SCIENTIFIC PROTOCOL

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Title: UW Withdraw from Tobacco Study: Enhancing and Evaluating Tobacco Withdrawal Assessment Psychometrics and Validity

Specific Aims

Specific Aim 1: To enhance and evaluate the validity of a self-report assessment of tobacco withdrawal, the revised Wisconsin Smoking Withdrawal Scales-2 (long: WSWS2-L; brief: WSWS2-B), in terms of their sensitivity to smoking abstinence in initially unmedicated individuals making a quit smoking attempt.

Specific Aim 2: To compare the validity of the WSWS2-L and the WSWS2-B with alternative withdrawal scales on the bases of psychometric criteria.

Specific Aim 3: To determine factors that most accurately predict withdrawal severity (peak, average, variability, and duration), including contextual factors, personality factors, lifestyle factors, pharmacologic factors, precessation symptomatology, reward sensitivity/response, and affective processing dimensions.

Significance

The Wisconsin Smoking Withdrawal Scale (WSWS) was developed over two decades ago to provide researchers and clinicians with a psychometrically sound, validated self-report assessment of nicotine withdrawal (Welsch et al., 1999). This 28-item scale includes a total symptom scale and 7 subscales addressing components of the tobacco withdrawal syndrome (e.g., anxiety, anger, sadness, craving, concentration difficulties, hunger, and sleep problems). The original scale has reasonable psychometric properties, is sensitive to smoking abstinence, related to tobacco dependence measures, and has moderate predictive validity regarding smoking cessation outcomes. The WSWS has been a valuable assessment instrument that has been used by numerous researchers worldwide for investigating the nature and correlates of tobacco withdrawal. However, the field's understanding of tobacco withdrawal has advanced in recent years and the population of smokers has changed substantially (e.g., reduced smoking heaviness; Jamal et al., 2018). Thus, there is a clear need to update and improve the assessment of withdrawal.

It is of considerable scientific and clinical importance to assess tobacco withdrawal accurately since withdrawal severity is highly determinant of smoking cessation success. In addition, smoking cessation pharmacotherapy produces its effects on smoking abstinence by suppressing such symptoms (Bolt et al., 2012). The current study aims to validate, and possibly enhance, a revised WSWS for use in research and clinical settings. We have recently

developed a psychometrically robust, revised version of the WSWS based on several recent smoking cessation trials conducted by UW-CTRI (WSWS2, Smith et al., in press). However, most previous research, including our own, has occurred within the context of the pharmacological treatment of smoking. In order to ensure that a measure of tobacco withdrawal is sensitive to severe withdrawal, it is essential to examine unmedicated smokers. Unmedicated smokers display withdrawal symptoms that vary greatly in severity, which will allow us to determine which WSWS2 items are sensitive to both mild and severe withdrawal symptomatology. Assessment of unmedicated withdrawal is rarely done and therefore this research will yield unusual and valuable data on withdrawal amongst today's smokers. It is also important to assess withdrawal amongst smokers who are using smoking medications since treatment guidelines (Fiore et al., 2008) recommend that virtually all smokers in formal treatment programs use such medication. Therefore, data gathered from smokers when they begin using medication will be highly relevant to the greater population of treated smokers.

The current study aims to validate a revised WSWS measure (WSWS2-L) in a new sample of unmedicated smokers who abstain from smoking for 1 week prior to receiving pharmacological smoking cessation treatment. Furthermore, the research will evaluate constructs that have emerged primarily in recent years for possible inclusion in the new WSWS (e.g., restlessness, anhedonia, pain). Depending on the results of such evaluation, items representing these constructs may be included in a future version of the WSWS instrument. Another reason for conducting more research on the WSWS is that the previous measure was quite lengthy, which reduced its routine use in both clinical and research contexts due to concerns over assessment burden. Therefore, the proposed research will validate a psychometrically valid short form of this instrument (the Brief WSWS2: the WSWS2-B) in addition to a longer form suited for in-depth analysis of withdrawal (WSWS2-L). Developing a short form is especially vital given the increasing use of mobile technology for assessment. Such technologies require the use of very brief but valid assessment instruments. As such, this study aims to validate both a full yet efficient comprehensive WSWS2-L as well as a brief and focused WSWS2-B for use across diverse clinical and research settings.

Study Overview

We propose recruiting up to 500 daily cigarette smokers who report a desire to quit smoking in order to enroll up to 250 participants. This is a treatment-delay, one-group clinical trial that is intended to enhance the assessment of tobacco withdrawal amongst participants who try to quit smoking with delayed use of cessation medication. In addition, it is intended to identify important determinants of withdrawal severity. Participants will not receive any pharmacotherapy during the first 1 week of their quit attempt. They will initiate pharmacotherapy 1 week past the target quit day (TQD) and continue treatment through 9 weeks past the TQD. This will allow for the examination of withdrawal symptoms for 1 week post-TQD in participants who are not using pharmacotherapy. Participants will receive 8 weeks of combination nicotine replacement therapy (C-NRT: nicotine patch + nicotine mini-lozenge) starting 1 week past the TQD. Participants will receive 4 counseling sessions that conform to the US PHS Clinical Practice Guideline recommendations (1 prequit, 3 postquit). Participants will complete 4 weeks of ecological momentary assessment (EMA) including a 2-week baseline (starting TQD-14) and 2-week post-TQD (1-week un-medicated, 1-week using C-NRT). Participants will be recruited via media (newspaper and television advertisements, and Facebook advertisements) to attend an Orientation Visit where the study will be explained and they will provide written informed consent. Once consented, the study will include three phases (described below): Orientation, Precessation and Cessation. Over the 2-week Precessation and the first 2 weeks of the

Cessation phase, participants will complete intensive daily mobile self-report assessment (mobile assessment) of withdrawal and other relevant variables.

The Orientation Phase. This will include an Orientation session for all participants and will entail completion of written informed consent, eligibility screening, a self-report assessment battery, and physical assessments (e.g., breath CO, urine nicotine/cotinine levels, blood pressure). Assessments delivered during these visits will include withdrawal assessment, smoking heaviness, use of all nicotine products, and potential mechanisms of treatment (e.g., expectations of smoking reinforcement, smoking contexts, affect). Eligible participants will be scheduled for a Precessation Call.

