Behavioral activation and varenicline for smoking cessation in depressed smokers

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STUDY OBJECTIVES

The overall aim of this randomized controlled trial is to enroll and randomize 576 daily smokers with current or lifetime major depressive disorder (MDD) to receive 12 weeks of either: 1) Standard behavioral cessation treatment (ST) + varenicline; 2) Behavioral activation integrated with standard cessation treatment (BASC) + varenicline; 3) ST + placebo; or 4) BASC + placebo. Randomization will be stratified by gender, severity of depressive symptoms (minimal/mild vs. moderate/severe), and clinical site (Northwestern, PENN).

We will secondarily address mediators of treatment effects, as well as the effects of incentives on research participation.

The following aims and hypotheses will be tested:

Primary Aim 1: Compare behavioral activation for smoking cessation with standard cessation therapy for enhancing abstinence among smokers with current or lifetime major depressive disorder. Hypothesis: BASC will increase bioverified 7-day point prevalence abstinence at 24-weeks post-quit versus ST among participants randomized to placebo.

Primary Aim 2: Compare varenicline with placebo for enhancing abstinence among smokers with current or lifetime MDD. Hypothesis: Varenicline will increase bioverified 7-day point prevalence abstinence at 24-weeks post-quit versus placebo among participants randomized to ST.

Primary Aim 2a: Compare varenicline with placebo on rate of adverse events (AE), including psychiatric and cardiovascular events, in smokers with current or lifetime MDD. Hypothesis: There will be no significant difference between conditions in AE rates.

Primary Aim 3: **Compare BASC plus varenicline with ST plus varenicline, BASC plus placebo, and ST plus placebo for enhancing abstinence among smokers with current or lifetime MDD.** Hypothesis: BASC plus varenicline will increase bioverified 7-day point prevalence abstinence at 24-weeks post-quit versus the other three conditions.

Secondary Aim 1: Evaluate anhedonia, cognition (attention/memory), cigarette reward value, and craving/withdrawal as mediators of the effects of BASC, varenicline, and their combination on abstinence among smokers with current or lifetime MDD. Hypothesis: Increases in hedonic capacity and cognition and decreases in craving and withdrawal will mediate the effects of treatment on bioverified 7-day point prevalence abstinence at 24-weeks post-quit.

Secondary Aim 2: Determine if the ethical concerns with incentives for research participation actually manifest. Hypothesis: Research incentives will augment participants' perception of research risks while not disproportionately encouraging economically disadvantaged participants to enroll.

Secondary Aim 2a: Assess the possible scientific and ethical benefits of financial incentives for RCT participation. Hypothesis: Research incentives will increase the enrollment fraction in the smoking cessation trial, thereby enhancing the scientific value and validity of the research by augmenting the precision of the study.

Secondary Aim 2b: Evaluate the cost-effectiveness of using financial incentives to increase RCT enrollment rates. Hypothesis: Incentives are sufficiently cost-effective to justify their use as a means to expedite recruitment in RCTs.

BACKGROUND

Problem of Tobacco Dependence in Major Depressive Disorder (MDD)

The prevalence of smoking among adults with current mental health disorders is 2-3 times higher than the rate among the U.S. population (40-60% vs. 19%) (Centers for Disease Control and Prevention, 2013), an alarming disparity that is widening (B. L. Cook et al., 2014; Lawrence, Mitrou, & Zubrick, 2009). MDD is one of the most common mental health disorders in the U.S. (Centers for Disease Control and Prevention, 2010). The 12-month prevalence of MDD is 6.7% while the lifetime prevalence is 16.5% (Kessler, Chiu, Demler, Merikangas, & Walters, 2005). The high comorbidity between tobacco dependence and MDD has been well documented (Grant, Hasin, Chou, Stinson, & Dawson, 2004; Lasser et al., 2000; Lawrence et al., 2009; Pratt & Brody, 2010). Smokers have a higher prevalence of MDD vs. never-smokers (Breslau, Kilbey, & Andreski, 1991; Glassman et al., 1990). Up to 43% of persons with MDD are smokers (Pratt & Brody, 2010). Tobacco dependence increases risk of first incidence and severity and recurrence of MDD (Breslau, Kilbey, & Andreski, 1993; Breslau, Novak, & Kessler, 2004; Breslau, Peterson, Schultz, Chilcoat, & Andreski, 1998; Leventhal, Kahler, Ray, & Zimmerman, 2009) and heavier smokers are at higher risk (Colman et al., 2011). Smokers with MDD are more likely to smoke heavily, perceive smoking as more pleasurable than many other traditionally rewarding activities, show greater tobacco dependence, and suffer more severe withdrawal (including craving) than smokers without MDD (Breslau, Kilbey, & Andreski, 1992; Pratt & Brody, 2010; Spring, Pingitore, & McChargue, 2003; Weinberger, Desai, & McKee, 2010). Psychological processes that are impaired in persons with MDD, namely hedonic capacity and cognition (attention and memory), are associated with smoking relapse (J. Cook, Spring, McChargue, & Doran, 2010; Leventhal, Waters, Kahler, Ray, & Sussman, 2009; Patterson et al., 2009).

Smokers with MDD and Interest in Quitting Smoking

An important barrier to the development and evaluation of smoking cessation treatment for smokers with MDD has been the perception among clinicians and researchers that they are not motivated to quit. About 25% of smokers with MDD are motivated to quit and do accept formal treatment (Acton, Prochaska, Kaplan, Small, & Hall, 2001; Haug et al., 2005; Prochaska et al., 2004). Severity of depression is unrelated to readiness to quit smoking (Prochaska et al., 2004). In a study of treatment acceptance among smokers with MDD (Haug et al., 2005), acceptors were more likely than refusers to report a desire to quit, to report expectancy for success, and to be taking antidepressant medication. Treatment acceptance was unrelated to severity of depression, degree of dependence, gender, age, or education. In contrast to the popular belief that quitting smoking causes or worsens depression, depression has been found to improve with abstinence (Prochaska et al., 2008; Shahab, Andrew, & West, 2013). Another barrier to addressing tobacco dependence among smokers with MDD has been the expectation that they will not be able to quit or achieve long-term abstinence (Hitsman, Moss, Montoya, & George, 2009).

MDD and Response to Smoking Cessation Treatment

The 2008 Public Health Service Clinical Practice Guideline (Fiore, 2008) recommends that the treatments found to be effective for the general population be applied to smokers with current mental health disorders. This recommendation is based on the premise that studies upon which the Guideline is based included them. However, little is known about treatment strategies that optimize cessation outcomes for smokers with current or lifetime MDD (Fiore, 2008; Gierisch, Bastian, Calhoun, McDuffie, & Williams Jr, 2012; Hitsman et al., 2009; Weinberger, Mazure, Morlett, & McKee, 2013), largely because almost all randomized controlled trials (RCTs)

excluded these smokers (Hitsman, Papandonatos, et al., 2013). Nevertheless, past major depression (MD) has been well-documented. We published a systematic review and meta-analysis of smoking cessation among smokers with and without past MD in 42 RCTs conducted 1988-2009 (Hitsman, Papandonatos, et al., 2013). Note: MD is distinguished from MDD to reflect that many of the studies in our database did not rule out lifetime manic or hypomanic episode or psychotic disorder, which is needed for a diagnosis of lifetime MDD. To minimize any influence of treatments (e.g., CBT mood management; MM) that might have selectively benefitted smokers with past MD (MD+), we analyzed data from only the lowest intensity control arms of the included studies. MD+ smokers had 17% lower odds of short-term abstinence (OR=0.83, 95% CI=0.72–0.95) and 19% lower odds of long-term abstinence (OR=0.81, 95% CI=0.67–0.97) than MD- smokers.

