Study Summary (Protocol) for Wisconsin Smokers' Health Study 2

Study Overview
The proposed research has 2 components: 1) a long-term health outcomes study that will include smokers and non-smokers who participated in the original Wisconsin Smokers' Health Study (Cohort 1) as well as newly recruited participants (Cohort 2); and 2) a comparative effectiveness smoking cessation trial that will include interested/eligible Cohort 1 and Cohort 2 participants.

The long-term health outcomes study goal is to examine the long-term effects of quitting smoking vs. continued smoking on physical and mental health over 3 years. The goal of the comparative effectiveness trial (CET) is to examine the relative efficacy of 3 different smoking cessation medications (nicotine patch, nicotine patch + nicotine lozenge, and varenicline [Chantix]) among eligible smokers who want to quit.

Recruitment & Study Entry
A total of 2100 participants will be recruited to participate in the WSHS2. All participants will complete a phone screen that will be conducted by trained undergraduate students using a computer-assisted interview. Screening data will be kept for research purposes but if a participant does not end up participating in the research, the identifying information will be deleted.

Cohort 1: Participants from the original Wisconsin Smokers' Health Study (WSHS) will be mailed letters informing them of the new study, its goals, its requirements, and to encourage participation. We will then call all of the original WSHS participants to invite them to participate in the new study. WSHS participants were not asked in advance whether we could contact them again to participate in new research, so all original WSHS participants will be contacted. For WSHS participants who we are not able to reach using contact information obtained during the prior study, we will conduct internet searches based on name and date of birth to see if reliable new contact information can be obtained. If we are still unable to reach a participant due to unavailable or inaccurate contact information, we will call and/or send a letter to the alternate contacts originally specified by the participant as part of the originally WSHS, designated as a contact for this specific situation. Interested participants will be scheduled for an in-person visit where, after learning about the new study and providing written consent, they will complete the baseline assessment battery (Table 1; See Baseline Qualtrics Assessment).

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<th>Evaluations/Procedures</th>
<th>Orientation &amp; Visit 1</th>
<th>Visit 2</th>
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<th>Call 2 Visit 3</th>
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We estimate about 600 of the participants from the parent (TTURC-2) cohort will volunteer for the new research (original parent study enrolled 1504 participants). We estimate ~175 participants from the parent study will be smoke-free and 425 will be regular smokers. During the telephone contact, participants will be asked if they smoke. The response to this question will determine who might be appropriate for a cessation intervention. Smokers who are

| Tobacco Dependence DSM-V questionnaire | X | X | X | 
| Fagerström Test of Nicotine Dependence (FTND) | X | X | X | 
| Revised Wisconsin Smoking Withdrawal Scale (WSWS) | X | X | X | X | X | 
| Short Inventory of Problems (SIP-2R) – Alcohol related problems | X | X | X | X | X | 
| Quality of Life assessment | X | X | X | X | 
| Sleep apnea questionnaire | X | X | X | X | 
| Menthol cigarette smoking assessment | X | X | 
| Vital Signs* | X | CO only | X | X | X | CO only | 
| Concomitant Medications | X | X | X | X | 
| Clinical Endpoint Interview | X | X | X | 
| National Comorbidity Survey – Revised (NCS-R-CIDI)* | X | X | X | 
| Carotid Intima-Media Thickness (IMT) and Plaque Ultrasound | X | X | X | 
| Treadmill Stress Test and 12-lead ECG* | X | ECG only | X | 
| Arterial Tonometry: Pulse Wave Velocity/Central Aortic BPs* | X | X | X | 
| Pulmonary Function Tests | X | X | X | 
| Pedometer Training and Assessment | X | X | X | 
| Blood/Urine Collection | X (Urine only) | X | X | X | X (Urine only) | X | 

**Time Required For Each Visit (in minutes): 180 180 240 10 120 5 10 5 200 120**

*Note: Participants who reach 42 and/or 48 months will also be called and asked about their smoking status and changes in their contact information.

*For Cohort 1 participants only who do not want to participate in the full 3-year study.

*Vital signs include CO, blood pressure, temperature, height, weight, and waist circumference.

*NCS-R-CIDI should last ~30 minutes. The CIDI assesses Axis 1 diagnoses and includes a screener (28 min) and the following modules: Depression (13.5 min), Panic Disorder (12 min), Social Phobia (9 min), Agoraphobia (8 min).

*Generalized Anxiety Disorder (13 min), Substance Use (19 min), Tobacco Use (8), and Chronic Conditions (20 min).

*Stress testing will be done only in Madison; 12-lead ECGs will be obtained for all participants.

*Arterial tonometry can be conducted while participants are undergoing CIMT assessment.

Note: if necessary to allow DNA analysis, a second DNA collection could occur at V3 or V5.
interested in quitting and do not have any of the exclusion criteria listed below will be invited to participate in the Comparative Efficacy Trial (CET), a smoking cessation clinical trial (this would include Visits 2a-2e; see Table 2 below). Regardless of their interest or eligibility to participate in the CET, all members of the original parent cohort will be invited to participate in the physical and mental health outcome study.

Because of the lower than expected recruitment of Cohort 1 individuals through the first 18 months of recruitment and in order to address those study aims related to assessing long-term health outcomes of smoking and quitting, we will offer an additional participation option to Cohort 1 individuals who have not responded to our contacts or have indicated that they are not able to participate in the full 3-year study. This option will consist of a single visit combining elements of Visit 1 and 2. Specifically, they will receive everything in these 2 visit protocols except the NCS-R-CIDI, treadmill stress test and pedometer assessment at a single, ½ day visit (the one-day health assessment option). These data, combined with the data from the parent study, will allow us to assess long-term health outcomes of participants who may or may not have quit smoking since initial study participation.

| Table 2. Schedule of Assessment and Treatment Visits (Txv’s) for Participants in the CET (Treatment Visit and Assessment Times are Relative to the Quit Day) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Assessments**                 | Visit 2a         | Visit 2b         | Visit 2c         | Visit 2d         | Phone           | Visit 2e         | Follow-up Call   |
| Withdrawal (WSWS) and Affect (PANAS) | Wk -1           | Wk 0            | Wk 1            | Wk 4            | Wk 8            | Wk 12           | Wk 26, 38, & 52  |
| Hedonic Tone                    | X               | X               | X               | X               | X               | X               | X               |
| Anxiety Sensitivity Index (ASI) | X               | X               | X               | X               | X               | X               | X               |
| Distress Tolerance Scale (DTS)  | X               | X               | X               | X               | X               | X               | X               |
| Depression Screener (PHQ-9)     | X               | X               | X               | X               | X               | X               | X               |
| Smoking Status                  | X               | X               | X               | X               | X               | X               | X               |
| CO Assessment of Smoking and Weight | X               | X               | X               | X               | X               | X               | X               |
| Wisconsin Dependence Development Scale | X               |                |                |                |                |                |                  |
| On-going EMA data collection    | X               | X               | X               |                |                |                |                  |
| Interventions                   |                |                |                |                |                |                |                  |
| AE/Safety assessment            | X               | X               | X               |                |                |                |                  |
| Counseling (in minutes)         | 20              | 20              | 20              | 10             | 10             | 10             |                  |
| Adherence assessment            | X               | X               | X               |                |                |                |                  |
| Tobacco, nicotine and other treatment assessment | X               | X               | X               |                |                |                |                  |
| Medication Distribution         | X               | X               | X               |                |                |                |                  |
| **Time Required for Each Visit (in minutes)** | 45          | 45             | 45             | 35             | 15             | 35             | 10             | 15             |

Cohort 2: Up to 1200 participants will be recruited via media recruitment methods (i.e., TV, radio, newspaper, and earned media) from Madison and Milwaukee, WI. Additionally, we will proactively ask current participants in this study to recruit their friends with approved flyers. We will also proactively invite those who have been enrolled in our past studies (if they are still smoking) and encouraged them to recruit friends by passing on information about the study so that interested friends can initiate contact with the study team (i.e. subjects won't be asked to
provide contact information for friends). Interested smokers will call the study phone number in the advertisements. Study staff will return smokers’ calls and screen them for eligibility. Potentially eligible participants will be scheduled to attend a group orientation session.

**Inclusion/Exclusion**

Long-term health outcomes study: There are no inclusion/exclusion criteria beyond being willing to engage in the study procedures. All Cohort 1 and Cohort 2 participants will be eligible for the long-term health outcomes study.