The Precessation Phase. This will include all participants (n=250) and last 2 weeks, ending at the participant's TQD. Participants will have 3 phone calls during this phase: at around 2 weeks, 1 week, and 1 to 3 days before the TQD. They will continue their normal ad lib smoking and receive no medication during this phase. They will complete 2 weeks of intensive daily mobile self-report assessment (via ecological momentary assessment; EMA) of tobacco withdrawal and related factors prior to the TQD. Counseling will be provided at 1 week before the TQD. This visit will encourage all participants to review their motivation for quitting and ensure that they have a good quit plan for their TQD (e.g., abstaining completely on their TQD). Counseling sessions will be audio recorded for quality assurance. The extensive withdrawal assessment battery will be repeated at the study calls and any EMA problems will be addressed.

The Cessation Phase. This will start on the TQD and will last 9 weeks. Participants will attend 2 study visits and 1 study call during the first two weeks of this phase: at 1-2 days post-TQD (call), 7 days post-TQD (visit), and 2 weeks post-TQD (visit). During these calls and visits participants will be given cessation counseling (15-20 min) that stresses complete abstinence from cigarettes and that is consistent with the PHS Smoking Cessation Clinical Practice Guideline (Fiore et al., 2008). Counseling at the 1-week and 2-week visits will also stress adherent medication use and ways to deal with medication side effects. Counseling sessions will be audio recorded for quality assurance. Extensive withdrawal assessment battery will be repeated at the study visit and calls. At the study visits physical assessment will include breath CO, urine nicotine/cotinine levels, and blood pressure. Participants will be given their medication at the study visit 1-week post-TQD and instructed to start using their medication the next day. At these study visits and calls we will assess withdrawal and relevant factors as well as timing of any lapses. Participants will receive 1 additional assessment study phone calls during this phase at 63 days post-TQD (9 weeks). This phone call will assess smoking status, withdrawal, medication adherence, and medication side effects. Participants who report abstinence at this call will be asked to attend an in-person visit for biochemical verification of abstinence (e.g., breath CO). Urine nicotine/cotinine levels will also be measured.

Participants

Two hundred participants (age ≥21; 50% women) who smoke ≥5 cigarettes per day, have a CO level ≥5 ppm, and report a desire to quit smoking, will be recruited from Madison and Milwaukee, WI. Participants must be willing to attempt to abstain from smoking for 1 week without the use of pharmacotherapy treatment or other nicotine use (e.g., e-cigarettes). See sections below for details on eligibility criteria, recruiting, and participant compensation strategies to enhance retention.

Inclusion/Exclusion Criteria

Self-reported inclusion criteria:

- Smoke ≥5 cigarettes per day for past year
- ≥21 years old
- Able to read and write English
- Desire to quit smoking
- Not currently engaged in cessation treatment
- Eligible to use combination nicotine replacement therapy
- Willing and able to attend study visits
- Have reliable smartphone access
- Not currently pregnant, trying to get pregnant, or breastfeeding
- Willing to respond to ecological momentary assessment prompts and other study activities

Other inclusion criteria:

- Baseline breath carbon monoxide (CO) ≥5 ppm

Self-reported exclusion criteria:

- Used pipe tobacco, cigars, snuff, or chew more than twice in the past week
- Used e-cigarette, vaping, or any other electronic nicotine delivery product more than twice in the past week
- Unwilling to try to abstain from all non-medicinal nicotine use (including e-cigarettes) for the duration of the Cessation Phase (other than nicotine replacement therapy provided by the study)
- Currently taking varenicline or bupropion
- Allergy to adhesive tape
- Previous reaction to the nicotine patch or mini-lozenge that prevented them from continuing to use it
- Unwilling to use study approved methods of birth control while taking study medication and for 1 month after discontinuing study medication [only for women of child-bearing potential]
- Hospitalized for a stroke, heart attack, congestive heart failure, ulcers, or diabetes within the last year
- History of seizure within the last year
- Diagnosis of and/or treatment for schizophrenia, other psychotic disorders, or bipolar disorder within the last 5 years
- End-stage renal disease
- Suicide attempt or suicidal ideation within the last 12 months

Other exclusion criteria:

- Severe hypertension > 180/100 mmHg

Recruitment

Participants will be recruited via media recruitment methods (e.g., social media, UW-CTRI website, TV, and earned media) from Madison and Milwaukee, WI. Additionally we will proactively ask current participants in this study to recruit their friends with approved fliers and business cards. Interested smokers will call the study phone number or click the web links in

recruitment advertisements. Web recruitment will direct to a UW-CTRI website that provides basic information about the study goals, treatment offered, participant requirements, and financial compensation. Participants may provide their telephone and/or mailing address contact information (via voicemail or UW Qualtrics website or REDCap website) for study staff to return their calls and screen them for eligibility. Potentially eligible participants will be scheduled to attend an in-person, Orientation Visit. Participants who are potentially eligible but do not attend the Orientation Visit will be re-contacted to invite them to reschedule if they remain interested.

Study Visits and Phone Contacts: *Orientation, Precessation, and Cessation Phases*

For Study Visit and phone contact schedule and procedures see Table 1 (Orientation, Precessation) and Table 2 (Cessation). Participants will receive one visit-reminder (call, email, and/or text) prior to each study visit.

Orientation Phase (TQD >-2 weeks)

Orientation Visit 1 (TQD >-2 weeks). Participants will be provided an overview of the study goals and procedures in an individual setting. They will then be presented a written consent form and their questions will be answered. Interested participants will sign the consent form. Following successful consent, participants will be screened for eligibility (e.g., questionnaires, blood pressure, expired breath CO sample). Participants will provide urine nicotine/cotinine samples and complete a computerized self-report assessment battery (via REDCap and/or Qualtrics, see Table 1). Participants will schedule their TQD and the various study visits/calls. Participants will be instructed how to complete smartphone ecological momentary (EMA) mobile assessments on their own phone. Participants will be asked when they would prefer to receive assessment calls and will be given a calendar that shows all the study calls, visits, and assessments required by the study as well as contingent incentive amounts.