In contrast to what we have learned about cessation outcomes for smokers with past MD, little is known about how to optimize outcomes for smokers with current or lifetime MDD (Fiore, 2008; Gierisch et al., 2012; Hitsman et al., 2009; Weinberger et al., 2013). To date, there have only been five RCTs of smokers with mood disorder including MDD. Three of these have been limited by sample sizes of less than 90 participants (Blalock, Robinson, Wetter, Schreindorfer, & Cinciripini, 2008; Chengappa et al., 2001; Evins et al., 2008). Hall et al. (2006) compared a stepped-care intervention that involved a computerized expert system and option of six 30-minute therapy sessions that included CBT MM, nicotine patch and bupropion. Participants were 322 smokers with MDD. Abstinence rates at 12-months were higher for the stepped-care group (20%) than for the brief contact control group (13%). In one recent RCT involving 525 smokers with current or recent (past two years) MDD, varenicline nearly doubled abstinence at 52 weeks vs. placebo (28.5% vs. 17.5%) (Anthenelli et al., 2013). These studies provide evidence that smokers with MDD can achieve abstinence. However, because more than two-thirds of smokers with MDD do not quit even with the best treatment (i.e., varenicline), novel interventions are needed to optimize smoking cessation for smokers with MDD.

In preparation for this project, we conducted a new meta-analysis of the 42 RCTs to re-evaluate which treatments are most effective for MD smokers. Our methods, including study characteristics, are described in Hitsman et al. (2013). Cognitive behavioral treatment (CBT) mood management (MM) doubled short-term (≤3 months) abstinence rates (OR=2.04, 95% CI=1.17, 3.57), while varenicline nearly tripled short-term rates (OR=2.92, 95% CI=1.73, 4.92) and more than doubled long-term (≥6 months) abstinence (OR=2.49, 95% CI=1.58, 3.95). While varenicline is promising for this subgroup of smokers, data are limited on its efficacy and safety for smokers with current or lifetime MDD. Further, among smokers with *past* MDD, CBT MM was not effective for long-term abstinence. The limitations of CBT MM for depression, including the complexity of treatment and efficacy that may depend in part on the skill of the individual therapist (S. Rhodes et al., 2014), could contribute to its lack of an effect on long-term abstinence by interfering with skill attainment and maintenance. A treatment that overcomes these limitations is behavioral activation (BA) (Cuijpers, van Straten, & Warmerdam, 2007; Dimidjian, Barrera, Martell, Munoz, & Lewinsohn, 2011; Jacobson et al., 1996; Lejuez, Hopko, & Hopko, 2001; MacPherson et al., 2010). The goal of BA, one component of CBT MM, is to increase engagement in rewarding activities, a problem for smokers with MDD who find smoking especially rewarding, by reducing patterns of avoidance, withdrawal, and inactivity. BA has greater dissemination potential because it is simpler to administer for clinicians with limited experience in psychotherapy (Cuijpers et al., 2007; Ekers, Richards, & Gilbody, 2008).

Another limitation of this literature is that the studies targeting smokers with current MDD have been limited to the clinic setting requiring face-to-face treatment. To achieve the critical goal of increasing access and scalability, treatment will need to extend beyond the clinic. CBT for MDD has been successfully administered by telephone (Mohr et al., 2005; Mohr et al., 2012; Mohr et al., 2010) and the effectiveness of phone-based cessation treatment has been well-demonstrated (Fiore, 2008). CBT MM for cessation has also been administered by phone. In a study targeting smokers with recent or past MDD, van der Meer et al. (2010) observed that 12 weeks (ten 30-minute sessions) of CBT MM (n=243) improved 24-week abstinence rates compared with standard treatment (n=242; 30.5% vs. 22.3%).

Psychological Barriers to Cessation for Smokers with MDD: A New Theory

Limited understanding of psychological barriers imposed by MDD stems from the few RCTs that have included smokers with MD. These smokers are more likely to suffer severe craving and withdrawal during cessation

than smokers without lifetime MD (Weinberger et al., 2010; Weinberger, McKee, & George, 2012). Severe craving and withdrawal have also been found for smokers with current MDD (Lyons et al., 2008; Malpass & Higgs, 2007). Anhedonia, a core symptom of depression, predicts relapse in smokers with and without past MD (J. Cook et al., 2010; Leventhal et al., 2013; Leventhal, Waters, et al., 2009), as does cognitive impairment (attention and memory) (J. Cook et al., 2010; Leventhal, Waters, et al., 2009; Patterson et al., 2009). Smokers with MDD perceive smoking as more pleasurable than other traditionally rewarding activities (Spring et al., 2003). This response may reflect a dysfunctional brain reward system that increases responsiveness to substances (e.g., nicotine) that activate these systems (Cardenas et al., 2002; Markou, 2007).

A major barrier to the development of smoking cessation treatments for smokers with MDD has been that there is no guiding theoretical framework for the psychological processes that serve to maintain tobacco dependence among persons with MDD (Hall, 2004; Ziedonis et al., 2008). To address this important gap, we developed the model presented in Figure 1, which integrates the findings reviewed above, those from our collective work (Audrain-McGovern et al., 2012; Audrain-McGovern, Rodriguez, Rodgers, & Cuevas, 2011; Hitsman et al., 2009; Schnoll, Leone, & Hitsman, 2013; Spring et al., 2008; Spring et al., 2003; Ziedonis et al., 2008), as well as our contribution to the 2010 Surgeon General's Report on the role of learning and conditioning processes in tobacco dependence (United States Public Health Service, 2010). We propose and plan to test here that tobacco dependence is maintained through highly conditioned effects involving anhedonia, depressed mood, and cognitive function. Smoking acquires high reward value through positive reinforcement **(a)** effects fostering cognitive enhancement and reward functioning in the context of a constricted range of positive reinforcers. The positive reinforcing action of nicotine is attributable in large part to its influence on core brain reward centers (Doyle et al., 2014). A meta-analysis by Heishman et al. (2010) found that nicotine improves cognitive performance (e.g., attention and memory) during satiated states. Negative reinforcement **(b)** processes are involved in that smoking dispels withdrawal symptoms, namely anhedonia, depressed mood, and cognitive impairment, which accompany brief periods of abstinence between cigarettes among heavy smokers like those with MDD. Because these withdrawal symptoms mimic depression, smokers with MDD acquire the generalized expectation that their depression (anhedonia, depressed mood, cognitive impairment) is relieved by smoking (Perkins, Karelitz, Conklin, Sayette, & Giedgowd, 2010)

Figure 1. Theoretical Model of the Psychological Effects of Smoking that Maintain Tobacco Dependence in Smokers with MDD

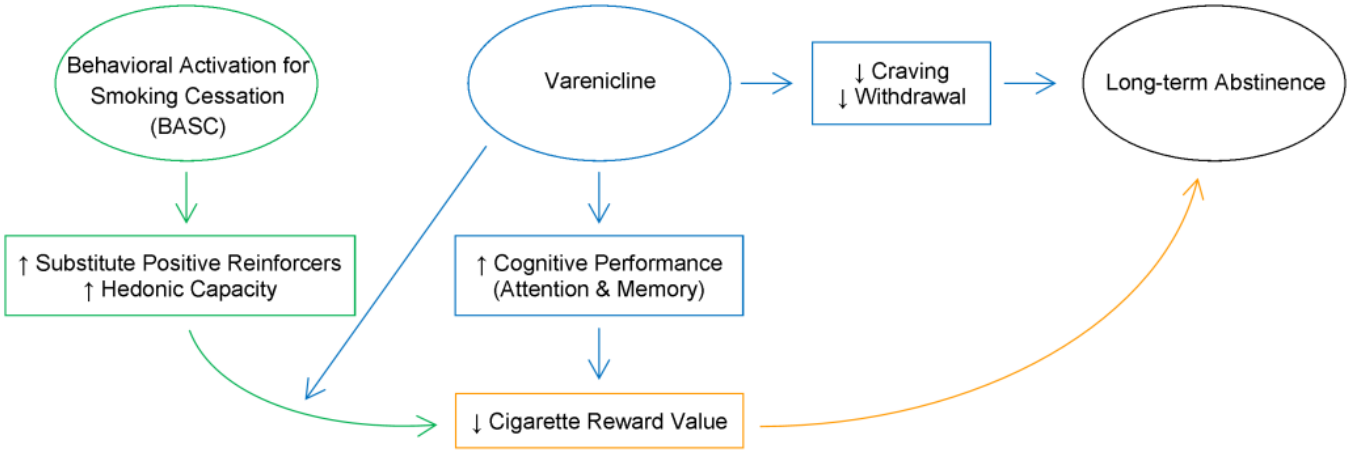
Targeted Treatment for Smokers with MDD

CBT MM and varenicline individually have shown promise for treating tobacco dependence in smokers with MDD. CBT MM, however, has a positive effect only on short-term quitting according to our meta-analysis findings. CBT MM for depression has been noted for several limitations, including the complexity of treatment (for the patient and the therapist) and efficacy that may depend in part on the skill level of the therapist (Cuijpers et al., 2007; S. Rhodes et al., 2014), which could contribute to its lack of benefit on long-term abstinence. A treatment that addresses these barriers is behavioral activation (BA) (Cuijpers et al., 2007; S. Rhodes et al., 2014) one of three components of CBT MM (Dimidjian et al., 2011; Jacobson et al., 1996; Lejuez et al., 2001). BA alone is as effective as CBT MM in treating depression (Cuijpers et al., 2007; Dobson et al., 2008; Jacobson, Martell, & Dimidjian, 2001). Given that BA is simpler to administer, especially for clinicians with limited experience in psychotherapy (Cuijpers et al., 2007; Ekers et al., 2008), it may have greater potential for broad dissemination. BA treatment targets increasing engagement in rewarding activities by reducing patterns of avoidance, withdrawal, and inactivity. We believe that it is well suited for smokers with MDD who prefer smoking over other traditionally rewarding activities and who use smoking as a primary avoidance coping strategy (Kahler, Brown, Strong, Lloyd-Richardson, & Niaura, 2003; Spring et al., 2003). A