Comparative effectiveness trial: Participants in the must: smoke 5 or more cigarettes per day, be ≥18 years old, be able to read and write English, desire to quit smoking but not be currently engaged in cessation treatment, willing to use the nicotine patch or nicotine lozenge or varenicline, have reliable phone access, can get to the office and, if female, must not be pregnant (assessed via self-report) and must be willing to use an acceptable birth control method during the treatment period of the cessation trial. Potential participants will be excluded if they report: end-stage renal disease with hemodialysis; prior suicide attempts within the last 5 years or current suicidal ideation; diagnosis of and/or treatment for schizophrenia; other psychotic disorders or bipolar disorder within the last 10 years; current PHQ-9 score indicative of moderately severe depression; severe untreated hypertension >200/100 mmHg; currently taking Wellbutrin, Zyban or bupropion; hospitalized for a stroke, heart attack, congestive heart failure or diabetes within the last year; have an exclusionary incidental finding (see Table 4 below); used pipe tobacco, cigars, snuff or chew more than twice in the past week; are unwilling to stop using electronic cigarettes for the duration of the study treatment. Participants must also biochemically confirm their smoking status via exhaled CO (CO <4 ppm will be excluded). Some of these are exclusionary because of an elevated risk for suicidal ideation/behavior106 and other safety concerns regarding varenicline.

Alternative treatment: In addition to the comparative effectiveness trial (CET), we are offering nicotine replacement treatment to participants who are interested in quitting but are not eligible to be in the CET, due to safety criteria exclusively related to varenicline use. Participants will be randomized to receive either nicotine patch alone or nicotine patch + nicotine lozenge (or to receive only one NRT if they are not able to use both) if they: smoke 5 or more cigarettes per day, are ≥18 years old, are able to read and write English, can get to the office, desire to quit smoking but not be currently engaged in cessation treatment, are willing to use the nicotine patch and nicotine lozenge, have reliable phone access, and, if female, are not pregnant (assessed via self-report) and are willing to use an acceptable birth control method during the treatment period of the cessation trial. Potential participants will be excluded if they report: currently taking Wellbutrin, Zyban or bupropion; hospitalization for a stroke, heart attack, congestive heart failure or diabetes within the last year; use of pipe tobacco, cigars, snuff or chew more than twice in the past week; are unwilling to stop using electronic cigarettes for the duration of the study treatment; and have an exhaled CO of <4 ppm. This treatment will include the nicotine patch and/or the nicotine lozenge and the same counseling intervention provided in the CET.

Cohort 1 participants who use of pipe tobacco, cigars, snuff or chew more than twice in the past week; are unwilling to stop using electronic cigarettes for the duration of the study treatment; are currently taking Wellbutrin, Zyban or bupropion will only be offered the patch only (or lozenge only if they cannot take the patch) and counseling intervention if they are still interested in smoking cessation treatment.
Cohort 1 participants who are unwilling to use the patch, lozenge and varenicline, smoke fewer than 5 cigarettes per day, are unwilling to discontinue their own form of nicotine replacement, are pregnant or are unwilling to use an acceptable method of birth control, or were hospitalized for any of the following: a stroke, heart attack, congestive heart failure, or diabetes will only be offered the counseling intervention if they are still interested in smoking cessation treatment. Participants receiving alternative treatments will not be included in the CET analyses. However, data from these participants will provide additional quitters for the long-term health study and will allow us to make additional inferences about combination NRT vs. patch alone.

Cohort 1 individuals only willing to participate in the one-day health assessment will not be required to complete an inclusion/exclusion interview.

Study Visits and Phone Contacts

**Baseline – Orientation & Visits 1 & 2.** At the Orientation session Cohort 2 participants will have the study explained, will provide written informed consent and will then complete self-report assessments (see Table 1). To reduce data collection errors, participants will enter data directly into the computer using Qualtrics™ (Qualtrics, Inc., 2010), a computerized assessment delivery resource with built-in quality assurance and security features. Databases will not permit skipped or out-of-range values. Data will be stored securely and accessed in accord with all regulations and recommendations of the UW School of Medicine and Public Health. At Visit 1 Cohort 2 participants will complete the assessments listed in Table 1. They will also be trained to use the pedometer, will wear the pedometer over the subsequent week, and return it at Visit 2. At Visit 2 participants will complete the assessments in Table 1, most of which are CVD tests such as carotid ultrasonography, arterial tonometry, and the treadmill stress test (in Madison only). Participants will also receive smoking cessation counseling and study medication, along with instructions for how to use the medication. Cohort 1 participants will only have a Visit 1 and all assessments and informed consent will be completed at that visit (see Table 1).

**Visits 2a-2e and Call 1.** Participants who are enrolled in the CET or alternative treatment will complete visits 2a-2e. At Visits 2a-2e, participants will complete minimal assessments (see Table 2) and will receive both counseling and study medication. During Call 1 participants will receive cessation counseling. Only AE’s will be assessed on this call, there will be no other study assessments (See Table 2).

**Follow-up calls.** All participants will be contacted at Weeks 26 and 52 to assess smoking status. CET participants will also be asked about withdrawal symptoms and affect and will have an additional call with similar assessments at Week 38.

**Years 1 and 3 – Visits 3, 4 and 5.** Visit 3 will take place ~1 year after enrollment and Visits 4 and 5 will take place ~3 years after enrollment. Self-reported and biochemically confirmed smoking status will be assessed via exhaled CO. Participants will also complete the assessments as listed for these visits in Table 1.

**Year 2 – Call 3.** At Year 2 participants will be contacted to assess smoking status and collect updated contact information.

**Phone Assessments.** These will occur every 6 months: e.g., at months 6, 18, 30, 42 & 48. No calls will be made at 12, 24, and 36 because of the annual in-person Visits 3-5 (Table 1). The 42- and 48-month calls will be delivered only to those participants recruited early enough in the study, allowing for more than 3 years of data collection. We will gather all data possible across time, even if it results in differential data collection across participants because our
analytical procedures can model time as a continuous dimension. If participants report not smoking at the 6-month phone call, they will be asked to attend an in-person clinic visit to measure their exhaled CO level and biochemically confirm abstinence.

For consented Cohort 1 and Cohort 2 WSHS2 participants who we are not able to reach using contact information obtained at the baseline and subsequent visits, we will conduct internet searches based on name and date of birth to see if reliable new contact information can be obtained. If we are still unable to reach a participant due to unavailable or inaccurate contact information, we will call and/or send a letter to the alternate contacts specified by the participant, designated as a contact for this specific situation.

* Special procedure for participants who have experienced incarceration: While the study does not target incarcerated individuals, incarcerations during the period of study involvement are anticipated within the population being recruited for this study. The study has made the following procedural accommodations for this: During the treatment phase of the study, incarceration will result in disenrollment by the PI. If the individual contacts the office or has a follow-up appointment scheduled, they will be sent a letter from the PI indicating that they are no longer eligible to participate in the study. If, during a follow-up contacts for data collection or appointment scheduling, an individual is reported to have been incarcerated, their involvement in the study will be suspended. If the report indicates that the individual will be available in the community during the allowed period of contact that will be noted and calls will re-commence at that time. If there is no indication of when the individual will be available, that contact will be recorded as missed and attempts to contact will start again at the next scheduled contact. If the individual reports a previous period of incarceration, no study services need to be altered. Incarcerations will not be reported to the IRB unless the above protocol has not been followed.

**Questionnaire, Interview, and Behavioral Assessments.**

Participants will complete all questionnaires using Qualtrix, a computer program that allows participants to directly enter their answers into the computer. The questionnaires will then be scored by research staff as part of the analysis procedures. Questionnaires will assess constructs to be used to develop a treatment assignment algorithm for the smoking cessation pharmacotherapies, to characterize smoking dependence/heaviness/history, to characterize the sample, and to assess health risk (see Table 1 for timing). The surveys and citations providing psychometric support, are: 1) The Smoking History Questionnaire which provides accurate information about the lifetime smoking pattern, family smoking, and environmental smoke exposure; 2) The Brief Wisconsin Smoking Dependence Motives questionnaire (Brief WISDM), and the Fagerström Test of Nicotine Dependence (FTND), which assess nicotine dependence; 3) The Wisconsin Predicting Patients' Relapse questionnaire (WI-PREPARE) which assesses relapse risks; 4) The Wisconsin Smoking Withdrawal Scale (WSWS) which assesses smoking withdrawal; 5) a Quality of Life Inventory; 6) Alcohol use and problems assessed with a quantity-frequency measure for the past week and the Short Inventory of Problems (SIP-2R); 7) sleep apnea assessment; 8) 7-day pedometry records using a pedometer with a digital output and the 9) Wisconsin Dependence Development Scale (WDDS) to assess smoking dependence factors for participants who will have a quit attempt the following week. The WDDS has been developed as part of this research to assess novel components of tobacco dependence; its psychometrics and predictive validity will be investigated using the data from this study. Participants will also complete the National Comorbidity Survey–Revised (NCS-R-CIDI), a computer-assisted diagnostic interview for assessment of psychopathology and health history, symptoms, and utilization. Trained, bachelor’s-level staff will complete the CIDI interview. These measures have been used successfully in our previous research. Participants in the CET will also
complete the assessments of Hedonic Tone, Anxiety Sensitivity Index, and the Distress Tolerance Scale all of which have been shown to be reliable and valid. Finally, all participants will be asked a brief series of questions regarding menthol cigarette use.