Precessation Phase (TQD -2 weeks to TQD)

There will be three phone contacts during the Precessation Phase.

Precessation Call 1 (TQD -2 weeks). Participants will engage in mobile assessments daily for 2 weeks during the Precessation Phase (EMA starting TQD-14d) while smoking ad libitum and prior to any pharmacotherapy treatment. The Precessation Call 1 will occur approximately 2 days after the start of EMA (TQD-12 days) to address any EMA problems (e.g., adherence or technical troubleshooting). Participants will complete a brief self-report assessment battery during this call.

Precessation Call 2 (TQD -1 week). Participants will receive smoking cessation counseling and complete self-report assessments at this phone call. This call will also involve dealing with any smartphone data assessment issues that arise during the Precessation Phase and instruction to continue mobile assessment for the next 1 week until the TQD.

Precessation Call 3 (TQD -1 to -3 days). This call will focus on preparing the participants for the TQD, reminding them of its date, and stressing the importance of complete abstinence after the TQD. Participants will complete the self-report assessments. This call will also address any EMA problems (e.g., adherence or technical troubleshooting).

Cessation Phase (TQD to +10 weeks)

Participants will attend 2 study visits and 3 study calls during this phase.

Cessation Call 4 (TQD Day +1-2). Participants will receive smoking cessation counseling, complete self-report assessments including any smoking since their TQD. Participants will be reminded to attempt to completely abstain from smoking and use of all nicotine products. Mobile assessment data will be reviewed and problems with collection of such data will be addressed.

Cessation Visit 2 (TQD Day +7). Participants will receive smoking cessation counseling, complete self-report assessments including any smoking since their last visit, and provide breath CO and urine nicotine/cotinine samples. Participants will be reminded to attempt to completely abstain from smoking and all nonmedicinal nicotine products. Participants will be provided with an 8-week supply of C-NRT including nicotine patches and nicotine mini-lozenges with instructions on how to use them (through TQD +9 weeks). Participants will be encouraged to start the medication the following day and to use their medication adherently. Mobile assessment data will be reviewed and problems with collection of such data will be addressed. If a participant is unable to attend Visit 2 or Visit 3 (2 weeks post-quit; described below) we will conduct the appointment over the phone. Most study activities can be conducted remotely (self-report assessments, quit smoking counseling, medication education) with the exception of medication dispensation and physical tests (breath/urine smoking bioverification and blood pressure). In these cases, we will mail participants their study medication so they can still receive their nicotine replacement medication as soon as possible rather than delaying their medication dispensation until they are able to attend an in-person visit.

Cessation Visit 3 (TQD Day +14). Participants will receive smoking cessation counseling and complete self-report assessments including any smoking since their last visit, and provide breath CO and urine nicotine/cotinine samples. Participants will be reminded to attempt to completely abstain from smoking and use of all nonmedicinal nicotine products. Participants will be encouraged to use their medication adherently and any medication problems such as side effects will be addressed. Participants will be reminded of the follow-up phone contact planned for 9 weeks post-TQD and the incentives for taking the call.

Cessation Call 5 (TQD + Week 9). Participants will receive a call on their final scheduled day of pharmacotherapy to assess smoking status, medication adherence, and assess any medication side effects. Participants will complete self-report assessments.

Cessation Visit 4 (TQD > Week 9). Participants who report abstinence from smoking at their Call 5 will be asked to attend an in-person visit for biochemical verification of abstinence (e.g., breath CO). Urine nicotine/cotinine levels will also be measured.

Table 1. Study Visit Schedule and Procedures: Orientation and Precessation Phases

Study Schedule, Assessment, and Procedures	**Visit 1**	**Call 1**	**Call 2**	**Call 3**
Study Phase	**Orientation**	**Precessation**		
Days +/- Target Quit Day: TQD	**> -14**	**-12**	**-7**	**-3 to -1**
Sign Informed Consent and HIPAA	X			
Inclusion/exclusion interview	X			
Smoking Status & Timeline Follow Back	X	X	X	X
Revised Wisconsin Smoking Withdrawal Scale (WSWS2-L)	X	X	X	X
Minnesota Tobacco Withdrawal Scale – Revised (MTWS-R)	X	X	X	X
Questionnaire of Smoking Urges (QSU)	X			
Demographics	X			
Smoking History	X			
Brief Wisconsin Inventory of Smoking Dependence Motives (Brief WISDM)	X			
Fagerström Test of Cigarette Dependence (FTCD)	X			
Wisconsin Predicting Patients' Relapse (WI-PREPARE)	X			
NIAAA Recommended Alcohol Questions	X			
Pain Numeric Rating Scale (PNRS)	X		X	
Graded Chronic Pain Scale (GCPS 2.0)	X			
Depression, Anxiety, Stress Scale (DASS21)	X			
Snaith-Hamilton Pleasure Scale (SHAPS)	X		X	
Distress Tolerance Scale (DTS)	X			
CO Breath & Blood Pressure	X			
Urine Collection	X			
Feedback Survey	X			
Interventions				
Counseling (in minutes)			15-25	

Table 2. Study Visit Schedule and Procedures: Cessation Phase

Study Visit Schedule, Assessment, and Procedures	Call 4	Visit 2	Visit 3	Call 5	Visit 4
Study Phase			**Cessation**		
Days +/- Target Quit Day: TQD	**+ 1-2**	**+ 7**	**+ 14**	**+ 63 (9w)**	**> 64 (>9w)**
Smoking Status & Timeline Follow Back	X	X	X	X	X
Revised Wisconsin Smoking Withdrawal Scale (WSWS-2)	X	X	X	X	X
Minnesota Tobacco Withdrawal Scale – Revised (MTWS-R)	X	X	X	X	X
Questionnaire of Smoking Urges (QSU)	X	X	X		X
Pain Numeric Rating Scale (PNRS)	X	X	X	X	X
Depression, Anxiety, Stress Scale (DASS21)		X			
Snaith-Hamilton Pleasure Scale (SHAPS)	X	X	X	X	X
CO Breath & Blood Pressure		X	X		X
Urine Collection		X	X		X
Feedback Survey		X	X		
Interventions					
AE/Safety assessment			X	X	
Counseling (in minutes)	15	15	15		
C-NRT Adherence assessment			X	X	

Self-Report Measures

WSWS-2. At all study visits participants will complete a newly revised set of Wisconsin Smoking Withdrawal Scale (WSWS2-L) items (Smith et al., in press). This 18-item assessment is intended to evaluate 6 subscales of craving, negative affect, difficulty concentrating, sleep difficulties, hunger, and restlessness. This assessment will provide data to validate a full version of the WSWS2-L. The brief 6-item version, the WSWS2-B, will be administered during EMA (see below).