small pilot study showed that BA for smoking cessation (n=35) vs. ST (n=33) increased long-term abstinence among smokers with elevated depressive symptoms but no MDD (MacPherson et al., 2010).

Treatment combining BASC and varenicline uniquely addresses the psychological barriers to long-term cessation for smokers with current or lifetime MDD. Barriers include anhedonia, cognitive impairment (attention and working memory), cigarette reward value, cigarette craving, and tobacco withdrawal. Figure 2 presents either known or predicted effects of BASC, varenicline, and their combination. Varenicline attenuates smoking reward, craving, and withdrawal severity (Cinciripini et al., 2013; Dolan et al., 2004; Hitsman, Hogarth, et al., 2013; E. A. McClure, Vandrey, Johnson, & Stitzer, 2013; Patterson et al., 2009; Perkins, Mercincavage, Fonte, & Lerman, 2010; Sofuoglu, Herman, Mooney, & Waters, 2009; West, Baker, Cappelleri, & Bushmakin, 2008) and has cognitive enhancing effects in treatment motivated smokers (J. D. Rhodes, Hawk, Ashare, Schlienz, & Mahoney, 2012) and non-smokers. It also reduces the cognitive impairment that accompanies withdrawal (Patterson et al., 2009). BASC decreases avoidance coping and increases pleasure through increasing engagement in rewarding activities (Cuijpers et al., 2007; Dimidjian et al., 2011; Hopko, Lejuez, Ruggiero, & Eifert, 2003). BASC may be an ideal complement to varenicline because varenicline attenuates smoking reward, but does not help smokers approach and access positive alternative rewards in their lives. Varenicline's attenuation of smoking reward also could enhance the effect of BASC on increasing engagement in alternative rewarding experiences and hedonic capacity, and further reducing smoking reward. Treatment combining BASC and varenicline has not been evaluated but represents a novel strategy that may optimize long-term cessation, especially for smokers with current or lifetime MDD.

Figure 2. Conceptual Model of Mediating Mechanisms for Combination BASC Treatment and Varenicline in Smokers with Current or Recent MDD



Note. Green=BASC, Blue=varenicline, Orange=combined effect of BA and vare-

We expect that treatment combining BASC and varenicline will achieve its effects by: 1) reducing anhedonia and cognitive impairment that maintain smoking behavior through positive reinforcement processes; 2) reducing tobacco craving and withdrawal that maintain smoking behavior through negative reinforcement processes – especially the affective and cognitive components that mimic depression; and 3) reducing cigarette reward value.

Incentives for Research Participation

As with other underrepresented groups, it can be challenging to engage and retain individuals with MDD in clinical trials. Through a partnership with the University of Pennsylvania-led Randomized Evaluation of Trial Acceptability by INcentive (RETAIN) study, we will conduct a sub-study to test a financial incentive strategy designed to maximize recruitment and retention. The sub-study's innovative design will enable a definitive test

of how patients make research decisions in the face of money, and will provide the best possible evidence regarding the scientific and ethical pros and cons of incentives for research participation.

PARTICIPANT ELIGIBILITY

Target Population

Five hundred seventy-six males and females who smoke at least 1 cigarette per day, have a current or lifetime DSM-5 diagnosis of MDD without psychotic features (first episode of MDD can be prior to past two years) will be randomized to treatment. Two hundred and eighty-eight participants will be enrolled at Northwestern (lead clinical site) and 288 will be enrolled at the University of Pennsylvania (PENN). Randomization will be stratified by gender, severity of depressive symptoms (minimal/mild vs. moderate/severe), and clinical site (Northwestern, PENN).

Key Inclusion Criteria

Eligible participants will be males and females who:

1. Are 18 years of age or older and who report daily smoking of at least 1 cigarette per day.
2. Have been diagnosed with current or lifetime MDD without psychotic features according to the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5); Note: first episode MDD diagnosis date may be prior to the past two years.
3. Have or are willing to acquire a personal email address and access to the Internet, fax machine, PDF scanner, or camera phone for submission of therapy practice assignments;
4. Are able to speak, read, and write fluently in English.
5. Are able to provide written informed consent, which includes compliance with requirements and restrictions listed in the combined consent/HIPAA form.
6. Intend to reside in the geographic area for >8 months.
7. If women of childbearing potential, based on medical history and regardless of sexual orientation, consent to use a medically acceptable method of birth control (e.g., condoms, oral contraceptive, contraceptive injection, contraceptive patch, tubal ligation) or abstain from sexual intercourse during the time they are taking study medication and for at least one month after the medication period ends.

Key Exclusion Criteria

Participants who present or self-report any of the following will not be eligible to participate in the study:

Smoking Behavior

1. Current enrollment or plan to enroll in another smoking cessation program in the next 8 months.
2. Regular (daily) use of e-cigarettes, chewing tobacco, snuff, snus, or other tobacco product.
3. Plan to use nicotine replacement therapy (NRT; e.g., gum, patch, lozenge, e-cigarette) or other smoking cessation pharmacotherapy in the next 8 months.

   Note: Once determined to be eligible for the study, participants will be instructed to refrain from using non-study smoking cessation pharmacotherapy for the duration of the study. However, if a participant reports cessation medication use during the study, s/he may be permitted to continue pending study physician and PI approval.

Medication

Current use or recent discontinuation (within last 14 days) of the following medications:

1. Smoking cessation medications (e.g. varenicline, bupropion - if prescribed specifically for smoking cessation - nortriptyline, NRT).

   Note: Once determined to be eligible for the study, participants will be instructed to only use the medication provided to them by the study staff. If a participant reports use of a non-study smoking cessation medication, the study physician and PI will evaluate the situation and determine if it is safe for the participant to continue.

2. Medications indicated for bipolar or psychotic disorder if specifically taken for bipolar or psychotic disorder.

Medical

1. Women who are pregnant, planning a pregnancy within the next 8 months, or breast feeding;
2. History of seizures or current seizure disorder without medication (if stable and medicated, requires physician approval).
3. History of severe (defined as stage IV or V) chronic kidney disease including current or prior end stage renal disease on either hemodialysis or peritoneal dialysis or prior renal transplant.
4. Any prior solid organ transplant or prior hematopoietic stem cell transplant.
5. Heavy drinking as defined by more than 28 drinks per week.
6. Cirrhosis or end-stage liver disease.
7. Systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg after two averaged readings or symptomatic uncontrolled stage II hypertension (systolic blood pressure >160 mmHg or diastolic blood pressure > 100 mmHg after two averaged readings with current reported symptoms of chest pain, dyspnea, headache, or blurred vision).
8. Unstable cardiovascular disease within 3 months prior to baseline assessment, including unstable angina, myocardial infarction, percutaneous coronary intervention, transient ischemic attack, stroke, or other cardiovascular disease requiring hospitalization.
9. Prior hospitalization for heart failure.
10. Previous allergic reaction to varenicline.