**Ecological Momentary Assessments (EMA).** Participants in the CET and those receiving alternative treatments will provide daily ecological momentary assessment data (meaning data that has been collected “in the moment”) for 1 week pre-quit through 4 weeks post-quit using IVR technology developed by this research team. Participants will complete one morning prompt, one afternoon prompt and one evening prompt every day for the first 3 weeks and then every other day for the remaining 2 weeks of the EMA period. This time frame should capture pharmacotherapy effects, the peak of withdrawal\(^ {109-110}\) and the majority of lapse occurrences\(^ {111}\). Participants will be prompted every evening to assess smoking, medication usage, withdrawal\(^ {61}\), affect, cigarette liking/effects, stressors, cue exposure, motivation, and any significant adverse events/side effects. These assessments will capture potential treatment mechanisms/mediators, treatment effects, and variables related to safety/side effects. The EMA protocol allows researchers to collect real-time data with minimal burden to participants (≤5 min/call) and yields high completion rates (e.g., ≈80%\(^ {58}\)).

**Follow-up Assessment for CET and Alternative Treatment Participants.** Blinded follow-up phone assessments will assess continuous and point-prevalence abstinence, use of other tobacco products, electronic cigarettes and cessation aids and new quit attempts, etc. at the follow-up phone calls (at 26, 38 and 52 weeks post quit) and at all yearly visits (see Table 2). Participants who report 7-day point prevalence abstinence at 6 months post-quit will be invited to come in for exhaled CO testing to biochemically confirm abstinence (standard at yearly visits).

**Physical Health Assays and Biomarkers: Rationale and Methods**

**Ultrasound carotid IMT and plaque assessment.** This well-accepted approach to evaluating atherosclerosis burden and arterial injury is a powerful predictor of future cardiovascular disease (CVD) events, such as CVD death, MI and stroke\(^ {60, 81}\). It will be used to assess change over time and will be performed by trained technicians using highly reproducible digital ultrasonography scanning, data transmission, and measurement techniques\(^ {19, 81, 82}\). The protocol will detect plaques in all carotid arterial segments, and measure mean and maximum CIMT of the far wall of each common carotid arterial segment\(^ {19, 81, 82}\). Ultrasound systems (Siemens Medical Systems CV70) and transducers are FDA-approved for clinical use and will undergo regular phantom evaluation and product maintenance. They are networked to the UW Atherosclerosis Imaging Research Program core lab (www.cvrc.wisc.edu/airp), which served as the Carotid Ultrasound Reading Center for the parent TTURC-2-2 study (Protocol #H-2004-0094 – Tobacco Dependence: Treatment and Outcomes, Subtitled: Pharmacotherapies: Efficacy, Mechanisms and Algorithms [Efficacy] AND Natural History of Smoking and Quitting: Longterm Outcomes [Longterm Outcomes]) and will be reading the data for the current study. These assessments will be made at baseline and after 3 years. Findings of clinical significance are uncommon in asymptomatic study participants, however those who have a carotid dissection will be notified immediately during the clinic visit and will receive an immediate referral (i.e., they will be sent directly from the research office to their physician’s office, a hospital, or urgent care). A follow-up letter documenting the information will be sent to the participant describing the findings. Reports also are provided for abnormalities detected during study procedures which require medical attention, but not on an emergency basis. An incidental finding form will be completed and sent to CTRI within 48 hours of the ultrasound testing. Notification of the study participant in writing, by CTRI staff, will occur within 1 week of receipt of the incidental findings form from the UW AIRP lab (see Carotid US Incidental Findings Form).
Incidental findings that will generate an incidental findings form include: 1) carotid peak systolic velocity (PSV) ≥ 130 cm/s; 2) visual appearance of ≥60% stenosis; 3) carotid artery occlusion; 4) carotid artery dissection; 5) thyroid mass or cyst ≥ 1 cm; 6) other, i.e. abnormal cervical lymph node, etc.; 7) blood pressure ≥160/100 mmHg; and 8) systolic blood pressure difference of ≥ 20 mmHg between the right and left arms. See Table 4 below for the list of findings that are exclusionary for the CET.

Arterial tonometry to assess aortic stiffness and central aortic BPs. Smoking causes endothelial dysfunction\textsuperscript{18} and its related adverse hemodynamic effects, including increased arterial stiffness\textsuperscript{27, 83}, which may link smoking with higher rates of hypertension\textsuperscript{84}. Arterial stiffness and wave reflections are important determinants of aging and smoking-related increases in BP\textsuperscript{27, 85} and are affected by traditional CVD risk factors. Accordingly, measures of arterial stiffness, including the effects of wave reflections on central and peripheral BPs, are important predictors of incident MI and stroke\textsuperscript{27, 85}. No study has longitudinally evaluated the effects of continued smoking and cessation on arterial stiffness and wave reflections\textsuperscript{27, 85, 86}. A recent review concluded that "the effect of smoking discontinuation on arterial stiffness remains to be established by prospective smoking cessation trials"\textsuperscript{27}. For this measure, and new to this research proposal, we will measure carotid-femoral pulse wave velocity (PWV), the "gold standard" measurement of arterial stiffness\textsuperscript{85}, by applanation tonometry using an Atcor Sphymacor Px system. This device has FDA 510k clearance. PWV has the strongest epidemiological evidence of predictive value for CVD events\textsuperscript{85}. We have performed it in large cohorts\textsuperscript{87}. We also will measure aortic augmentation index (normalized to a heart rate of 75 bpm) by tonometry of the radial artery and application of a validated generalized transfer function to estimate central aortic pressures\textsuperscript{87}. These assessments will be made at baseline and after 3 years and will help characterize the pathophysiology of arterial changes due to cessation vs. continued smoking. We will link previously acquired endothelial function data with arterial stiffness, permitting the first-in-human investigation of these measures in smokers across time\textsuperscript{18}. This is a painless test with no physical risks. Palpation and tonometry of the femoral artery may be embarrassing to some participants. If so, it will be omitted at the subjects’ request. No incidental findings of clinical significance are expected from this procedure.

Treadmill stress testing. Parameters measured during treadmill stress testing such as peak exercise capacity, heart rate recovery, hemodynamic changes, and inducible ischemia are predictive of all-cause mortality, CVD mortality, and incident CVD events\textsuperscript{88}. Less is known about the predictive value of stress testing parameters and how they mechanistically relate to atherosclerosis and arterial function in smokers. We believe that no prior studies have: 1) evaluated heart rate recovery or the time course of improvement of exercise capacity amongst successful abstainers; 2) examined stress testing parameters in women who smoke vs. successfully quit; or 3) mechanistically tied changes in exercise parameters with arterial function and injury. Thus, treadmill stress testing in this study will provide unique physiological and mechanistic data regarding CVD and CVD risk amongst smokers, especially female smokers.

We will use the same methods used previously in our parent cohort study (Protocol # H-2004-0094). Participants will undergo a fasting treadmill stress ECG test using a modified Balke protocol (where patients walk on the treadmill and then the researcher gradually increases the speed and incline of the treadmill), to determine peak METs (the metabolic equivalent oxygen uptake estimate from peak workload), maximum heart rate increase, heart rate reserve, maximum rate-pressure product, heart rate recovery, inducibility of arrhythmias (including PVCs/minute), and inducibility of ischemia. Incidental findings on this test will result in participants being moved from the CET to an alternative treatment arm. Evaluations will be performed on Madison participants only at the Atherosclerosis Imaging Research lab located at...
the UW Hospital only at baseline and after 3 years. All studies will be performed by a certified
exercise physiologist, under supervision of Patrick E. McBride, MD or James H. Stein, MD. The
exercise physiologist will assess self-report indices, blood pressure assessment, resting 12-lead
ECG and carotid ultrasound and tonometry results prior to the exercise treadmill test (ETT) for
the presence of any conditions that preclude safely conducting the stress test. Subjects with the
following conditions will not be permitted to have ETT: progressive angina pectoris, including
but not limited to nocturnal angina; uncontrolled symptomatic heart failure; severe or suspected
severe aortic stenosis; acute myocarditis or pericarditis; severe dyspnea, murmur suggestive of
significant, aortic stenosis, acute infection (test and enrollment may be re-scheduled); severe
untreated hypertension >200/100 mmHg (test and enrollment may be re-scheduled). The ETT
is performed according to the standards from the American Heart Association and the American
College of Sports Medicine92, 93 and the results are reviewed immediately by certified exercise
physiologist or MD. If any incidental findings are identified, the ETT recordings and results are
brought to the attention of Dr. Patrick McBride, Dr. James Stein, or his back-up designee
following standard lab operating procedures. An incidental finding form will be completed and
returned to CTRI within 48 hours of study completion (see ETT Incidental Findings Form).
Incidental findings include: atrial fibrillation; Mobitz II 2nd degree heart block; 3rd degree heart
block; bradycardia - heart rate < 40 bpm; tachycardia - heart rate > 120 bpm; ventricular
tachycardia; Q waves myocardial infarction; ST changes highly suggestive of ischemia; acute
ST elevation myocardial infarction; left bundle branch block; right bundle branch block; long QT
time interval - QTc >= 480 msec. Conditions requiring an alert will be brought immediately to the
supervising MD’s attention and these include: 3rd degree heart block; acute ST elevation
myocardial infarction ventricular tachycardia, probable ischemia with ST depression >1.5 mm
(uupsloping or above baseline abnormality) or >1.0 mm (horizontal or downsloping) mm in 2
contiguous leads; acute ST elevation myocardial infarction; atrial fibrillation; Mobitz II 2nd degree
heart block; 3rd degree heart block; ventricular tachycardia (>3 consecutive beats); sustained
supraventricular tachycardia (>30 consecutive beats); excessive PVCs (>7/minute in any
stage); hypotensive blood pressure response to exercise (>10 mmHg); hypertensive blood
pressure response to exercise (>200/100 mmHg); severe dyspnea in the absence of ECG
ischemic changes (later participation not precluded if determined to not be cardiac in origin);
severe angina pectoris in the absence of ECG ischemic changes (later participation not
precluded if determined to not be cardiac in origin). See Table 4 below for the list of findings
that are exclusionary for the CET.

