine patch and nicotine mini-lozenge are available over the counter. The Food and Drug Administration (FDA) has approved using a combination of two forms of NRT (e.g., nicotine patch + nicotine mini-lozenge) for smoking cessation and using NRT prior to cessation[151]. These interventions have also been studied and used safely in multiple clinical trials, are used by knowledgeable clinicians in clinical practice, and are reviewed in the 2008 PHS Guideline[3] and in a recent review in the *New England Journal of Medicine*[29]. The PHS Guideline, in fact, recommends combination NRT as a particularly effective treatment. The nicotine patch is generally well tolerated, but up to 50% of participants may have a local skin reaction, and rarely, individuals may have a more systemic allergic reaction. The most likely side effects associated with the nicotine mini-lozenge are heartburn, hiccup, nausea, upper respiratory tract infections, coughing, and sore throat. Although most smokers have tolerance to nicotine, symptoms of acute nicotine toxicity (nausea and vomiting) are possible. The most common side effects associated with varenciline are nausea and sleep disruption. It is also important to note that some individuals may experience worsening of psychiatric conditions or symptoms such as anger, agitation, depression, or suicidal thoughts. Varenicline may be associated with a small,

increased risk of certain heart problems in people with heart and blood vessel disease. Finally, individuals often attempt to stop smoking without the use of medication. As the 2008 PHS Guideline[3] shows, this method is considerably less likely to produce long-term cessation. Those not successful in quitting bear the health risks associated with continued smoking.

Finally, there is a small risk of loss of confidentiality. This could occur through a number of possible avenues, all highly unlikely due to the data security measures in place. UW-CTRI's computer system is linked to the UW network through a firewall, which is managed by the School of Medicine and Public Health network team, via a fiber link which is maintained by the UW Division of Information Technology. No data are stored on individual computer hard drives. All data are transmitted from the point of collection to the UW-CTRI server through secure, encrypted web connection. There are rare occasions when, due to a loss of internet access or computer hardware failure, data are collected in paper forms, which could be taken or lost. In addition, consent forms are obtained in paper copy; these forms contain the participant name and signature. Finally, the University of Wisconsin and the National Cancer Institute may inspect the signed consent forms. Because of this possible need to release information to these parties, we cannot guarantee absolute confidentiality.

Adequacy of Protection Against Risks

Recruitment and Informed Consent. To ensure that our findings are maximally relevant to real-world healthcare application, we will screen smokers presenting to 8 primary care clinics in two participating health systems located throughout Southern Wisconsin. All EHR-identified smokers in a clinic will receive an invitation (in their preferred modality: mail, MyChart messages from the EHR, text) to find out more about smoking treatment by calling a Care Manager (CM). In addition, clinic roomers (e.g., Medical Assistants) will be prompted by the electronic health record (EHR) to invite all smokers attending primary care clinic in-person or tele-health visits. The MA will then send the contact information of interested patients to the CM. We have developed and used this successfully in our past research. The CM will call patients and offer interested patients an opportunity to participate in this smoking cessation study. The CM will then screen the participant to verify eligibility. If the patient is eligible and interested, the CM will complete an oral consent and HIPAA authorization process. During this process, participants will be read a consent script that conveys the key points regarding study procedures; risks; and participant rights, protections, and benefits in accessible, lay language. Prospective participants will be given an opportunity to ask questions and raise concerns during this process, which will be addressed prior to assessing participant consent to participate in the study. Informed consent for study participation will be formally documented electronically in a REDCap database. Following consent, study staff will send the participant the Study Information Sheet that will remind the participant of study procedures and will include detailed information including all required elements of informed consent and HIPAA authorization.

After the patient provides oral consent, the CM will notify the patient's primary care physician (PCP) that the patient has indicated they are interested in a study with C-NRT or varenicline and that the PCP should notify the CM if the patient should *not* receive *either* agent, as required by the collaborating healthcare systems. This will occur within 5 business days.

Those who decline the screening invitation, do not meet eligibility criteria, or do not provide oral consent for study participation will be advised to quit smoking and offered standard smoking cessation treatment (told to make an appointment with their primary care provider and/or referral to the Wisconsin Tobacco Quit Line).

Records collected in this research will allow us to complete a full CONSORT diagram.

Protection Against Risk. Risks related to medications are minimized through close monitoring. The Project Leader, working in consultation with the Program Project's physician (Dr. Brian Williams), will be responsible for routine monitoring of unanticipated health events. This risk protection includes procedures for contacting the emergency physician or psychologist and monitoring of all events through scheduled biweekly meetings with study staff and review of written documentation. Unanticipated health 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 Project Leader and the Program Project Co-Principal Investigators have ultimate responsibility for ensuring that unanticipated health events are detected and reported in a timely manner. Health events that raise concerns (e.g., allergic reaction, symptoms suggestive of nicotine toxicity, significant change in mood) will be immediately reported to the study physician who will determine an appropriate course of action.