Psychiatric

1. Active suicidal ideation within the last 30 days with at least some intent to act, with or without a specific plan. This would be reflected in a score of 4 or 5 on the Suicidal Ideation section of the Columbia Suicide Severity Rating Scale (C-SSRS).
2. As measured using the C-SSRS, a suicide attempt over the past 12 months, not including preparatory acts or behavior, defined by a potentially self-injurious act committed with at least some wish to die as a result of the act.
3. Lifetime bipolar or psychotic disorder as determined by either self-report or Mini International Neuropsychiatric Interview (MINI).

General

1. Any medical condition or concomitant medication that could compromise participant safety or treatment, as determined by the PI or study physician.
2. Inability to provide informed consent or complete any of the study tasks (e.g., medical condition with a life expectancy < 1year) as determined by the PI or study physician.

Vulnerable Populations

Children under 18 years of age, pregnant women, fetuses, neonates, or prisoners will not be included in this study. Socioeconomically disadvantaged persons will be included in this study, but not targeted for recruitment. It is possible that Northwestern and PENN employees or students may choose to participate. However, status of participation in the study will be independent of the participant's work or school activities.

Recruitment and Accrual Procedures

Treatment Sites

The research teams at Northwestern (lead site) and PENN have extensive experience with smoking cessation and other behavioral trials (depression, obesity, multiple behavior change). At Northwestern, the trial will be conducted in the Department of Preventive Medicine, which has been the site for large smoking cessation (Goelz et al., 2014) and depression (Mohr et al., 2012) studies. At PENN, the trial will be coordinated by the Center for Interdisciplinary Research on Nicotine Addiction, which has been the site for several large smoking cessation trials (Schnoll et al., 2010). Our two sites collaborated on a recently completed trial (R01DA025078) for which we enrolled, with no targeted recruitment, 18.7% (98/525) of participants with current or past MDD.

Participant Recruitment

We will recruit via multiple channels in the Chicago and Philadelphia metropolitan areas, including targeted print and electronic advertisements in the community and on relevant social media (i.e., targeted Facebook and Twitter advertising). Recognizing: 1) the need for a large sample; and 2) the goal of including a community sample, we developed infrastructure and partnerships with the Departments of Public Health in Chicago and Philadelphia, community-based mental health centers in Chicago and Philadelphia, and the primary care networks at Northwestern and PENN to recruit the participants. As done in our previous clinical trials, we will use targeted print and electronic media ads (public transportation, newspaper, radio, television, internet, and social media groups/sites) as the primary form of recruitment. Our 30-second television advertisement will run on targeted broadcast channels designed to reach a diverse group of cigarette smokers who may be interested in participating in the study. Where applicable, we will provide a secure link within electronic ads to an online pre-screener (managed through REDCap and NU NITRO Recruit) or landing page (UPENN's iConnect) within which readers may provide their contact information if they express interest in learning more about the study. We will use media sources with a varied range of viewership or listenership as doing so in our past clinical trials has allowed us to ascertain large (i.e., >500) and diverse (i.e., >30% racial/ethnic minorities) samples.

In addition, we will recruit within clinical departments and services at Northwestern-and PENN-affiliated hospitals. Through our collaboration with researchers in the Department of Psychiatry and Behavioral Sciences at NU, we will use the NU-CRP Recruitment Pipeline (IRB #59328) to identify potentially eligible patients who have previously agreed to be contacted regarding future research projects. We will use Research Match through NUCATS; Research Match (www.researchmatch.org) is an online registry that connects research studies with a database of candidate participants. It was created through collaborations between the Clinical & Translational Science Awards (CTSA) Consortium and funded by the National Center for Research Resources, a component of NIH. We will also recruit via outreach to our community partners through the extensive Cook County Health and Hospital System (at Northwestern, facilitated by Andrew Segovia Kulik, M.D., Interim Chairman of Psychiatry, CCHHS) and community medical- and mental health centers.

Potential participants and data may also be identified through reports generated by the Northwestern Medicine Enterprise Data Warehouse (NMEDW), a joint initiative across the Northwestern University Feinberg School of Medicine and Northwestern memorial HealthCare (NMHC), a corporate parent of Northwestern Memorial Hospital, Northwestern Memorial Group, and Northwestern Medicine Lake Forest Hospital. NMEDW data sources include Cerner PowerChart, PRIMES, Epic, IDX, eNOTIS, and 50+ other systems from the campus. Once approved by the treating provider, potential participants reported by NMEDW to the Project Director may then be contacted with an opt-out letter followed by telephone calls, and provided with study information and asked if they are interested in completing the telephone pre-screen. Additionally, the PENN site will use the volunteer registry in iConnect to identify potential participants.

The PENN site will also collaborate with mental health clinics in the Philadelphia metropolitan area for direct recruitment. Clinics that agree to refer patients to the trial will provide study staff with contact information for patients identified as potentially eligible based on an internal medical record review. A Research Assistant will contact these patients to assess interest in the study and screen for initial eligibility.

Potential participants and data may also be identified through reports generated by the University of Pennsylvania Data Analytics Center through the Penn Data Store. Data sources include Aria, TheraDoc, EMTRAC, DocuSys, MedView, Sunrise, EPIC, Cerner and HDM & ClinTrac. Potential participants identified by the reports may then be contacted with an opt-out letter followed by telephone calls, and provided with study information and asked if they are interested in completing the telephone pre-screen.

After obtaining the necessary training and clearances to access PennChart for participating UPHS departments, PENN Research Assistants will review patient electronic medical records to identify potential subjects on a weekly basis (patient smoking status indicated on the record). Individual medical records will be evaluated for eligibility based on the inclusion and exclusion criteria for this study. RAs will contact potentially eligible patients after EMR review by telephone based on their provider's specified research contact preference. Providers may choose one of the following contact options: 1) all patients identified as initially

eligible may be contacted 2) all patient records identified as initially eligible will be sent to the provider via PennChart for review and approval prior to contact 3) all patient records identified as initially eligible may be sent to the provider, who assumes full responsibility and discretion regarding the research contact (no contact may be made by the research staff). Those patients deemed eligible for contact will be contacted by telephone. RAs will introduce the research study and the collaboration between the researchers and the patient's provider. After assessing the patient's interest, he or she will then be provided with additional study information and an opportunity to assess his/her intake eligibility based on a screening questionnaire.

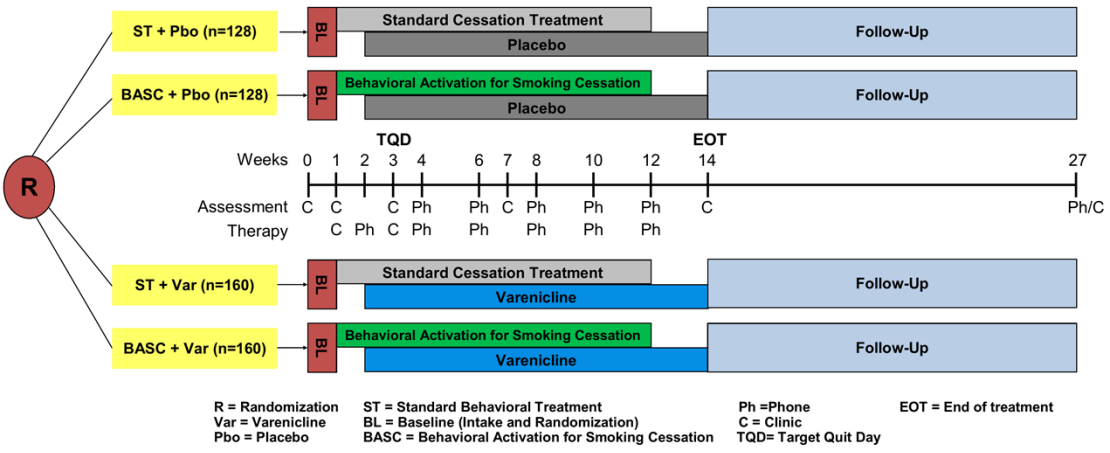
Research Recruitment Best Practice Advisories (BPAs) will also be integrated into electronic medical record recruitment at PENN. BPAs are designed to fire passive alerts within PennChart at the point of care, notifying providers that a patient may be eligible for a specific study. This specific BPA will evaluate if a patient meets specific criteria associated with the trial and will present the provider with the option to indicate if a patient is interested in participating in the study or not. This BPA will only present if the patient meets the initial screening criteria based on smoking status and problem list diagnoses and will only present in specified departments (Internal Medicine and Family Medicine). This indication of interest only serves to trigger a notification to study staff that a patient has met initial screen criteria and further follow-up is requested to determine eligibility of the patient. This alert is a passive alert and will not interrupt the provider's workflow, but will be listed in the same section as other clinically warranted BPAs.