12-lead ECG. Using parent cohort (Protocol # H-2004-0094) methods54, ECGs will help
identify myocardial infarction, cardiac chamber enlargement, and conduction system/rhythm
abnormalities. ECG findings will be integrated with CVD event ascertainment and biomarker
data to identify individuals at increased CVD risk. ECGs will be obtained at baseline and after 3
years at both the Atherosclerosis Imaging Research center and at the CTRI Milwaukee site.
After the ECG is performed, it will be reviewed by Dr. Adam Gepner or his designee within 24
hours. If any incidental findings are identified, the ECG should be brought to attention of Dr.
James Stein or Dr. Richard Page, or their back-up designee, following standard lab operating
procedures. Immediate alerts should prompt contact of Dr. Gepner or Stein (Madison) or Dr.
Thomas Jackson (Milwaukee) or their designees. Immediate alerts almost always will lead to
the patient being sent for urgent medical attention. The incidental finding form will be completed
and returned to CTRI within 48 hours of study completion (see ECG Incidental Findings Form).
Incidental findings include: atrial fibrillation; Mobitz II 2nd degree block; 3rd degree heart block;
bradycardia - heart rate < 40 bpm; tachycardia - heart rate > 120 bpm; ventricular tachycardia;
Q wave myocardial infarction; ST changes highly suggestive of ischemia; acute ST elevation
myocardial infarction; left bundle branch block; long QT interval - QTc >= 480 msec. Detection
of a clinically relevant ECG abnormality will most often result in exclusion of the subject from the
randomized clinical trial component of this study. Other abnormalities will not affect participation. It is important to note that the automatic reading/diagnoses generated by the computer will be ignored and considered to be, by definition, inaccurate. Only physician readings are considered valid for this study. See Table 4 below for the list of findings that are exclusionary for the CET.

**Pulmonary Function Test.** Spirometry will be obtained in accordance with the American Thoracic Society guidelines and using the NHANES-III methods.85. Maneuvers are repeated a maximum of 8 times or until 3 acceptable spirograms are obtained while the patient is seated, wearing nose clips. The following variables will be recorded: FEV1, FVC, FEV1/FVC and FEF25-75. We expect that a subset of participants will have airway obstruction [FEV1/FVC ratio <0.70]. Participants with obstruction will be given 4 puffs of albuterol by metered-dose inhaler and spirometry repeated 15 minutes later to determine reversibility. Those who have post-bronchodilator FEV1/FVC ratio lower than 0.70 would meet the GOLD definition for chronic obstructive pulmonary disease (COPD). Pulmonary function tests will be conducted in both the Madison and Milwaukee sites by trained study personnel.

**Laboratory Tests.** These will be performed by experienced phlebotomists in CLIA-certified labs at the UW Hospital and Aurora Sinai Hospital with rigorous, core lab-level quality assurance procedures. Participants will have fasted and not smoked for at least 12 hours prior to Visits 2 and 3. Labs will include assays associated with CVD risk, including lipids, glucose, insulin, hemoglobin A1C, hsCRP, CBC (for WBC count), fibrinogen, D-dimer, and hsCRP, myeloperoxidase, and urinary F2 Isoprostanes. Blood will be stored for DNA extraction. Note: A full blood/urine collection and shipping protocol/procedure is uploaded separately with this protocol. This shows the amount of blood or urine collected by the Aurora and UW labs, type of tube or container, processing, shipping and storage procedures and timeframes for the labs collecting and the labs processing and providing data. Sample processing will occur at UW and Aurora labs, as well as Cleveland Heart Lab in accord with this protocol. Samples will be processed in less than 2 weeks following receipt (generally much less time). No samples will be stored beyond the point of providing data required by the study. Samples will be identified in the collection labs by name, study id, date of draw and date of birth. Samples will be transmitted to external labs without names but with other identifiers (draw date and date of birth) in order to ensure back-up identification of samples that might have had a problem with a data field. Analytic results will be securely transferred by all the labs to UW-CTRI, generally in Excel spreadsheet format.

**Nicotine/Cotinine assessment.** At Visits 1 and 4 (baseline and Year 3), participants will provide a urine sample to assess nicotine/cotinine levels, which can be used to estimate smoking heaviness and environmental smoke exposure, and for proteomic/metabolonomic analyses. This urine sample is separate from the sample collected at Visits 2 and 3 because it requires the person to have smoked as normal prior to the sample collection. Nicotine/cotinine levels will be detected using a TobacAlert or NicCheck tests; TobacAlert will be used for participants who report no smoking in the last 7 days and the NicCheck tests will be used for those who report smoking in the last 7 days. This differential use of test kits is based on the fact that TobacAlert is more sensitive to low levels of cotinine whereas NicCheck has greater sensitivity at higher levels, consistent with someone who is smoking regularly. Trained study staff at UW-CTRI will collect the participant’s urine and follow procedures according to TobacAlert/NicCheck directions to get a test reading within the same day. All samples and test results will be labeled with the date of collection and the subject’s numerical ID. Urine will be disposed of after nicotine/cotinine levels are read and recorded. (See the "WHS2 Cotinine Protocol " for more specific details and procedures)
DNA assessments. Samples for DNA analysis will only be taken from those providing consent for this. If the initial sample has an insufficient yield of DNA, we will ask the participant for an additional sample at their Year 1 follow up appointment (or at their Year 3 visit if they do not attend the Year 1 visit). This second sample will be collected at the time when blood is being collected for other assays (i.e., this will not an additional venipuncture). Consent for this second sample will be collected using the consent form addendum (if the original consent form was already signed at a past baseline appointment) or the newer version of the consent form. As outlined in the blood/urine collection protocol, DNA samples will be processed at the UW Biotechnology Center and stored until shipped in batches to Washington University. Banking will occur at Washington University in St. Louis within a genetics research facility operated by Laura Beirut. In this facility samples are stored with identifiers that do not include any HIPAA identifiers that can be connected back to the study other than the study ID, which allows connecting additional data secured from participants at later visits. 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 by Washington University researchers to a 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. We will apply for separate funding to conduct genotyping. This is the approach that we used in the parent TTURC-2 study where we obtained NIDA funding for a GWAS.

If funding is obtained for the additional DNA analysis, Dr. Neal Benowitz will also collaborate with us on conducting genotyping analyses. We are members (with Dr. Benowitz at the University of California, San Francisco) of the NIH Pharmacogenetics of Nicotine Addiction Treatment Consortium (PNAT) and already have contributed both DNA samples from the parent cohort. Using DNA analysis results from Washington University, we intend ultimately to test associations with nicotine dependence, smoking cessation success, pharmacogenetics of smoking cessation (for treatment matching), and CVD disease biomarkers (e.g., the 930A/G CYBA gene polymorphism, the ε5δ4α3 nicotinic receptor haplotypes97, 98). Note: Dr. Benowitz will submit a separate IRB application to his institution and we will verify approval prior to providing any data.

Note: Participants can withdraw their DNA by request to the study PI at any point.