To facilitate safety, participants who may not be medically appropriate to use either pharmacotherapy will not be included in the study (e.g., no severe renal disease, no allergic reactions to tested pharmacotherapies). Once enrolled, follow-up protocols will assess for medication side effects and unanticipated health events at all study contacts. We will recommend dosage/use alterations as per good clinical practice if the participant experiences symptoms of nicotine toxicity or other troublesome side effects once they begin medication treatment. We will refer participants their primary care provider as needed. Should either excessive risk to study participants and/or 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.

Participants who are pregnant or planning to become pregnant are not eligible to participate in this study. We ask participants who are capable of becoming pregnant to use appropriate measures (e.g., abstinence, acceptable birth control) to avoid pregnancy. Should a participant become pregnant during the study, they will be told to discontinue all study medications (which represents the key risk during pregnancy) but they will be allowed to remain in the study and receive any remaining coaching interventions and complete all remaining assessments. If a participant becomes pregnant, that is a critical time for them to quit smoking which is something that the cessation counseling in this study can support.

In terms of confidentiality risk, the UW-CTRI Information Technology Administrator, Jonah Stankovsky, manages the hardware, data, security, and infrastructure below the firewall. Access to the network is limited to only UW-CTRI owned and actively managed devices. All devices automatically lock and are password protected after 15 minutes of inactivity. All portable devices are encrypted for data security and no PHI is stored on local devices. All data stored on the network file server is limited by the principle of least privilege. Healthcare systems will transmit identifying information to UW-CTRI via secure, HIPAA compliant means (either a secure FTP site or a secure interface to the EHR).

As stated above, no data are stored on individual computer hard drives. All data are transmitted from the point of collection to the UW-CTRI server through secure, encrypted web connection. On those rare occasions when, due to a loss of internet access or computer hardware failure, data are collected in paper forms, these forms will be stored securely in the clinic and transported personally by the case manager to UW-CTRI. No identifying data other than a participant ID number is entered on any data form. Any data collected on paper are entered into

the computer immediately upon receipt at UW-CTRI and the paper document is disposed of securely.

Finally, 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 smoking cessation counseling and pharmacotherapy, two evidence-based treatments that can double a smoker's odds of quitting successfully, at no cost. Considerable research has demonstrated that, at no matter what point a smoker quits successfully, health benefits occur[17]. In addition, quitting smoking reduces the burden of secondhand smoke exposure to others. Finally, the benefit of reduced healthcare costs and morbidity and mortality related to smoking is a societal benefit from quitting smoking.

The health and economic benefits to the individual and society greatly outweigh the risks in terms of discomfort, side effects of medication, and loss of confidentiality.

Importance of the Knowledge to be Gained

This factorial trial will identify the optimal use strategies for varenicline and combination NRT, the two most effective smoking cessation pharmacotherapies currently available, and the optimal counseling modality for use with these medications.

As outlined above, the risks of this study are minimal and limited to the discomfort of quitting smoking, generally mild side effects of medication, and small risk of breach of confidentiality. The potential study impact on increased numbers of smokers across clinical settings nationally far outweigh these risks.

Data and Safety Monitoring Plan

The Data Safety and Monitoring Plan (DSMP) for this Program Project 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 of the Program Project are responsible for routine monitoring of the progress of this research. This includes scheduled biweekly meetings with study staff and review of written documentation of all research projects. Data reviewed at these meetings will 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, 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, which may include discontinuation of medication. As data become available, the Director of Research Administration, Project Leader 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 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 NCI.

Plans for the reporting of unanticipated health 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 that is severe, unexpected, and possibly related to study medication or protocol. Because this Program Project research involves pharmaceutical agents, if an 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. Examples of 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 problems will be monitored and reported to the DSMC. These are events that meet the following criteria: 1) suggest the research places subjects or others at increased risk of harm, 2) are unexpected (in terms of nature, severity or frequency) given the research procedures that are described in the study-related documents, and 3) possibly related to study participation. Any SAE will be queried and reported if it meets the definition of unanticipated problem. The Project Leader and 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 Project Leader and 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 a clinical trial. In the case of a temporary suspension, the Principal Investigators and Project Leader will develop a plan for continuation of the project 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 Project Leader, supported by CTRI analysis staff will develop plans for assuring data accuracy and protocol compliance. Such plans will include data verification and protocol compliance checks. The Data Manager and IT Manager shall 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.

Data and Safety Monitoring Committee

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). All three proposed clinical research projects (Health System Reach Interventions, Cessation Screening, and Optimized Care) in this Program Project conform to the NIH definition of a clinical trial. All of the trials in this P01 application are Phase IV clinical trials using FDA-approved medications that are not multicenter in nature (the projects are testing existing interventions delivered through new methods to determine population effectiveness). The DSMP specifies overall monitoring that will be conducted by Principal Investigators for all projects, including timely reporting of AEs and SAEs. Every six months, the Program Project-wide 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 Program Project-wide 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. James Sosman and 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 make the final determinations as to study continuation.

ClinicalTrials.gov Requirements

This research project will be registered with clinical trials.gov prior to the enrollment of the first subject. Final data (including outcomes and adverse events) will be reported to clinicaltrials.gov within 1 year of the conclusion of the trial.

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