To ensure high retention and adherence in this trial, we will: 1) educate participants about the benefits of adherence (Ebbert, Wyatt, Hays, Klee, & Hurt, 2010); 2) schedule sessions at convenient times; 3) incorporate a medication adherence component into the BASC and ST protocols (Gariti et al., 2009; Schnoll et al., 2008); and 4) as is standard practice in smoking cessation trials (Niaura et al., 2005; Schnoll et al., 2010), provide modest financial compensation for session completion and transportation costs. We expect that ≤20% of participants will withdraw from the study and >70% of participants will complete follow-up evaluations, which would exceed rates in varenicline trials (Jorenby et al., 2006).

STUDY DESIGN

This is a Phase IV, randomized, double-blind, placebo-controlled, two-site clinical trial (Figure 3).

Figure 3. Study Design

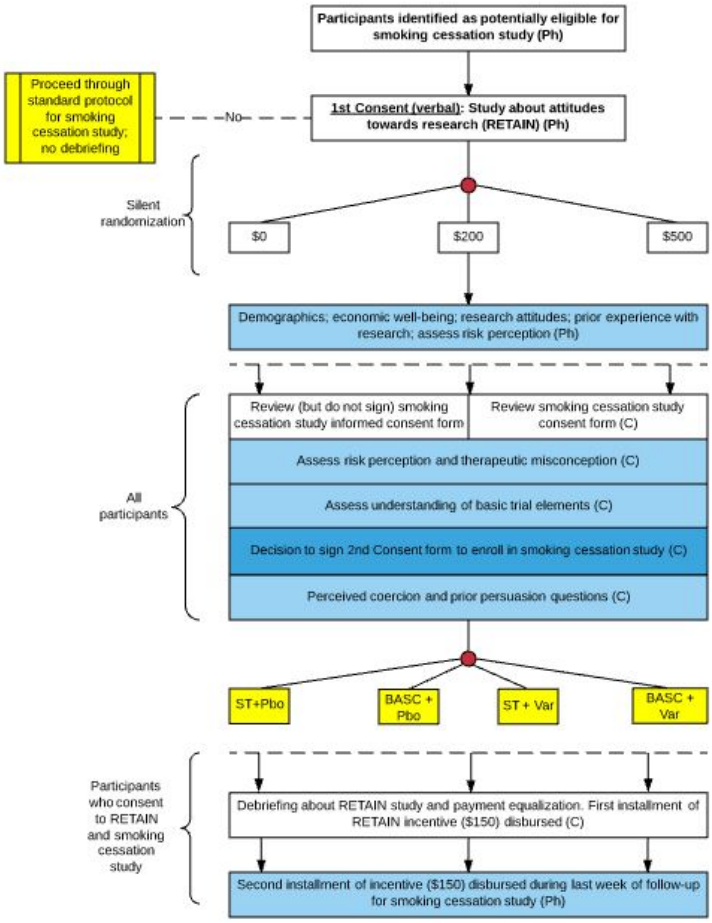


Rationale for Treatment and Design

We chose combination BA and varenicline for smokers with current or lifetime MDD given the results of our meta-analysis of treatment response among smokers with past MD. Varenicline had the strongest association with long-term abstinence but CBT MM was effective for only short-term abstinence. Compared with CBT MM, BA is simpler to administer, time-efficient, and less complicated for patients (Dimidjian et al., 2011; Jacobson et al., 2001; Lejuez et al., 2001) and thus may enhance skill acquisition/maintenance and long-term abstinence. BA alone is as effective as CBT MM for depression (Cuijpers & Schoevers, 2004) and preliminary efficacy of

BA for long-term cessation has been found in smokers with elevated depressive symptoms but screened out for current MDD (MacPherson et al., 2010). Combination BA and varenicline has the potential to optimize long-term cessation considering: 1) the psychological impairments in MDD; 2) the psychological factors associated with smoking behavior and cessation, especially in smokers with MDD; 3) the documented behavioral effects of BA in MDD; and 4) the psychological effects of varenicline during smoking cessation. We chose the 2x2 design because it provides comparison arms to evaluate efficacy and mediators of combination BA and varenicline vs. either BA alone or varenicline plus ST. This design also provides the placebo control to fully evaluate AEs in smokers with MDD for whom varenicline has been discouraged given safety concerns (Williams, 2012).

Figure 4. RETAIN Study Schema



Length of Study Participation

Participants will be involved in study-related activities for approximately 7 months (28 weeks) from initial eligibility assessment through follow-up. A participant's length of involvement may be affected by site or participant scheduling conflicts.

Study Timeline (Table 1)

We expect to complete accrual in about 48 months, enrolling about 12 participants per month.

DRUG/DEVICE INFORMATION

Study Medication (Varenicline Tartrate)

Medication Course and Dosing

Participants will begin medication during week 2 (Pre-Quit 2) and continue for 12 weeks according to the following regimen in accordance with FDA-approved labeling for varenicline: Day 1-Day 3 (0.5mg once daily); Day 4-Day 7 (0.5 mg twice daily); Day 8-Day 84 (1.0 mg twice daily) (Gonzales et al., 2006; Jorenby et al., 2006). The TQD will occur on Day 8 of varenicline or placebo, the first day of full-strength dose. The first two weeks of medication (week 2-3) will be dispensed at week 1 (Pre-Quit 1). Medication blister packs for weeks 4-7 will be dispensed at TQD; blister packs for weeks 8-13 will be dispensed at the Week 7 in-person assessment. Fifty-five percent (n = 320) of the participants in the BASC and ST arms will be randomized to receive active varenicline while the remaining 45% (n = 256) of participants across both arms will receive placebo pills that look and taste like active varenicline medication. Participants will take this medication until Day 84. If a participant is not able to attend a medication pick-up visit (Weeks 3 or 7) within the specified window (see details below), the session will be completed by telephone and, if able to safely continue with the medication after potential side effect review, one week of medication will be mailed to the participant by the research pharmacy or a brief in-clinic pick-up will be arranged. Participants will need to attend a clinic visit to

Table 1. Project Timeline

	Year 1				Year 2				Year 3				Year 4				Year 5			
Task/Months	1-3	4-6	7-9	10-12	13-15	16-18	19-21	22-24	25-27	28-30	31-33	34-36	37-39	40-42	43-45	46-48	49-51	52-54	55-57	58-60
Refine/test DMS and train staff (1-3)																				
BASC refinement/therapist training (1-6)																				
Recruitment/baselines(6-54)																				
Treatment (6-57)																				
Outcome assessments (12-60)																				
Analysis/manuscripts (48-60)																				

complete a blood pressure assessment before additional medication is dispensed. Participants may also be asked to visit the clinic for a brief medication pick up if a complete course of medication is not available on a scheduled medication pick-up visit or if the participant loses medication and requires replacement kits. Because no data is being collected during these brief encounters, no additional compensation will be provided. Participants who discontinue study medication for 14 or more consecutive days will require approval from the PI and study physician before restarting the study medication.

Side Effects and Adverse Events (AEs)

Following a large-scale trial supporting the safety of varenicline for smoking cessation among those with and without a current psychiatric disorder (Anthenelli et al., 2016), the FDA removed the boxed warning on varenicline in December, 2016. Several additional varenicline trials of smokers with lifetime mental health disorders have provided evidence of safety (Gibbons & Mann, 2013; Hays, Croghan, Schroeder, Ebbert, & Hurt, 2011; J. B. McClure et al., 2009; Meyer et al., 2013; Pachas et al., 2012; Philip, Carpenter, Tyrka, Whiteley, & Price, 2009; Spirling, Stapleton, & Sutherland, 2008; Stapleton et al., 2008; Wu et al., 2012). In the only RCT of varenicline to target depressed smokers (Anthenelli et al., 2013), there were no suicidal ideation or behavior events in the varenicline condition. In the placebo condition (N=269), there were three cases of suicidal ideation and a case of self-injurious behavior. Approximately 75% of the sample was antidepressant medication stable (i.e., ≥2 months without a dosage change), while the remaining 25% of the sample was not currently on medication for mood (R. Anthenelli, personal communication, December 7, 2015). Analyses indicated no differences in side effects or adverse events between the medicated and unmedicated groups, and the medication was shown to be safe overall. Although we will assess for potential antidepressant-varenicline interactions in the current trial, varenicline has no known pharmacokinetic interactions (Faessel et al., 2010; Rollema, Wilson, Lee, Folgering, & Flik, 2011) or clinically meaningful interactions with other medications that are renally cleared, such as antidepressants ("Clinical Pharmacology [database online]," 2014). Please also see “Potential Study Risks” section.