Assessment Battery. Participants will complete a battery of self-report questionnaires using REDCap or Qualtrics on a computer or tablet at the Orientation Visits (see Table 1). A smaller assessment battery will be re-administered at subsequent study visits and calls (see Tables 1-2). Participants will complete several questionnaires designed to evaluate factors related to smoking experiences, nicotine dependence, and relapse risks. These questionnaires include the Minnesota Tobacco Withdrawal Scale-Revised (MTWS-R, (Hughes, n.d.), Smoking History Questionnaire, Brief Wisconsin Smoking Dependence Motives (Brief WISDM; Smith et al., 2010), Fagerström Test of Cigarette Dependence (FTCD; Fagerström, 2012), and Wisconsin Predicting Patients' Relapse (WI-PREPARE; Bolt et al., 2009). Participants will be asked a brief series of questions regarding menthol cigarette use, inhaled agents, noncombustible tobacco use, and e-cigarette use. Participants will complete a battery of assessments of affective and other personality traits, chronic pain, alcohol use, and psychiatric symptoms. These questionnaires include the Distress Tolerance Scale (DTS), Snaith-Hamilton Pleasure Scale (SHAPS; Snaith et al., 1995), Depression, Anxiety, and Stress Scale (DASS21; Lovibond &

Lovibond, 1995), Graded Chronic Pain Scale (GCPS 2.0), Pain Numeric Rating Scale (PNRS), and the NIAAA Recommended Alcohol Questions (NIAAA, 2003).

Ecological Momentary (mobile) Assessment (EMA). Participants will provide daily ecological momentary assessment data (meaning data that has been collected "in the moment") for 4 weeks total during the study (over 2 weeks of Precessation and 2 weeks of Cessation). Mobile online surveys technology using smartphones will be used to acquire data. For most of the EMA portion of the study, participants will complete 3 assessments per day (morning, midday, and evening). Daytime EMA prompts will be brief (10 min) to include the brief WSWS2-B focused on motivationally relevant affective/cognitive features of withdrawal (e.g., excluding sleep which will only be assessed at the evening EMA) and smoking (# cigarettes since last assessment). The evening assessment will include a larger battery of questionnaires to include the WSWS2-B and additional targeted assessments (see below). Versions of these EMA protocols have been used effectively in multiple large scale smoking cessation clinical trials over the past two decades with very high completion rates (~80%). The frequency of EMA will be increased for 5 days from 1-day pre-TQD to 3-days post-TQD in order to provide intensive monitoring of withdrawal symptoms on a more fine-grained time course during the early period of abstinence. During these 5 days participants will complete 6 EMA reports/day at within 2 hours of waking, waking + 3 hours, waking + 5 hours, waking + 7 hours, waking + 9 hours, and retiring. Participants will complete the full 18-item WSWS2-L (rather than the WSWS2-B) during the evening EMA during these 5 days (1x/day).

In addition to the WSWS2-B items, at each evening assessment (1x/day) or when a participant reports his/her first 3 post-TQD smoking events, they will also complete an expanded battery of EMA assessments regarding smoking, person-related, and contextual factors that day. These will include smoking (# cigarettes since last assessment), cessation self-efficacy, location (e.g., home, work, vehicle), activity (job, school, household), social context (e.g., social, work, stressful interaction), eating or drinking (e.g., eating, drinking caffeine, drinking alcohol), cigarette cues (e.g., lighter, ashtray, others smoking, tobacco ads), other inhaled substances (yes/no), cigarette availability (e.g., easy, hard, not available), medication use, pain (e.g., average, worst), smoking restrictions (e.g., home restriction, work restriction, public place restriction), with whom (e.g., friends, family, partner, co-worker), smoking triggers (e.g., see/smell cigarettes, stress, drink alcohol), tempted to smoke, coping strategies (e.g., cognitive, behavioral, none), and pre-coping intention.

Table 3. Intensive Longitudinal Data Collection Schedule (Ecological Momentary Assessment: EMA)

EMA and Medication Schedule	**Precessation**	**TQD**	**Cessation**	
	TQD -14 to -2	TQD-1 to TQD+3	TQD +4 to TQD+14	TQD +15 to TQD+21
Total: 5 weeks	13 days	5 days	11 days	7 days
# Daily Assessments	3/d	6/d	3/d	
Medication Status	no medication			C-NRT (Start TQD+8)

Bio-verification Measures

Carbon monoxide Assessment. At all study visits, participants will provide expired breath sample of carbon monoxide (CO; Smokelyzer) for biochemical verification of abstinence. CO is used as both a measure of smoking heaviness at baseline as well as to confirm self-reported abstinence from smoking following the TQD. The higher of two samples recorded will be used as the value for data analysis. A cutoff of ≤5 ppm will be used as the criteria to be considered abstinent.

Nicotine/Cotinine Assessment. At all study visits, participants will provide a urine sample to assess nicotine/cotinine levels, which can be used to estimate smoking heaviness and environmental smoke exposure. Trained study staff at UW-CTRI will collect the participants' urine within the same day. All samples and test results will be labeled with the date of collection and the participant's numerical ID. Urine will be disposed of after nicotine/cotinine levels are read and recorded.