Methods to Obtain Medical and Death Records

A secondary, goal of this research is to track disease endpoints. Medical and death records will be reviewed to assess important CVD (i.e., coronary death, myocardial infarction, significant arrhythmias, revascularization procedures), pulmonary (i.e., chronic obstructive pulmonary disease and pneumonia) and oncologic (i.e., cancers) outcomes. We will obtain consent from both continuing and new participants to obtain death certificate information and all hospitalization records from health care entities to establish causes of death, hospitalization, and to identify relevant medical intervention (e.g., revascularization). Record review will focus on three types of disease groups: CVD, pulmonary disease, and cancer. A standing cardiovascular, oncologic, and pulmonary adjudication committee will comprise: Dr. Stein (Cardiology), Dr. Page (Cardiology), and Dr. McBride (Family Medicine) to adjudicate all possible CVD-related events; Dr. Jarjour and Dr. Fiore to adjudicate all possible pulmonary-related events, and Dr. Traynor and Dr. McBride to adjudicate all possible oncology-related events. Record review will include the past and future funding periods for continuing patients.
Occurrences of clinical endpoints will be documented by a checklist completed by study personnel at annual visits and supplemented by interim reporting as needed, and will refer to appropriate ICD codes. Diagnoses will be supported by copies of death certificates, discharge summaries and face sheets. In the case of death (documented by death certificate), the underlying cause of death will be classified by the clinical events adjudication committee as due to: 1) Coronary Heart Disease, 2) Other Cardiovascular Disease, 3) Pulmonary Disease, 4) Neoplastic Disease, 5) Other Medical Causes, or 6) Non-Medical Causes. A National Death Index (NDI) Search will be performed near the end of the study to identify any undocumented deaths. We will also contact primary care physicians of patients who were lost to follow-up to determine cause of death.

Promoting Continued Experimental Participation

We will promote long-term participation via strategies that were effective in the parent study and in other research. We will: 1) provide free, state-of-the-art smoking cessation treatments; 2) send participants newsletters and birthday cards; 3) allow flexibility in scheduling; 4) provide the participant with a single, consistent liaison and counselor; 5) compensate participants for visits (up to $425 for Cohort 1 participants who enroll in the cessation trial and Cohort 2 participants; up to $325 for Cohort 1 participants who only enroll in the health outcomes study); 6) provide health data at baseline, Year 1 and Year 3 that will include: HDL, LDL and total cholesterol, blood sugar, pulmonary function test results, complete blood count test results, and stress test results (Madison participants only); and 7) ensure that research staff are culturally sensitive. Cohort 1 participants who are unwilling to enroll in the full 3-year study but willing to come for the one-day health assessment will receive $200 for completing that set of study procedures.

CET Interventions

Pharmacotherapy. Participants will be randomly assigned to receive varenicline (38.6% of sample), combination NRT (patch + nicotine lozenges; 38.7% of sample), or the nicotine patch (22.7% of sample), open label. Participants will receive 12 weeks of pharmacotherapy during the post-quit period (with an additional 7 day pre-quit run-in for varenicline) as per package instructions. For varenicline, participants will be asked to take a 0.5 mg pill once a day for the first 3 days and then increase to a 0.5 mg pill twice a day (8 hours apart) for 4 days. On the 8th day, their target quit date, they will increase to their target maintenance dose of a 1 mg pill twice daily. If participants report significant adverse events such as nausea, a dose reduction to two 0.5 mg doses per day will be advised. Combination NRT (patch + nicotine lozenges) will be implemented as in our previous successful studies, with participants starting on the morning of their assigned quit day. Participants will receive 12 weeks NRT. Patch dosing will be 8 weeks of 21 mg, then 2 weeks of 14 mg, then 2 weeks of 7 mg (those smoking 5-10 cigs/day will receive reduced patch dosing). In addition, participants will be given 2 mg or 4 mg lozenges based on morning smoking latency, and will be given package insert use instructions. They will be urged to use at least 5 pieces/day, unless this amount produces adverse effects. This level of use has been associated with prior success using combination NRT. Participants will receive medications, medication use and dosing instructions at treatment visits 2 – 2d. Participants will also be given a number to call with questions or in case of side effects/toxicity at these visits. Medication use will be assessed via EMA reports. We will monitor adverse events and self-harm likelihood at all Treatment Visits (2-2d) and at the Week 8 counseling phone call. Participants who report concerning symptoms will be interviewed by a study physician or clinical psychologist and medication will be discontinued if necessary. Participants will be referred, as needed, to the appropriate emergency medical or psychiatric services.
protocol is consistent with the 2009 FDA\cite{150} warning for varenicline, and will be used with all participants. In our studies using varenicline involving more than 500 participants, we have never had to discontinue medication due to psychiatric concerns\cite{115-119}.

**Counseling.** Participants will receive 5 in-person counseling sessions (10-20 minutes each) and 1 phone counseling session (10 minutes; Table 1) that conform to the PHS Clinical Practice Guideline recommendations for an intensive counseling intervention (motivational, supportive, and skill training elements\cite{29}). Counselors will be bachelors-level health educators supervised by licensed psychologists. Quality/fidelity assurance strategies, developed in our prior work\cite{31,58,59,122} will include intensive training in counseling techniques and ethical conduct (20 hours over 2 weeks), practice sessions, regular supervision including review of audiotapes, and quarterly team meetings to discuss safety, confidentiality, and counseling fidelity. Participants will be paired with a single counselor.

Participants in the alternative treatment arms will be randomized to receive either nicotine patch or nicotine patch + nicotine lozenge. These treatments are identical to those listed above and will be administered using the same treatment protocol used with CET participants. If Cohort 1 participants are unwilling or unable to use both the nicotine patch and the nicotine lozenge, they will be asked to use whichever medication is feasible, or, in some cases (e.g., pregnancy) will receive no medication. All participants in the alternative treatment arms will receive the same counseling as those in the CET arms.

**Analytical Plan**

Three major types of effects will be tested. The 1\textsuperscript{st} is the effects of the CET cessation treatments on cessation and related outcomes (e.g., withdrawal severity). The 2\textsuperscript{nd} concerns the long-term effects of cessation vs. continued smoking (e.g., due to cessation failure) on health (biochemical, physiological, and imaging biomarkers) and psychosocial outcomes. This type of analysis will also use baseline smoker characteristics to identify those at greatest risk for progression on biomarkers and risk factors due to continued smoking; predictors will identify those most likely to benefit from cessation. These health outcome analyses will examine effects obtained within this funding period (e.g., effects of cessation comparing CET smokers vs. quitters within the 3 year follow-up) and effects obtained across the previous funding period (parent TTURC-2) and the time span of the current proposal, combined. The latter will examine the effects of abstinence vs. smoking using up to 9 years of data. Secondary analyses will relate cessation vs. continued smoking and biomarkers, with clinical endpoints such as death, CVD, etc. Below we provide examples of some of the analyses that would be used to address these types of effects. Careful inspection of the data (e.g., missingness, distributional properties) may influence analytic strategies.

**Smoking cessation (CET) effects.** In these analyses, each experimental condition is compared with the nicotine patch control condition, and then with each other (see Primary Aim 1). Dichotomous outcome data (point-prevalence and prolonged abstinence) at the end of treatment, and at 6 months, and 12 months post-quit, will be tested using logistic regression models. These data will also be jointly analyzed as a multivariate outcome using generalized estimating equations\cite{123,124}, which account for the correlational structure across repeated observations\cite{125}. Survival analysis will be used to analyze key milestones, including time to lapse, time to relapse, and lapse-relapse latency\cite{126,127}. We also will compare pharmacotherapy side effects, and suppression of withdrawal symptoms. Multilevel growth models will be used in the latter analyses as in our previous research\cite{62,59,128}. In each of these analyses, we will conduct and report contrasts of treatment effects both with and without covariates. Covariates will include sex, age, prior use of cessation medications, study site, dependence level,
expectations of success, depression history, and new vs. continuing status. Thus, we will test for cohort effects related to the new group of smokers added to the study. We will also collaborate with The Methodology Center at Penn State University to perform statistical analysis of the ecological momentary data using their innovative time-varying effects models as well as other novel methodological approaches to better understand the withdrawal process and the influence of treatment. They will receive coded, de-identified subject level data including demographics, tobacco dependence, IVR and outcome. Their work will be overseen by the UW IRB. Finally, CRUISE decision tree models will be used to generate algorithms to optimize medication assignment. Tested models will control for experimentwise error via families of related tests via the Holm correction and via significant omnibus models.