Supply, Preparation, Storage, Packaging and Dispensing of Study Medication

Varenicline and matching placebo is provided at no-cost by Pfizer and packaged and stored at Northwestern Memorial Hospital’s (NMH) Investigational Research Pharmacy. The NMH Research Pharmacy will oversee the randomization and labeling of study medication, and will assign each kit, which contains 12 weeks of medication for one participant, a unique Pharmacy Randomization Number (PRN) or kit number. Once a new participant is enrolled and eligible, the research staff will assign the participant the PRN kit number based on the blinded randomization scheme. Blister packs will then be labeled with the participant’s full name per Illinois Pharmacy Practice Act regulations. The PRN and participant’s name must match for each blister pack.
A centralized system helps to preserve internal validity and maintain study blinding of clinical site personnel. The Northwestern project director will work with the NMH pharmacy to ensure that an adequate supply of medication is available at both sites. Medication will be stored in locked, climate controlled cabinets. Medication supply, in increments, will be given to participants at Week 1 (Pre-Quit 1), Week 3 (TQD), and Week 7 sessions.

Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed by the research personnel who perform the reconciliation. At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated by the research staff. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Once a participant has completed the course of the study drug (i.e., 12 weeks) and medication adherence data has been recorded, any remaining pills will be destroyed on site or sent to a recognized third party disposal agency and this will be documented in the study files.

STUDY PROCEDURES

Screening and Baseline Procedures

Initial Eligibility Screening

Study candidates will complete an initial eligibility assessment in the clinical site from which they were recruited (Northwestern or PENN) or by telephone. This assessment reduces the likelihood that participants will attend an intake session only to learn that they are ineligible, and allows us to ascertain physician's clearance should the participants have a medical condition that requires approval. Participants who are initially eligible will be screened against our registration database to confirm that they are not currently participating in another research study at our Center and have not previously reported a condition or circumstance that would make them ineligible for the current study. Those participants who are deemed initially eligible during a telephone screening who remain initially eligible will then be invited to attend an Intake Visit at our Center (completed within 60 days of the initial eligibility screening) during which they will be presented with the IRB-approved Informed Consent Form and have their final eligibility confirmed. during which the purpose and procedures of this study will be described to them and final eligibility will be confirmed. Participants may be mailed a letter detailing the study visit, directions to the study site, and contact information. Callers who do not pass the pre-screening may be directed to other research studies they may be interested in (e.g., clinicaltrials.gov, The Center for Behavioral Intervention Technologies [CBITs] at Northwestern or Mood and Anxiety Disorders Program at PENN) or provided with other smoking cessation resources (e.g., the Illinois/Pennsylvania State Quitline), as appropriate.

Once a participant is determined to be preliminarily eligible for MDD, the research staff will ask the RETAIN eligibility prompt to assess for prior knowledge of the specific incentives or randomization used for RETAIN. Participants who do not have prior knowledge of the RETAIN incentives or randomization will be silently randomized by the research staff to one of three incentive conditions via the MDD trial's DMS ($0, $200, or $500; described under Data Analysis below), and immediately present participants with information regarding their assigned condition. Participants who are randomized to the RETAIN sub-study will complete baseline questionnaires over the phone to assess 1) demographics and personal financial well-being, 2) attitudes towards biomedical research, 3) previous experience in research, and 4) perceptions of research risk.

Prospective participants who have prior knowledge of the incentives or randomization used for RETAIN will not be randomized, enrolled, or receive RETAIN-related messaging on the phone call. They will receive the standard study information regarding session and travel compensation for the MDD trial without RETAIN messaging. These participants will not be debriefed or paid the RETAIN incentives.

<u>Baseline Intake Session (Week 0): Eligibility, Consent, Randomization, Baseline Measures</u>
Participants who pass the pre-screening will be invited to attend a 2-3½ hour Intake session where the following activities will occur:

1. Informed consent/HIPAA forms will be reviewed with participants, during which they will hear a description of all study procedures, risks, benefits, and information about the study medication. Participants' questions will be answered. Following this discussion, the combined informed consent and HIPAA form will be completed.
2. A urine pregnancy test will be administered to all female participants.
3. A carbon monoxide (CO) breath assessment to measure recent tobacco exposure. The handheld device uses a disposable mouthpiece, reports CO in parts per million (PPM), and takes about three minutes to administer.
4. A 5mL saliva sample (about 1 teaspoon) will be taken to assess nicotine metabolic rate.
5. A 12.5 mL blood sample will be drawn to measure cholesterol and glucose levels for participants who consent to this procedure.
6. A structured psychiatric interview (Mini-International Neuropsychiatric Interview, Columbia Suicide Severity Rating Scale) with a trained research staff member.
7. Medical history and evaluation of vital signs and anthropometry to be completed by research staff.
8. A concomitant medication review, including antidepressant medication.
9. Once the above steps have been completed and if eligible at this point, the participant will complete baseline paper and pencil measures to assess: 1) variables that may serve as covariates and that allow for the assessment of antidepressant-varenicline interactions (antidepressant medication use and type) and external validity (e.g., demographics); 2) mediator variables (e.g., hedonic capacity); 3) psychiatric symptoms; and 4) smoking behavior.

10. If eligible, the participant will be randomized to treatment condition using a randomization scheme provided by Dr. Papandonatos and implemented through the data management system. Randomization will be stratified by clinical site, gender, and severity of depressive symptoms (minimal/mild vs. moderate/severe, as defined using the BDI-II (Beck, Steer, & Brown, 1996)) and will be by permuted blocks of fixed size (18 participants per block) with unequal 4:4:5:5 allocation ratio across the four study arms, such that a minimum of N=128 participants be assigned to each psychological treatment group (BASC, ST) receiving placebo, while a minimum of N=160 participants be assigned to each psychological treatment group (BASC, ST) receiving varenicline.
11. Once randomized, participants are scheduled for the first treatment session (Pre-Quit, Week 1). There must be no more than two weeks between the intake session and the first treatment session.

At the baseline intake session, participants who are randomized for the RETAIN sub-study will complete the following additional procedures:

1. Informed consent/ HIPAA forms with additional information regarding the RETAIN sub-study randomization condition, viewed via REDCap survey. We will assess the amount of time participants spend reading each part of the main trial consent form by presenting each section (e.g., Study Introduction, Procedures by Visit, Possible Risks and Discomforts, etc.) as a survey in REDCap. A timestamp function will allow us to assess the time at which participants move from one section of the consent to the next. Research staff will then administer a trial quiz assessing understanding of key trial elements, and review responses with participants. Participants will have the opportunity to ask any questions they have regarding information in the Informed Consent and HIPAA forms prior to providing their signature.
2. Before signing, participants will complete brief questionnaire measures of a) perceptions of research risk, b) perceptions of the difference between research and individualized patient care, and c) understanding of the smoking cessation study via a trial elements quiz. The responses to the quiz will be reviewed with participants, during which participants' questions will be answered.
3. After signing, participants will complete brief questionnaire measures of a) perceived coercion, and b) prior persuasion (described in Measures section below).
4. Lastly, participants will receive a full debriefing regarding the purpose of the RETAIN sub-study. Research staff will explain that all RETAIN sub-study participants receive up to $500 ($300 RETAIN incentive payment and up to $200 for time and travel), regardless of what was stated in the Informed Consent Form.