Smoking Cessation

Pharmacotherapy. An 8-week supply of nicotine patch and nicotine mini-lozenges will be distributed at the visit 1-week post-TQD (Visit 2). Participants will be instructed to initiate C-NRT following the study visit on TQD +8-days. Nicotine patch and mini-lozenge dosing will be based off the 2008 PHS Clinical Practice Guideline and package insert with adjustments to account for the delayed start 1-week post-TQD. All participants will receive 2mg mini-lozenge due to the superior palatability of the 2mg lozenges. Participants are encouraged to use at least 5 mini-lozenges per day for the full 8 weeks. Participants who report any smoking or nicotine use (e.g., even a cigarette puff, e-cigarette use) in the 3 days before C-NRT distribution will receive 4 weeks of 14mg and 4 weeks of 7mg nicotine patches. Participants who report complete abstinence from smoking and nicotine in the 3 days before C-NRT distribution will receive 8 weeks of 7mg nicotine patches. This dosing schedule based on abstinence status is determined to balance the goals to ensure participants receive a sufficient dose of nicotine replacement while minimizing the likelihood of experiencing nicotine toxicity. The study staff will recommend dosage/use alterations as per good clinical practice if the participant experiences side effects.

Participants will be given the package insert use instructions and verbal guidance on medication use. Medication use will be assessed via evening EMA reports and at study phone calls. We will monitor adverse events at all study calls/visits as well as gather additional data on medication use. All participants will be given a phone number to call in case of medication issues or any other significant problems related to their participation.

Table 4. Combination Nicotine Replacement Therapy (C-NRT) Schedule

Medication Schedule	**Precessation**	**Cessation**	
	TQD -14 to -1	TQD to TQD+7	TQD +8 to TQD+63
	2 weeks	1 week	8 weeks
Medication	No medication		C-NRT (8 weeks)

Counseling. Participants will receive counseling at 1 Precessation call and 3 Cessation calls/visits (≈15 min, see Table 1-2). Counseling will conform to the US PHS Clinical Practice recommendations for an intensive counseling intervention (motivational, supportive, and skill training elements). Counseling will not explicitly focus on psychoeducation regarding withdrawal symptoms. Counselors will be bachelors-level health educators supervised by licensed psychologists. Quality/fidelity assurance strategies developed by our prior work will include intensive training in counseling techniques and ethical conduct, 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 whenever possible.

Participant Compensation Strategy

Participants will receive free evidence-based smoking cessation treatment including both counseling and 8 weeks of C-NRT. In addition, participants will be compensated financially for completing study activities and EMA/mobile assessments. Participants will receive $20 for the Orientation Visit. Participants will receive $30 for each study visit and $10 for each telephone call in the Precessation Phase ($30), and Cessation Phase ($80). Participants who report abstinence at Call 5 and complete Visit 4 will receive $50 for this visit. Participants will be compensated for completing > 80% of the EMA assessments ($100). Thus, the total compensation available to participants is $130 (visits) + $50 (calls) + $100 (EMA bonus) = $280. Importantly, payments will be linked to visit/assessment completion, but not to smoking status so as not to induce participants to incorrectly report their smoking status. This is essential to encourage participants' accurate and honest reporting, particularly as lapse will be an important outcome for evaluating WSWS-2 validity. Compensation will be delivered via checks mailed to participants' residence or distributed at study visits.

Analytic Plan

Specific Aims: WSWS-2 and WSWS-2BR Validation
Psychometric analyses of the 18 item pool will be conducted to validate a full and brief version (6 items) of the WSWS2 in this sample of medicated and unmedicated smokers. The aims include clarifying the dimensional structure and the best-performing items to construct the final scales. Subscales will be evaluated with respect to internal consistency (e.g., Cronbach's alpha ≥.8), item-analysis (response distributions, item-to-total correlations, IRT analyses), and confirmatory factor analyses (CFA) and measurement invariance (e.g., across at least 2 post-TQD time points).

Concurrent, discriminant, and predictive validity will be considered in evaluating and constructing the final scale. The WSWS2-L should demonstrate meaningful relations with measures of tobacco dependence (WISDM-PDM, FTCD, time to first cigarette), other published withdrawal scales (Minnesota Withdrawal Scale), and prediction of cessation outcomes (e.g., time to lapse/relapse, survival analyses). In analyses predicting cessation outcomes both pre-post increase in withdrawal symptoms and post-TQD symptoms per se will be used in prediction models. In addition, such models will be tested with and without (primary) covariates (gender, and race). The WSWS2-L should demonstrate a characteristic time-course of a withdrawal syndrome including sensitivity to abstinence (rise over first 12-24 hours and 2-4 days) and decrease over time following a peak in post-TQD. The time course will be examined with growth curve models that evaluate different trajectory components (i.e., linear, quadratic) with time

varying covariates for smoking lapse occurrence, exposure to temptation events, dependence level. The WSWS2-L should also be sensitive to medication use (e.g., decrease with C-NRT). This will be tested by determining the effects of C-NRT during Cessation on WSWS2-L scores versus precessation and unmedicated cessation levels. The WSWS2-L will be correlated with variables that assess relevant person factors such as affective disorder, distress tolerance, and the various measures of tobacco dependence.

We will conduct parallel set of psychometric and validation analyses of the WSWS2-B as we do with the WSWS2-L, except when not possible due to constraints placed on single-item subscales (e.g., subscale internal consistency, CFA).

Exploratory Analyses:
This study will produce a rich data set for exploratory analyses to both examine the robustness of the primary aims as well as hypothesis generation for future studies. We provide a brief summary of planned theory-driven exploratory analyses, but it is likely that further avenues of analysis will be applied to the data set. We will report all analyses transparently as hypothesis-testing versus exploratory in presentations and published manuscripts. We will examine candidate predictors and moderators of smoking cessation treatment effects in secondary analyses.