Effects of abstinence vs. continued smoking on health and psychosocial outcomes. An example of this would test the effects of smoking cessation on change in CIMT or plaque presence over the 3-year follow-up interval in the proposed work (see Primary Aim 2). Here, smoking status could be coded as the proportion of the measurement period that is smoke-free (via time-line follow-back smoking data) or modeled as cotinine levels. Residualized change scores will be modeled such that baseline CIMT scores will be entered as a covariate, smoking status as the chief predictor of interest, with follow-up CIMT scores as the outcome. Control variables would include: age, sex, ethnicity, second-hand smoke (from self-report and cotinine levels), and smoking burden (e.g., baseline pack-years, CO, serum cotinine). The relative impact of smoking would be contrasted with other risk factors that will be entered as covariates (e.g., dietary components, BMI/waist circumference, exercise/activity, weight gain, serum lipids, BP). The interrelations of all these risk factors and moderation effects will be examined via correlational analyses. If high levels of multicollinearity are present, data reduction techniques (e.g., principal component scores) may be used in place of the original covariates. The effects of cessation vs. continued smoking can be analyzed in all participants for up to 8-9 years of data, gathered both in continuing and new participants. Dynamic factor models can be used for multiple dependent variables with multiple waves of collection (e.g., BMI) and longitudinal panel methods for a small number of data points (e.g., for the 4 CIMT measures across the total assessment period). Because time-line follow-back data will capture monthly smoking status over the 8-9 year period and because smokers will quit (and relapse) throughout this period (not just during formal CETs), we will have the opportunity to investigate patterns of growth/change in relation to smoking status change. The consistency of patterns observed across smokers and the nature of the outcome(s) studied may necessitate different analytic strategies. For example, we might expect timepoint-to-timepoint fluctuations in physiological measures (e.g., BMI, CIMT) that will be better captured in a time series analysis (as in dynamic factor analysis), while outcomes such as blood pressure may be more amenable to growth modeling (e.g., piece-wise growth models). We will explore the distributional properties and need for transformation of CIMT and other measures. Growth mixture models, which we have used in past research, can identify subgroups corresponding to distinct patterns of growth in longitudinal data and can be used to estimate the prevalence of the patterns and to relate the patterns to covariates. Such models do not require the same number of data points or timing of assessments, meaning that participants from the parent study and the newly recruited participants can be combined in such analyses (with terms used to reflect cohort effects for common time periods). Multiple regression models can be used to index change from baseline CIMT to last CIMT value along the lines of the residualized change analysis described above (with coding for inter-measure interval). We will also conduct formal mediation analyses to link change in specific biomarkers with occurrence of CHD outcomes or other endpoints. Tested models will also examine moderators of change (e.g., sex, age, weight status, ethnicity; cf. ). The moderation of the effects of smoking cessation vs. continued smoking on progression of biomarker status will suggest individual difference factors (sex, smoking burden,
lipid values, BMI, etc.) that predict heightened vulnerability to the effects of continued smoking (see Primary Aim 3). These predictors of risk will be used to construct best-fitting models for risk progression and will also be used in CRUISE decision tree models that identify those at greatest risk for biomarker progression as a function of smoking. We believe our temporal sampling of biomarkers will be satisfactory given evidence regarding biomarker lability/stability over time (e.g., see our previous findings\textsuperscript{17, 139}).

**Assessing the predictive validity of biomarkers and identifying optimal predictive models of clinical endpoints.** These analyses will address the second of the secondary aims; i.e., to identify which of the measured markers provides the best prediction of important clinical endpoints such as death, MI, revascularization, and diabetes mellitus. The analytic steps will be to assess appropriate modeling strategies (e.g., linearity\textsuperscript{80}), examine intercorrelations of biomarkers with one another in cross-sectional analyses, and then regress change in these measures across common time periods (revealing for instance, the extent to which change in arterial stiffness is related to change in lipoproteins, blood pressure, and CIMT\textsuperscript{27}), then build best-fitting logistic regression models\textsuperscript{140} or survival models\textsuperscript{141} depending on the nature of the clinical endpoint. Models can combine new and continuing participants in analyses that span up to 9 years of data (with proper coding of cohort and time). Finally, CRUISE decision tree models\textsuperscript{142-145} will be computed in which multiple relevant variables (e.g., age, sex, smoking burden, biomarker change, diet, exercise, genetic factors, menthol use) are entered into models. Decision tree models will complement the logistic models in predictions of binary outcomes and are ideal for testing models with multiple predictors that may have collinear effects and will avoid model misspecification because the algorithm generates the optimal decision tree taking all included variables into account (see\textsuperscript{41} for an example from our own research).

**Power for Two Primary Outcomes**

**6-month point-prevalent abstinence in the CET.** Based upon considerable evidence and experience\textsuperscript{26, 31}, we hypothesize a 6-month abstinence rate of 24\% in the nicotine patch control condition (N=227) and abstinence rates > 34\% for both varenicline and the combination NRT (N=387 each)\textsuperscript{29, 116}. Power analysis (2-tailed test, α=.05) between the patch control and either of the other two conditions yields power=0.80 (24\% vs. 35\%). We believe that a difference in cessation outcome of 10\% is clinically significant, so we have powered this study to show a difference between the varenicline and combination NRT treatments with one having an abstinence rate of 35\% and the other of 44\% power = 0.71. Based upon other data\textsuperscript{26, 31}, we fully expect both varenicline and the combination NRT conditions to differ significantly from the patch control condition, and the combination NRT condition may be superior to varenicline alone\textsuperscript{26}.

The greater number of participants assigned to the combination NRT and varenicline conditions reflects the possibly smaller difference in effect sizes between these conditions and the importance of distinguishing between them.

**Long-term smoking status and atherosclerotic progression.** To generate CIMT effect size estimates we used Atherosclerosis Risk in Communities Study (ARIC) data\textsuperscript{146} gathered using the same imaging protocol (for CCA) slated for the proposed work and used in the parent trial. We have demonstrated consistency between our data and the ARIC core lab data\textsuperscript{82}. Moreover, the ARIC smokers and smokers in the parent study are very similar in regard to age, smoking history, and even baseline CIMT (e.g., baseline mean CIMT in the parent and ARIC smokers were 0.70 and 0.66 mm, respectively; with slightly higher CIMTs in our study attributable to larger BMIs, 28.3 vs. 26.1). While the CET outcome analyses will use the intent-to-treat principle, attrition will affect the denominator in health outcome analyses. Our parent TTURC-2 study suggests that attrition will be ~20\% to the Year 3 Visits 5 & 6. Using a conservative 25\% attrition rate, we estimate that we will have 1575 participants at Health Care Visits 5 & 6. We expect...
higher rates of abstinence at these visits amongst those in the CET (30% at Year 3) than in TTURC-2 because the cessation interventions will be more effective and there will be no placebo control condition. Some stability in this rate will occur because new quitters will replace those that relapse by Year 3, meaning that we will have approximately 540 quitters over the course of the study, and 1260 continuing smokers (based upon a 30% 3-year abstinence rate in CET participants, and modest change in smoking status amongst continuing participants with long-standing smoking/abstinence dispositions). Based on ARIC data, a primary hypothesis (tested without alpha protection) is that the CIMT of continuing smokers will progress at a rate of about 43 μm/3 years and former smokers will progress at a rate of about 35 μm/3 years for an absolute difference of 7-8 μm/3 years, a relative decrease (treatment effect) of 17%. Assuming an SD=2.6 μm (for the change score from multivariable ARIC models with suitable covariates), and assuming a similar difference with the projected N’s in this research, this yields an effect size >3, and power >0.90147, across a range of pre-to-post score correlations from 0.5-0.8. Such effects would be clinically meaningful (e.g., with regards to statin effects and association with clinical endpoints148). This ample power will allow us to test important interactions (e.g., with regards to hypertension and diabetes146).

A secondary aim of this proposal is to provide estimates of effect sizes for relations of biomarkers with clinical endpoints (e.g., MI, stroke). Given the sample size, there will be limited power for detecting such effects. However, obtained effect size estimates will suggest the relative predictive values of the different biomarkers, and power will increase as the longitudinal sample is tracked over time. There will be adequate power to detect a few clinical endpoint differences related to smoking status. For instance, as in other relevant trials (e.g., ALLHAT, ACCORD, SPRINT [as per Dave Reboussin, personal communication]) we will examine composite CVD outcomes (e.g., coronary death, MI, stroke, and hospitalizations for heart failure and unstable angina pectoris). It is difficult to extrapolate across trials since they differ in inclusion criteria, smoking rates, age and age range, recency (since CVD rates have decreased over time), and somewhat different event/composite definitions. However, examination of such trials yields composite event rates ranging from 5.9%/year (ALLHAT), and 3.4 %/year (ACCORD: SPRINT Appendix 3). As in the SPRINT trial, we estimate lower rates than ALLHAT and ACCORD (as a function of age and recency, but which may be countered by high smoking), and propose a rate averaging 3.0%/year across years amongst the continuing smokers over up to 8-9 years of observation (combining new and continuing smokers). We hypothesize a 30%/year reduction effect size as a function of cessation, a clinically valid level of reduction (e.g.,145). Using appropriate assumptions regarding accrual and other influences, and with α=0.05, and two-tailed tests, power >0.81 with conservative estimates of verifiable rates for 540 quitters over the course of the study, and 1260 continuing smokers. Power should be greater using continuous coding of smoking over follow-up time periods and coding of covariates such as cohort and sex.

Protection of Human Subjects

Risks to the Participants

Human Subjects Involvement and Characteristics: The 1800 CET participants will be individuals who smoke 5 or more cigarettes per day. The inclusion and exclusion criteria are detailed in Table 3 below. There will be no restriction based on gender or ethnicity but our prior recruitment shows that at least 15% will be African-American and about 58% will be female.