Procedures During Treatment

Psychological Treatment Plan (Weeks 1-12)

All participants will receive manual-based treatment from a therapist trained and supervised by Drs. Jackie Gollan (Northwestern), Anita Hole (PENN), and Brian Hitsman (PI). After final eligibility has been confirmed by either the project director, study physician or PI (lead and PENN clinical site), participants will be randomized to receive either the BASC or ST interventions. BASC treatment will integrate behavioral activation therapy (Dimidjian et al., 2011; Jacobson et al., 1996; Lejuez et al., 2001) and ST. ST will be based on the 2008 PHS Clinical Practice Guideline (Fiore, 2008) and on ST in our recently completed and ongoing two-site trials (R01DA025078 and R01CA165001, respectively). BASC and ST will be delivered in eight 45-minute sessions over 12 weeks, weekly for the first four sessions and every other week for the final four sessions. Session frequency and duration are based upon past CBT MM trials (Haas, Munoz, Humfleet, Reus, & Hall, 2004; Patten, Martin, Myers, Calfas, & Williams, 1998). BASC and ST will follow the same schedule, equated on number of sessions and total participant-therapist contact time. The schedule for both psychological treatment arms is described next.

Pre-quit sessions 1 and 2 (Weeks 1 and 2): BASC and ST begin with two "Pre-Quit" therapy sessions (Pre-Quit 1 in-person, Pre-Quit 2 by phone) designed to help participants prepare for the target quit day (TQD/Week 3). These sessions focus on reviewing participant's history and experience with quitting and, per random assignment, will also introduce either the BASC or ST treatment models and participants will initiate a quitting plan that aligns with techniques from the assigned therapeutic approach. Two weeks of medication are dispensed at Pre-Quit 1 and participants will be instructed to wait until the day of Pre-Quit 2 (Week 2) to start

taking the study medication. During the Pre-Quit 2 (Week 2) phone session, participants will be instructed to take their medication starting that day. The therapist will contact participants two days later to ensure that instructions regarding medication use are being followed.

Target quit day session (Week 3): At Week 3, participants will complete their in-person "Quit Day" session to review the initial quit attempt, identify potential reasons for relapse, and review their quit plans. Medication for weeks 3-7 will be dispensed at this visit.

Booster therapy sessions (Weeks 4, 6, 8, 10, and 12): Participants will then receive five additional 1-hour therapy sessions by phone at Weeks 4, 6, 8, 10, and 12 which either reinforce success and review the quit plan or reestablish a quit date and restart the cessation process. The sessions are designed to use BASC- or ST-specific strategies to assist the person in developing skills to quit and avoid relapse, instruct the smoker on varenicline use, and address medication compliance or study participation adherence (as applicable).

Session windows: The first Pre-Quit session (Week 1) must occur within 2 weeks of the baseline intake visit. Any exception to this procedure will require PI approval and re-administration of the BDI-II by phone, to ensure current assessment of depressive symptoms for stratification purposes. Pre-Quit 2 (Week 2) may occur 5-10 days after completion of Pre-Quit 1. The TQD session (Week 3) may occur +3 days from the target date (Day 8 of study medication). Week 4 may occur +/- 4 days from the target date (Day 15 of medication). Weeks 6, 8, 10, and 12 sessions may occur +/-1 week from their target date. The Week 7 assessment session must occur after the Week 6 therapy session +/- 3 days from the target Week 7 date. The Week 14 session must occur on or up to +1 week after the participant has completed drug treatment. The Week 27 follow-up session may occur -1 or up to +2 weeks from the target date. Participants who report abstinence at the Week 27 phone session may complete the Week 27 in-person clinic visit anytime immediately after completing their Week 27 phone session and up to 2 weeks after their Week 27 phone session. Throughout the study period, a session will be considered missed if it is not completed within the session window. Following any missed session(s), the participant will be contacted for the next scheduled session according to the study calendar.

Behavioral Activation for Smoking Cessation Intervention

BASC aims to increase engagement in rewarding activities by reducing patterns of avoidance, withdrawal, and inactivity. Our BA treatment model is based on Jacobson et al.'s BA model (Jacobson et al., 1996) given its emphasis on reward management and session sequence that can be integrated with 12+ weeks of ST consistent with the current conceptualization of tobacco dependence as chronic and requiring longer-term treatment (Fiore, 2008). Key components of BASC include activity monitoring and rewarding activity scheduling, assessment of personal goals and values, assessment and altering of avoidance behavior and other maladaptive coping strategies, and contingency management. BASC focuses on reducing stress pile-up and loss of pleasure that accompanies the cessation process and on identifying and establishing environmental/social changes that will promote abstinence. BASC addresses smoking as a behavior that prevents and restricts opportunities for contact with healthy rewarding behaviors. These changes are achieved through altering daily routines that had been previously been associated with smoking in ways that increase pleasure and mastery across life domains, reducing rumination, and increasing behavioral skills to prevent return to smoking as a means of avoiding stressors.

Two pre-quit sessions (Pre-Quit 1 and 2) will introduce participants to: 1) self-monitoring of mood and behavior using the Daily Activity Monitoring Record; 2) assessment of personal values to refine the treatment plan; and 3) scheduling of substitute rewarding activities that align with their abstinence goal. Participants will submit their completed homework (or follow-through) assignments to their study therapist by either email/fax, completed electronically using web-based forms, or camera phone.

At the TQD session (Week 3), participant experiences with abstinence will be reviewed and functional analysis of behavior will be introduced, especially as it relates to smoking and avoidance patterns. Information obtained will be used to help generate behavioral activation plans that increase rewarding activities and relationships, reduce avoidant responses to distressing experiences, and facilitate successful implementation of smoking trigger management strategies.

Booster sessions 4-8 will incorporate strategies to address avoidance patterns, especially those involving smoking, and to replace them with adaptive coping strategies. Strategies include managing stress pile-up using step-by-step task deconstruction (i.e., breaking large tasks into small manageable steps), recognizing rumination (Stiles-Shields, Kwasny, Cai, & Mohr, 2014) as avoidance coping, becoming more proactive and less mood-dependent, short-term goal setting, especially as it pertains to relapse prevention, and long-term goal planning to promote increased pleasure and mastery that aligns with personal life goals.

Standard Treatment Intervention

The ST protocol is based on U.S. PHS guidelines for smoking cessation treatment (Fiore, 2008) and used in our recently completed and ongoing trials at Northwestern and PENN (R01 DA025078 and R01CA165001, respectively). ST arm will focus on self-monitoring of smoking behavior, identifying smoking triggers and alternative trigger management strategies, relaxation, social support for non-smoking, and relapse prevention. Two pre-quit sessions help prepare participants for their TQD by reviewing their experience with quitting, beliefs about smoking/quitting, perceived barriers to cessation, and creating a quit plan to identify smoking triggers and implement alternative strategies to manage those triggers without smoking. TQD and booster sessions will help participants use “avoid, alter, or substitute” strategies for trigger management to prevent relapse.

Treatment Fidelity

The same study therapists will conduct both the BASC and ST interventions. Therapists will use condition-specific session checklists to guide session content. Sessions will be audio-recorded and a random sample of 25% of BASC and ST sessions, respectively, will be assessed for protocol adherence per study site. Drs. Gollan (Northwestern) and Hole (PENN) will perform independent ratings. The fidelity assessment will provide scores for therapist competence, adherence, and contamination. To assure ongoing fidelity, therapists will attend bi-weekly supervision by teleconference with Drs. Gollan and Hole for review of audio-recorded sessions. Retraining will be triggered if adherence is less than 90% or if there is any evidence of cross-condition contamination. Because the therapist will handle both the BASC and ST interventions, s/he will not conduct any assessments, if possible. Therapists will be blind to study drug randomization.

Pharmacological Treatment Plan (Weeks 2-14)

A 12-week course of varenicline or matched placebo will be used in accordance with FDA approved labeling: Day 1-Day 3 (0.5mg once daily); Day 4-Day 7 (0.5 twice daily); Day 8-Day 84 (1.0 mg twice daily). The first week of medication (Week 2) will be dispensed during Pre-Quit 1 (Week 1). Medication blister packs for weeks 3-7 will be dispensed on the TQD (Week 3); blister packs for weeks 8-13 will be dispensed at the Week 7 in-person assessment. At each session following Pre-Quit 2, medication adherence will be evaluated by self-report. Therapists will monitor and address medication adherence issues as a regular part of therapy sessions. For the TQD session and the Week 7 and 14 sessions, adherence will also be evaluated by pill count. Specific strategies to address non-adherence will be used, if necessary. Our approach to evaluating medication adherence assesses participant reasons for medication non-adherence using scenarios and counters with specific strategies to enhance compliance.