Candidate predictors of cessation treatment effects, gathered from EMA and follow-up phone assessments will be: medication use and side effects, withdrawal symptoms (e.g., craving, negative affect), anticipatory pleasure from smoking, adverse events, nicotine reward, nicotine anticipation, and reports of cue-elicited urges. The occurrence of smoking during the quit attempt will be statistically controlled. One-week abstinence will be the primary outcome, which will be modeled via a weighted least squares approach in Mplus. We will attempt to characterize orthogonal routes to outcome change and also examine how certain events such as stressor occurrence or exposure to smoking cues affect withdrawal symptoms via time varying effects modeling.

Analysis of moderators of abstinence outcomes will use both logistic regression with model-fitting techniques and regression tree analyses that reflect differential treatment responses in 1-week abstinence. The logistic regression and regression tree approaches are complementary since the former fits interactions in the entire sample whereas the latter identifies the most robust interactions amongst subpopulations of a sample (groups of participants nested within levels of another predictor, which could include either a covariate or treatment condition. Candidate moderators of treatment effects on abstinence will include tobacco dependence, contextual factors such as household smoking, and biological variables such as sex. In the logistic regression analyses moderators will be evaluated with regards to their interactions with treatment effects.

Power and Sample Size Justification

Based on the average expected communalities and the variables-to-factors ratio (factor overdetermination) of the proposed analyses, we believe the sample sizes proposed will provide good power the exploratory factor analyses and other covariance structural modeling (R. C. MacCallum et al., 2001; Robert C. MacCallum et al., 1999). A key prediction concerns the relation between a dichotomized scoring of the WSWS-2B and likelihood of abstinence at follow-up. We propose that those with low withdrawal scores will have an abstinence likelihood

of .40 while those with a high score will have an abstinence likelihood of .20. Assuming p=.05 and B=.80, the N for a regression of .20 = 95 (Hsieh et al., 1998). Therefore, we believe the design is adequately powered for the expected results, which would be of clinical significance.

Protection of Human Subjects

Risks to the Participants

Human Subjects Involvement and Characteristics: Up to 400 adult smokers will be consented from the community in order to enroll at least 250 participants. Participants must: have the ability to read and write in English, smoke ≥5 cigarettes per day, be ≥21 years old, desire to quit smoking but not be engaged currently in cessation treatment, expired breath carbon monoxide ≥5 ppm, willing to use nicotine patch and nicotine lozenge, willing and able to attend study visits, have reliable smartphone access, willing to respond to EMA prompts and other study activities, and if female, not be pregnant, trying to get pregnant, or breastfeeding. Exclusion criteria include: use of pipe tobacco, cigars, snuff, chew, e-cigarettes/vaping, or other electronic nicotine delivery product more than twice in the past week, unwilling to try to abstain from all nicotine use (including e-cigarettes) for the duration of the Cessation Phase (other than study-provided NRT), currently taking varenicline or bupropion, diagnosis of and/or treatment for schizophrenia, other psychotic disorder, or bipolar disorder within the last 5 years; suicide attempt or suicidal ideation in the past 12 months; severe hypertension (>180/100 mmHg), on dialysis or being told you have severe kidney disease; hospitalization for a stroke, heart attack, congestive heart failure or uncontrolled diabetes mellitus within the past year; currently participating in a smoking cessation study, or unwilling to use study approved methods of birth control while taking study medication and for 1 month after discontinuing study medication (only for women of child-bearing potential). Study approved methods of birth control include abstinence from sex with men, condoms, diaphragm, birth control pills, injectable contraceptive (e.g., Depo-Provera), contraceptive implant (e.g., Implanon), IUD, have had hysterectomy or tubal ligation, or are more than 2 years post-menopausal.

Sources of Materials: Participants will provide data for the express purpose of research. Data will consist of answers to questionnaires and interviews assessing smoking history, demographics, nicotine dependence, personality, affect and psychiatric history, disease status and health history. These will include provision of urine samples that will later be used for nicotine/cotinine tests. Breath tests and a brief questionnaire will be used to assess exhaled carbon monoxide. Counseling sessions will be recorded for purposes of clinical supervision and quality assurance.

Potential Risks: None of the medical, physiologic, self-report, or behavioral assessments constitute a significant risk. The use of cessation medications poses a risk of side-effects. Participants will be made aware of the common nicotine replacement side effects before they consent to participate in the study. It should be noted that the nicotine patch and nicotine mini-lozenge are available over the counter. The Food and Drug Administration (FDA) has approved using a combination of two forms of NRT (e.g., nicotine patch + nicotine mini-lozenge) for smoking cessation. These interventions have also been studied and used safely in multiple clinical trials, are used by clinicians in clinical practice, are available over-the-counter, and are reviewed in the 2008 PHS Guideline. The PHS Guideline, in fact, recommends combination NRT as a particularly effective treatment. The nicotine patch is generally well tolerated, but up to 50% of participants may have a local skin reaction, and rarely, individuals may have a more systemic allergic reaction. The most likely side effects associated with the nicotine mini-lozenge are heartburn, hiccup, nausea, upper respiratory tract infections, coughing, and sore throat. Although most smokers have tolerance to nicotine, symptoms of acute nicotine toxicity (nausea and vomiting) are possible. Participants will be informed that NRT is typically initiated on or before the TQD rather than 1 week after quitting. To reduce the risk of nicotine toxicity by over-dosing after the 1 week period of reduced or no nicotine use: 1) initial nicotine patch dose will be

determined based on smoking/nicotine abstinence status in the 3 days prior to patch distribution; and, 2) submaximal dosages of both NRT products are used (e.g., no 4mg mini-lozenge or 21mg patch). Finally, individuals often attempt to stop smoking without the use of medication. As the 2008 PHS Guideline shows, this method is considerably less likely to produce long-term cessation and for this reason C-NRT is provided to increase participants' likelihood of achieving abstinence. Those not successful in quitting bear the health risks associated with continued smoking.

There is always a remote, but existing, possibility that sensitive or personal information about a participant could be divulged as a function of his/her research participation. Other than cannabis use no additional information about illegal behavior will be collected by research staff or entered into research data bases. Finally, smoking withdrawal is associated with a number of unpleasant symptoms, such as sleep disturbance, hunger, craving, and negative mood. Most smokers have tried to quit before and are familiar with these phenomena. Though unpleasant, smoking withdrawal symptoms pose minimal health risk. Participants will be informed about the possible effects of smoking withdrawal. Individuals who elect not to participate in this research, or are eliminated due to screening failure, will be given a list of alternative smoking cessation programs at any point during the pre-consent process.