Table 3. Inclusion and exclusion criteria
Inclusion criteria

- 18 years of age or older
- End-stage renal disease with hemodialysis
- A daily smoker
- Prior suicide attempts within the last 5 years or current suicidal ideation
- Motivated to quit smoking
- Diagnosis of and/or treatment for schizophrenia, other psychotic disorders or bipolar disorder within the last 10 years
- Medically able and willing to use any of the smoking cessation medication treatments being tested
- Current PHQ-9 score indicative of moderately severe depression
- Not pregnant, trying to get pregnant or breastfeeding
- Severe hypertension >200/100 mmHg
- Able to read and write English
- Current PHQ-9 score indicative of moderately severe depression
- Willing to respond to ecological momentary assessment prompts (e.g., interactive voice response calls and other study activities)
- Planning to remain in the catchment area for at least 12 months
- Used pipe tobacco, cigars, snuff or chew more than twice in the past week
- If using e-cigarettes or nicotine replacement, willing to stop for the duration of study treatment

Self-report exclusion criteria

- End-stage renal disease with hemodialysis
- Prior suicide attempts within the last 5 years or current suicidal ideation
- Diagnosis of and/or treatment for schizophrenia, other psychotic disorders or bipolar disorder within the last 10 years
- Current PHQ-9 score indicative of moderately severe depression
- Able to read and write English
- Current PHQ-9 score indicative of moderately severe depression
- Smoking cessation medication treatments being tested
- Severe hypertension >200/100 mmHg
- Willing to respond to ecological momentary assessment prompts (e.g., interactive voice response calls and other study activities)
- Planning to remain in the catchment area for at least 12 months
- Used pipe tobacco, cigars, snuff or chew more than twice in the past week
- If using e-cigarettes or nicotine replacement, willing to stop for the duration of study treatment

*Participants who are ineligible for these reasons, may be eligible for alternative treatments, including randomization to patch or patch + lozenge treatment.

It should be noted that if any incidental findings arise in the course of the study health assessments (e.g., ultrasound, tonometry, ECG, exercise stress test; see Table 4 for potential incidental findings), the study cardiologist may assign those Cohort 1 participants to a non-randomized treatment group that will receive nicotine patch and the same counseling given to those in the randomized trial. Cohort 2 participants with the incidental findings in Table 4 will be excluded from the study and referred to the Wisconsin Tobacco Quit Line.

Table 4. Incidental findings that exclude participants from the CET*

<table>
<thead>
<tr>
<th>IMT/ Tonometry</th>
<th>ECG/Treadmill Stress Test</th>
<th>Self-report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid artery peak systolic velocity ≥ 130 cm/s</td>
<td>Mobitz II 2nd degree heart block</td>
<td>Progressive angina pectoris, including but not limited to nocturnal angina</td>
</tr>
<tr>
<td>Visual appearance of ≥ 60% carotid stenosis</td>
<td>3rd degree heart block</td>
<td>Uncontrolled symptomatic heart failure</td>
</tr>
<tr>
<td>Carotid artery occlusion</td>
<td>Bradycardia - heart rate &lt; 40 bpm</td>
<td>Severe or suspected severe aortic stenosis</td>
</tr>
<tr>
<td>Presence peripheral arterial disease (PAD), When we measure bilateral blood pressures during the tonometry test, if we find someone with a difference between right and left brachial</td>
<td>Tachycardia - heart rate &gt; 120 bpm; Q wave myocardial infarction</td>
<td>Acute myocarditis or pericarditis</td>
</tr>
</tbody>
</table>
BPs of more or equal to 20 mmHg we should exclude them for the study.

<table>
<thead>
<tr>
<th>Difference between right and left arm brachial blood pressures ≥ 20 mmHg</th>
<th>ST changes highly suggestive of ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>left bundle branch block</td>
<td></td>
</tr>
<tr>
<td>long QT interval - QTc &gt;= 480 msec</td>
<td></td>
</tr>
<tr>
<td>ventricular tachycardia</td>
<td></td>
</tr>
<tr>
<td>probable ischemia with ST depression &gt;1.5 mm [upsloping or above baseline abnormality] or &gt;1.0 mm [horizontal or downsloping] mm in 2 contiguous leads</td>
<td></td>
</tr>
<tr>
<td>acute ST elevation myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>ventricular tachycardia (&gt;3 consecutive beats)</td>
<td></td>
</tr>
<tr>
<td>sustained supraventricular tachycardia (&gt;30 consecutive beats)</td>
<td></td>
</tr>
<tr>
<td>excessive PVCs (&gt;7/minute in any stage)</td>
<td></td>
</tr>
<tr>
<td>hypotensive blood pressure response to exercise (&gt;10 mmHg)</td>
<td></td>
</tr>
<tr>
<td>hypertensive blood pressure response to exercise (&gt;200/100 mmHg)</td>
<td></td>
</tr>
<tr>
<td>severe dyspnea in the absence of ECG ischemic changes [later participation not precluded if determined to not be cardiac in origin]</td>
<td></td>
</tr>
<tr>
<td>severe angina pectoris in the absence of ECG ischemic changes [later participation not precluded if determined to not be cardiac in origin]</td>
<td></td>
</tr>
</tbody>
</table>

*Participants who are ineligible for these reasons, may be eligible for alternative treatments, including randomization to patch or patch + lozenge treatment.*
Table 5. Incidental findings that do NOT exclude participants from the CET

<table>
<thead>
<tr>
<th>Findings that will not exclude pts from the CET but for which we will send a letter:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid mass or cyst ≥1 cm</td>
</tr>
<tr>
<td>atrial fibrillation</td>
</tr>
<tr>
<td>Other, i.e. abnormal cervical lymph node, etc</td>
</tr>
<tr>
<td>Q waves myocardial infarction (non-acute)</td>
</tr>
<tr>
<td>Blood pressure ≥160/100 mmHg</td>
</tr>
</tbody>
</table>

Sources of Materials: Participants in this program 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, a wide range of physiologic and medical tests will be done that assess disease status or biomarkers thought to index disease risk. These will include blood tests, ultrasonography, arterial tonometry, electrocardiography, physical tests (e.g., pulmonary function and treadmill stress tests), and provision of biologic samples that will later be used for genetic and proteomic/metabolomic assays. Breath tests will be used to permit determination of carbon monoxide, and pedometers will be used to detect activity level. Health and death data will be collected from medical records and from the coroner’s office. Across the research, data will be derived from blood, urine, DNA, imaging, performance measures, breath, self-report, and medical/coroner records.

Potential Risks: Risks associated with this research are judged to be low. None of the medical, physiologic, self-report, or behavioral measures constitutes a significant risk. The treadmill stress electrocardiogram test does pose a low risk of a cardiac event; however, appropriate pre-screening in accordance with good clinical practice will be used to screen out individuals at high risk for a complication or injury during the stress test. The use of cessation medications poses a risk of side-effects. In particular, the combination NRT, which is approved by the FDA for smoking cessation, could produce an allergic skin reaction or systemic reaction to the adhesive in the nicotine patch. 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. In addition, current labeling for varenicline (FDA, 2009) includes a black box warning that 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. It should also be noted that 2 new FDA-sponsored studies found no increase in psychiatric hospitalization for neuropsychiatric events among smokers taking varenicline vs. those taking nicotine replacement therapy to quit smoking. Varenicline labeling also notes that some individuals with pre-existing psychiatric conditions may experience worsening of their conditions.

The FDA has also notified the public that varenicline may be associated with a small increased risk of certain cardiovascular adverse events in patients who have CVD. This safety information was added to the Warnings and Precautions section of the varenicline physician labeling. No specific guidance for additional screening or monitoring was provided, other than advising health care providers to “Weigh the known benefits of Chantix against the potential risks of its use in smokers with cardiovascular disease” and to “Counsel patients to seek medical attention if they experience new or worsening symptoms of cardiovascular disease while taking Chantix.” Per our protocol cardiologist and study PI Dr. James Stein and our protocol cardiology consultants (Dr. Patrick McBride and Dr. Richard Page), varenicline is
routinely used in clinical practice in patients with CVD. Screening patients for active CVD symptoms and review of an ECG for severe abnormalities suggestive of active heart disease would be considered good clinical practice. In this study, all subjects will have a 12-lead ECG performed and reviewed by a physician before they are allowed to enroll in the RCT portion of this study. They also will be queried by study personnel for the presence of anginal chest discomfort unexplained dyspnea (at rest or with exertion), or a recent overnight hospitalization for heart problems in the past 6 weeks. They will be advised to contact study personnel if they experience new or worsening symptoms of CVD (such as chest pain, dyspnea, or hospitalization for heart problems) while taking varenicline. Per Dr. Stein and our cardiology consultants, additional testing is not needed for safe clinical or research use of varenicline. However, we realize that we are acquiring research subject data that may indicate previously unknown increased CVD risk, such as severe carotid atherosclerosis or peripheral arterial disease (during the carotid ultrasound and arterial tonometry protocols performed at Madison and Milwaukee), or inducible myocardial ischemia or arrhythmias during stress testing (in Madison only). In the interest of protecting subject safety, if these abnormalities are found, subjects will be assigned to a non-randomized treatment arm (i.e., nicotine patch + counseling).