Adequacy of Protection Against Risks

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

Participants will be recruited in the Milwaukee and Madison metro areas. Advertisements and publicity will contain a phone number for interested individuals to call and/or link to UW recruitment website to contact study personnel. Study staff will call potential participants and conduct an initial phone screening to rule out those with clear contraindications. The study will be briefly described, questions answered, and potentially qualifying individuals will be invited to attend an Orientation Visit. Participants will provide verbal consent to complete the initial phone screen. Participants identifying contact information will be stored securely and retained until study completion and the CONSORT diagram is created. Without this altered authorization, it would not be feasible to keep track of who has tried to screen into the study and failed because staff would not be able to identify these renewed attempts to enroll in a study that might not be appropriate based on answers to the phone screen.

At the Orientation Visit the general requirements for participation will be reviewed (e.g., session attendance, participation in assessments). In addition, participants will be informed of the nature of the interventions involved. They will be told about the pharmacotherapy and counseling interventions that will be provided. Everyone will be told that they will receive counseling designed to aid them in their cessation attempt. The risks of taking C-NRT will be described including the most common side effects. All participants will be informed as to the various parts of the study and what will be entailed in each part. After answering any participant questions about research participation and intervention, participants will be given a combined HIPAA/consent form to review, ask additional questions, and sign the consent form. Individuals will then be screened for any remaining exclusion factors. Should eligible smokers decide not to participate in the research at the Orientation Visit, the personally identifying information collected at the Orientation Visit and the screening phone call will be de-identified following study completion (i.e., at the point that data for a study CONSORT diagram have been cleaned

and analyzed). Participants will be encouraged to ask any further questions about the study protocol throughout the study.

Protection Against Risk: As noted above, participants will be screened by study staff to ensure that they are medically and psychiatrically fit to use C-NRT. Study staff (bachelor-level health counselors or undergraduate students) are trained to administer eligibility screening questions that are entered into a database. The determination of eligibility is based on a computer algorithm that is driven by participants' responses to these questions. UW-CTRI Study Physician and Study Clinical Psychologists will be available for consultation should any additional unexpected eligibility questions or concerns arise during this process. Study participants will be closely monitored in accordance with current FDA recommendations as well as the consensus recommendations of the 2008 Guideline Panel (Fiore et al., 2008), 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 nicotine patch or nicotine mini-lozenge. We will recommend dosage/use alterations including stopping medication treatment as per good clinical practice if the participant experiences troublesome side effects once they begin medication treatment. If a participant reports using non-study quit smoking medications (varenicline, bupropion, or nicotine replacement therapy) after we have distributed the study medications (>1 week after target quit day) – we will instruct participants stop using study-provided medications, and counsel participants not to combine medications or exceed recommended dosage. However, we will not withdraw these participants from the study (e.g., for follow up data collection). Thus, we will take extraordinary care to ensure the safety of study participants.

Face-to-face research activity will be conducted according to institutional policy at the time in-person visits begin, should COVID-19 related restrictions continue to be in place.

Study participants will be carefully monitored for side effects. Monitoring for these symptoms or conditions will be accomplished through assessment of adverse events (AEs) and serious adverse events (SAEs) at each study visit and phone contact during which the participants are receiving study medication. For all AEs and SAEs, study staff will take appropriate action to ensure the safety of the participant as follows: 1) Non-urgent AEs will be reported in a timely manner to study clinical staff (MDs); and 2) SAEs or AEs that raise concerns (e.g., allergic reaction; severe, unresolved changes in mood or any suicidal ideation) will be immediately reported to the study physician who will determine an appropriate course of action. In addition, participants will be given a telephone number to contact study staff in the event that participants have questions or concerns about study medication or medical/psychiatric reactions that may be related to study medication or participation, as well as instructions on when to seek emergency medical assistance. Individuals who report any significant mood change or suicidal ideation will be contacted immediately by a licensed staff psychologist or physician who will assess the level of risk and provide referrals as needed.

Pregnant women will not intentionally be recruited to the study. However, due to the longitudinal nature of the study, someone who was originally eligible for the study (not pregnant and agreed to take measures to avoid pregnancy) when they enrolled and then becomes pregnant will be allowed to continue participation (their choice) with the assurance that regardless, we will take actions to make sure she is permanently taken off study medication. She will still be allowed, if she chooses, to continue counseling and assessments for her remaining time in the study. Because the risks of the study medications to an unborn child are unknown, should a participant report that she has become pregnant, she will be advised to immediately stop using study

medications and to return any unused medications as safety precautions. No further medications will be given to this study participant while in the study. Study team members will be trained to respect and carry out the participant's wishes to stay or leave the study as they would any other participant.

Protecting the privacy and confidentiality of participant information during the pre-enrollment and consent process (phone screening and Orientation Visit) will be accomplished in several ways. However, we cannot guarantee absolute confidentiality. Over the phone, participants will be told about the study, provide oral consent to participate in the phone screen, and will then answer questions to assess eligibility and willingness to participate.

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.

In terms of confidentiality risk, the UW-CTRI Information Technology Administrator manages the hardware, data, security, and infrastructure below the firewall. Access to the network is limited to only UW-CTRI owned and actively managed devices. All devices automatically lock and are password protected after 15 minutes of inactivity. All portable devices are encrypted for data security and no PHI is stored on local devices. All data stored on the network file server is limited by the principle of least privilege.

As stated above, no data are stored on individual computer hard drives. All data are transmitted from the point of collection to the UW-CTRI server through secure, encrypted web connection. On those rare occasions when, due to a loss of internet access or computer hardware failure, data are collected in paper forms, these forms will be stored securely at UW-CTRI. No identifying data other than a participant ID number is entered on any data form. Any data collected on paper are entered into the computer and the paper document is disposed of securely. Consent forms are obtained in paper copy; these forms contain the participant name and signature. These are retained in secure files at the UW-CTRI office, where they are securely stored.