NRT risks are well-documented, given their wide-scale use and over-the-counter availability. The nicotine patch and nicotine lozenge are available over the counter. The nicotine patch has few side effects, but up to 50% of participants may have a local skin reaction, and rarely, individuals may have a systemic allergic reaction. The most likely side effects associated with the nicotine 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.

Blood draws can be painful and very rarely can lead to infection or fainting. In addition, there is always a remote, but existing, possibility that sensitive or personal information about a patient 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 in the past 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.

Adequacy of Protection Against Risks

Recruitment and Informed Consent: As in our previous research, new (cohort 2) participants will be recruited via advertisements in newspapers, radio, television, billboards, and other media. In addition, free media (e.g., press releases and conferences) will be utilized. 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 or, alternatively, the study registration web address (www.endcigs.com). That website will contain a brief version of the same information about the study and allow the person to enter a phone number and convenient time to receive a call. After calling this number, participants will undergo 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 that pharmacotherapy and counseling interventions will be studied. Participants will also be told that varenicline may worsen pre-existing psychiatric illness and about the small, increased risk for adverse cardiac events in patients who have cardiovascular disease. The cardiovascular protections are numerous, conservative, and are described above.
Individuals will then be screened for additional exclusion factors. After answering any participant questions about research participation and intervention, participants will be given a combined consent and HIPAA form to take home. Individuals will be encouraged to ask any further questions about the study protocol throughout the study.

Participants from the original Wisconsin Smokers’ Health Study (WSHS) will be mailed letters informing them of the new study, its goals, its requirements, and to encourage participation. We will then call all of the original WSHS participants to invite them to participate in the new study. Interested participants will be scheduled for an in-person visit where, after learning about the new study and providing written consent, they will complete the baseline assessment battery. If they are participating in the randomized control trial, the full procedures regarding drug related risks will be the same as the Cohort 2 description above. Those only participating in the health study will continue with that visit schedule, assuming they provide consent.

Protection Against Risk: As noted above, participants will be screened to ensure that they are medically and psychiatrically fit to take varenicline or NRT. Study participants will be closely monitored in accordance with current FDA recommendations as well as the consensus recommendations of the 2008 Guideline Panel, 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. In theory, the combination NRT could constitute a risk due to nicotine toxicity, but it has been used in numerous studies and clinical applications with minimal side effects (e.g., 29, 31, 39). We will take steps to ensure that all individuals receiving NRT are informed of signs of nicotine toxicity, and we will use a sliding dose schedule as a function of smoking heaviness to reduce exposing relatively light smokers to too much nicotine. We will recommend dosage/use alterations including stopping NRT treatment as per good clinical practice if the participant experiences symptoms of nicotine toxicity or other troublesome side effects once they begin medication treatment. Thus, we will take extraordinary care to ensure the safety of study participants.

Participants will be carefully monitored for changes in behavior, agitation, depressed mood, suicidal ideation, side effects, and suicidal behavior as well as changes in cardiac symptoms. 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. For all AEs and SAEs, study staff will take appropriate action to ensure the safety of the participant as follows: 1) Non-urgent AEs will be reported in a timely manner to study clinical staff (MDs and RNs); and 2) 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. In addition, participants will be given a telephone number in order 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. Individuals who report any significant mood change or suicidal ideation will be contacted immediately by a licensed psychologist or physician who will assess the level of risk and provide referrals as needed.

With respect to the treadmill stress electrocardiogram tests, participants will participate only if they do not have contraindications and are clinically stable. Participants will be screened prior to the test by trained exercise physiologists for absolute and relative contraindications to stress testing, using physician-reviewed protocols and good clinical practice operating procedures. Informed consent will be obtained. Twelve-lead ECGs, carotid ultrasounds, and medical history will be reviewed by trained technologists with physician back-up prior to the test to ensure that the participant does not have ECG or clinical contraindications to the test. Test termination criteria are also standard for stress testing, including the development of chest pain, >1 mm
horizontal or downsloping ST segment depression in standard leads and other usual ECG criteria in addition to clinical criteria including abnormal hemodynamics, serious arrhythmias, abnormal symptoms, significant dyspnea, or any other conditions placing the participant at risk.

The ETT is performed according to the standards from the American Heart Association and the American College of Sports Medicine following strict safety procedures. Studies are performed in the UW AIRP lab in the H6/3 module of the Clinical Science Center (CSC). All staff that perform stress tests are certified exercise physiologists, are Basic Cardiac Life Support (BCLS) certified, and trained to use an automated external defibrillator (AED). An AED, code blue crash cart, and dedicated phone line are in the stress testing suite. The UWHC Adult Blue CART or Medical Response teams can be called (2-0000) if needed. In addition to the supervising exercise physiologist, another person always is present to assist with subject safety and calling 2-0000 if needed. The results are reviewed immediately by a certified exercise physiologist or MD. If any incidental findings are identified, the ETT tracings and results are brought to the attention of Dr. Patrick McBride, Dr. James Stein, or his back-up designee following standard lab operating procedures. A "study physician on-call" will be designated each day, with an emergency back-up of the cardiology fellow on-call and CCU attending on-call always being available to assist if needed. SOPs are in place for emergency procedures and physician back-up. Procedures for this study are even more conservative and safer than in TTURC-2. No adverse effects from stress testing were observed in TTURC-2.

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 and these were implemented in 2009. 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 obtained a Certificate of Confidentiality, related to both the collection of genetic material and the collection of sensitive psychological and substance use information. No publications or presentations resulting from this research program will contain any identifying information about individual participants.

Participant data will be transmitted to other collaborators in accord with their role in the study as described in this protocol. The following confidentiality measures are in place for these data:

1. Only data directly relevant to the analysis will be sent and all data will contain the minimum amount of identifying information required to ensure that the analysis can be performed accurately. With the exception noted in the protocol above for transmission of blood samples (which will include a draw date and date of birth in order to ensure accuracy), the only personal identifier transmitted with any other data will be the study ID.

2. All collaborators will operate in compliance with HIPAA standards at their institutions, requiring all data and samples to be securely stored. Study data will be stored in secure
computers in files that are regularly backed up.

3. All data transfers are done through secure electronic transmission (FTP or other).

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 pharmacotherapy, both of which double a smoker’s odds of quitting. Also, participants can learn information about their health. As in our past research we will provide individuals with their test results and other information about their health because it is appropriate clinical practice and has been very influential in reducing attrition. Such information has included blood pressure, serum lipid values, and so on. Also, if a health issue of clinical significance arises (say, in the treadmill test), we will alert the participant to this so s/he can seek appropriate medical care. We will inform participants, though, that they cannot rely upon their health assessments to constitute a comprehensive physical health exam. Their research participation will not replace other appropriate health care. 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 in force when smokers are enrolled in the study as well as the consensus recommendations of the 2008 Guideline Panel. 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 NRT 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 is more effective for smoking cessation and which works better for which type of patient. Also, this research will produce valuable new information on the health risks of smoking and the mechanisms via which quitting enhances health. 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, to motivate smokers to stop smoking, and to identify smokers who are at greatest risk for negative consequences from their smoking. Such smokers can be targeted for both increased smoking cessation and preventive medical interventions.

Given the limited risks of varenicline and combination NRT, 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 and society.

Data and 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 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, the Scientist, Research Administrator and Principal Investigators will review the data on a regularly scheduled basis (typically biweekly) 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 lack of measurable benefit to study participants be determined, the CET will be stopped and all participants notified in a manner appropriate to the nature of the risk and/or lack of benefit.

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. Because this study involves pharmaceutical agents, if an SAE might be related to 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 AEs would include less serious problems that merit reporting 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 intervention 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 have developed plans for assuring data accuracy
and protocol compliance, which will be reviewed and approved by the Principal Investigators.

The plans includes data verification and protocol compliance checks performed electronically within the database in real time, reviewed by project site supervisors and shared by project administrative staff with the Research Director and PI's at least monthly. All protocol deviations are reviewed and analyzed for any need for training or other action. The Data Manager and Principal Investigators are 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 protocol deviations are reviewed and analyzed for any need for training or other action. The Data Manager and Principal Investigators are 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 (DSMC) 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 a 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. \textit{Every six months through July 2014, once in the first quarter of 2015 (end of all treatment) and then annually thereafter}, 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. James Sosman, Dr. Burke Richmond, and the PI's Dr. Fiore and Dr. Stein. Dr. Sosman is an Internist who has collaborated on clinical trials with UW-CTRI during the second round of TTURC funding. Dr. Richmond is an otolaryngologist who has served on independent DSMBs for Phase II and III trials involving a nicotine vaccine. Neither has direct involvement with any of the proposed research.


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NIHMSID:211104