All UW-CTRI staff members have completed HIPAA/human subjects training and are aware of the sensitivity of study-related data. The UW SMPH has developed school-wide data security policies and procedures. UW-CTRI data security policies and procedures conform to those of the SMPH. UW-CTRI will use an enterprise-level database that supports audit trails such as access, change logging, and more sophisticated access control for managing and tracking user access privileges. In addition, this project has a Certificate of Confidentiality, related to the collection of baseline information on substance abuse and information on sexual orientation. No publications or presentations resulting from this research program will contain identifying Protected Health Information (PHI) about individual participants. We will make de-identified participant data publicly available online on the NHLBI database and OSF (Open Science Framework or similar platform) in accordance with UW and NIH policy and principles of transparent science practices (Aczel et al., 2019; Meyer, 2018).

Potential Benefits of the Proposed Research to the Participants and Others

The potential benefits for smokers participating in this study is the increased chances of successfully quitting smoking and the associated health benefits of smoking cessation. The risks of this research are chiefly associated with the provision of C-NRT as the

pharmacotherapy. These risks are reasonable because these medications have been shown to be safe in numerous large clinical trials as well as the consensus recommendations of the 2008 Guideline Panel (Fiore et al., 2008). Because the health risks associated with continued smoking dramatically outweigh those associated with C-NRT use, 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 C-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 provide important data to validate a revised assessment of smoking withdrawal for use in research and clinical settings. Further, this study will provide a description of the course of unmedicated withdrawal in today's smoker. This information will be gathered in a contemporary population of smokers so the results will be highly relevant to today's smokers and clinicians, and can be used to motivate clinicians to intervene and to motivate smokers to use evidence-based treatments to stop smoking.

Summary

Given the limited risks of C-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 study participant and society.

Data Safety Monitoring Plan

The Data Safety and Monitoring Plan (DSMP) for this research comprises not only the research conducted directly by the University of Wisconsin Center for Tobacco Research and Intervention (UW-CTRI) researchers, but also research conducted by other investigators collaborating with UW-CTRI-funded projects. All investigators must agree to comply with the procedures outlined in this DSMP.

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

To facilitate participant safety, study participants must meet study inclusion and exclusion criteria. Once enrolled, study protocols will assess the presence of AEs and SAEs at all study

visits and follow-up contacts. Should either excessive risk to study participants and/or convincing evidence of lack of measurable benefit to study participants be determined, the study will be stopped and all participants notified in a manner appropriate to the nature of the risk and/or lack of benefit. When taking that step the investigators will consult with the IRB and NHLBI.

Plans for assuring compliance with requirements regarding the reporting of adverse events. This DSMP requires that investigators notify NIH and the University of Wisconsin IRB in a timely manner (consistent with IRB and NIH policies) of the occurrence of any SAE or any AE which is severe, unexpected, and possibly related to study medication or protocol.

Because this study involves pharmaceutical agents, if an unexpected SAE might be related to study drug use, both the Food and Drug Administration (FDA) and the manufacturer/supplier will also be notified within five days of investigators becoming aware of the event. The Principal Investigator will assist the study medication manufacturer/supplier in investigating any unexpected AE/SAE and will provide any follow-up information reasonably requested by the study medication manufacturer/supplier. Examples of SAE would be untoward medical or intervention occurrences that result in death, are life-threatening, require hospitalization or prolonging of existing hospitalization, create persistent or significant disability/incapacity, or involve congenital abnormality/birth defects.

Unanticipated problems will be monitored and reported to the DSMC. These are events that meet the following criteria: 1) suggest the research places subjects or others at increased risk of harm, 2) are unexpected (in terms of nature, severity or frequency) given the research procedures that are described in the study-related documents, and 3) possibly related to study participation. Any SAE will be queried and reported if it meets the definition of unanticipated problem. The Principal Investigator or designee 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 Investigator has 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 Investigator deems 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 Study Director and Principal Investigators will develop plans for assuring data accuracy and protocol compliance. Such plans will include data verification and protocol compliance checks. The Data Manager and Principal Investigator shall also be responsible for ensuring that the data for the project are securely stored, that storage is in compliance with University and federal regulations and that no unauthorized persons have access (electronic or physical) to any participant-identifiable data. All HIPAA regulations and guidelines will be followed, and all study staff must complete approved human subjects and HIPAA training programs.

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

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

The existing UW-CTRI DSMC is chaired by Dr. James Cleary, leader of the Cancer Control Program of the UW Comprehensive Cancer Center. Dr. Cleary is an experienced physician and clinical trial researcher with no involvement in any of this project's research activities. Dr. Cleary is joined on the DSMC by Dr. Burke Richmond and Dr. James Sosman. Dr. Sosman is Associate Professor of Medicine and Medical Director of the HIV/AIDS Comprehensive Care Program at UW Hospital and Clinics who has previously collaborated on a clinical trial of smoking cessation with UW-CTRI. Dr. Richmond is an otolaryngologist who has served on independent DSMBCs for Phase II and III trials involving a nicotine vaccine. Neither has direct involvement with any of the proposed research. The Principal Investigators will report to the DSMC; the three DSMC members will be informed as to treatment conditions and will make the final determinations as to study continuation.

Data Sharing with the Public

ClinicalTrials.gov Requirements

This study will be registered at ClinicalTrials.gov prior to its initiation. The UW Office of Clinical Trials offers comprehensive support services to UW investigators conducting clinical trials. The Principal Investigator and UW-CTRI staff will ensure that this trial conforms to all clinicaltrials.gov reporting requirements.

Open Science and NIH Data Sharing Policy

We value the principles of open science and will take several steps to promote transparency and reproducibility. We will preregister our study design and publish the study protocol along with the publication of the primary outcome paper. Finally, we will make de-identified data and analysis code publicly available on the Open Science Framework (OSF: https://osf.io) or similar platform in accordance with NIH policy and principles of transparent science practices (Aczel et al., 2019; Meyer, 2018).

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