Mid-treatment Assessments

Assessments will be conducted at Weeks 0, 1 (Pre-Quit 1), 3 (TQD), 4, 6, 7, 8, 10, 12, and 14 (EOT) by a research assistant and supervised by the study physician and study psychologist. Assessments during phone sessions will require ~20 minutes to complete and will be conducted before therapy sessions. Assessments at Weeks 1, 7, and 14 in-person visits will take ~90 minutes to complete. Assessments include measures of mediating variables, psychiatric status, side-effects, treatment adherence (pill count, collection of blister packs), and smoking behavior. Only the research assistants, blind to condition, will conduct assessments, if possible.

Side Effect Monitoring

Repeated assessments will permit close monitoring of participant safety as done in our completed and ongoing two-site trials involving pharmacotherapy (R01DA025078 and R01CA165001/**STU00064871**, respectively).

The research team has clinical psychologists and physicians at each clinical site to review ongoing eligibility status and to monitor and address potential AEs associated with the study drug during the trial.

As is done in another IRB-approved protocol involving varenicline (STU00064871), we will regularly assess participant reactions to treatment with a previously-used varenicline adverse event checklist and validated depression and suicidality scales. These assessments are conducted 10 times during the study before, during and after the treatment phase by research staff supervised by the clinical site study physician and psychologist. Given conflicting reports indicating there may be potential risk of adverse cardiovascular effects from varenicline (Prochaska & Hilton, 2012; Singh, Loke, Spangler, & Furberg, 2011) participants will undergo evaluation of recent medical history, blood pressure, and heart rate at Weeks 0, 1, 3, 7, 14, and 27 to monitor cardiovascular reactions to study medication.

We will use an established coding and reporting system for adverse events used in our ongoing two-site trial of varenicline for smokers (R01CA165001/**STU00064871**). Study personnel are trained by physicians and psychologists to administer adverse event instruments, including validated depression and suicidality scales. If an adverse event or serious adverse event report or a score on a scale indicates a safety concern, site PIs and physicians or psychologists are immediately notified and determine a course of action (e.g., stop medication). Participants are instructed to contact their counselors if an AE occurs, as well as given contact information so that they can contact the study physician at each site 24 hours/day if an SAE occurs. Adverse events are also coded and managed by PIs and site physicians or psychologists. All SAEs are subject to reporting to the IRB, NCI, FDA, and Pfizer as outlined in the Data Safety Monitoring Plan and may be referred to an outpatient or emergency department. Lastly, a study-specific Data Safety and Monitoring Board (DSMB) will be convened for this trial to monitor side effects.

Follow-Up Procedures

Outcome Assessments

The primary outcomes will be 7-day point prevalence abstinence at Week 27 (24-weeks post-TQD) confirmed with CO (Hughes et al., 2003), and AE rates. CO-verified 7-day point prevalence abstinence at weeks 7 and 14 (4- and 10-weeks post-TQD, respectively) will be secondary outcomes. Other outcomes at 24-weeks post-TQD will include: prolonged abstinence (relapse defined as 7 consecutive days of self-reported smoking after a 2-week grace period), continuous abstinence (no smoking between TQD and follow-up), and time to 7-day relapse (no grace period). All participants will be asked to attend in-person sessions at Weeks 7 and 14 to provide CO breath samples. At Week 27, all participants will complete the assessments by phone and only those who self-report abstinence will be asked to attend an in-person session for CO verification. Safety Assessments Side effect monitoring, suicidality assessments, medication adherence assessments will be administered as done during the treatment phase of the trial. A follow-up session will occur in-person at the end of treatment (EOT, Week 14) and at 6-months post-TQD for participants who report abstinence (Week 27).

Measures (see Table 2)

Screening/Covariates

Medical and psychiatric history: All medical conditions and medications related to risk for potential adverse reactions to varenicline will be assessed. A urine pregnancy test will be conducted for women. Blood pressure and heart rate will be assessed at each clinic visit. Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) mood, psychotic, and substance use disorders (current/past) will be evaluated using: 1) the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) adapted to the DSM-5; and 2) the Columbia Suicidality Severity Rating Scale (C-SSRS; www.cssrs.columbia.edu). The MINI is a 30-45 minute structured interview developed by the World Health Organization to assess psychiatric diagnoses. Administered at the intake session, the MINI permits both current (past 30 days) and lifetime assessments of psychiatric disorder. The MINI modules to be administered include: major depressive episode, (hypo)manic episode, panic disorder, agoraphobia, social anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, psychotic disorders, alcohol use disorder, substance use disorder, and generalized anxiety disorder. Suicidality will be assessed in more detail at each session using the Columbia Suicide Severity Rating Scale (C-SSRS). The C-SSRS is a semi-structured interview that assesses suicidal ideation (passive, active, and intensity of ideation) and four types of suicidal

behaviors (actual, interrupted, and aborted attempts, and preparatory acts or behavior). It was developed and designed to track suicidal events across depression treatment and provides standardized, explicit definitions of suicidal ideation and behaviors to improve safety monitoring data collection.

Blood pressure: At the baseline intake visit study candidates will have two blood pressure readings taken, each after a five-minute period in which the person will be instructed to sit comfortably in a quiet setting. If, after taking the average of the two readings, a candidate has a blood pressure reading above either: (a) 185 mmHg systolic and/or 110 mmHg diastolic, or (b) above 160 mmHg systolic and/or 110 mmHg diastolic with co-occurring symptoms of chest pain, dyspnea, headache, or blurred vision, s/he will be ineligible for the study. Blood pressure will be measured at every clinic visit. If a participant presents with elevated blood pressure (≥185/110 or ≥160/100 and symptomatic, averaged from two readings) at any clinic visit following the intake session, the study physician will be notified to determine how to proceed. For example, the participant may be discontinued from study medication and invited to continue in the trial to complete psychological treatment and assessments only. Additional study drug will not be given to the participant until cleared by the study physician.

Psychiatric treatment and depression/anxiety symptoms: We will collect information about treatment history, including psychotropic medication, psychotherapy, and hospitalization. Use and type of antidepressant medication will be measured across treatment using a timeline follow-back (TLFB) interview (Brown et al., 1998) and recorded on a depression medication adherence questionnaire. This TLFB interview is the same as what we have used in our completed and ongoing two-site trials involving pharmacotherapy (R01DA025078 and R01CA165001/**STU00064871**, respectively). The depression medication adherence questionnaire also asks about reasons why participants have missed taking their antidepressants. Depression symptoms will be measured using the Beck Depression Inventory (BDI-II) (Beck et al., 1996). The BDI-II yields a total score ranging from 0-63, with scores of 0-13 indicating minimal depression, 14-19 indicating mild depression, 20-28 indicating moderate, and 29-63 indicating severe depression. Anxiety symptoms will be measured using the Beck Anxiety Inventory (BAI) (Beck & Steer, 1990). The BAI also yields a total score ranging from 0-63 points, with scores of 0-7 indicating minimal anxiety, 8-15 indicating mild anxiety, 16-25 indicating moderate anxiety, and 26-63 indicating severe anxiety.

Demographic and smoking history: We will collect demographic and smoking history data (e.g., age at smoking initiation). The Fagerstrom Test for Nicotine Dependence (FTND), a 6-item measure of nicotine dependence validated in smokers with mental health disorders, will be administered (Buckley et al., 2005; Fagerstrom, Heatherton, & Kozlowski, 1992; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). The brief Wisconsin Inventory for Smoking Dependence Motives (WISDM; (Smith et al., 2010)) will be administered to assess smoking motives.

Caffeine consumption: A brief questionnaire is being used to measure caffeine consumption and positive and negative effects of caffeine. Participants are instructed to report on their caffeine consumption and caffeine-related effects over the past month. Participants are asked at the intake session (Week 0) to indicate whether their current consumption of caffeine containing beverages, foods, medication or dietary supplements reflects a change from their usual consumption. This questionnaire will be used to assess the degree to which baseline caffeine consumption changes across treatment or is associated smoking cessation. It will be given to participants at intake, week 7, and week 14, and takes about 5 minutes to complete.

Mediators

Cigarette reward value: Preferences for engaging in smoking vs. other traditionally rewarding activities will be measured using a questionnaire developed by Spring and colleagues (Spring et al., 2003). The test requires participants to make 15 forced choices between smoking and a variety of rewards likely to be accessible and enjoyed. The choice of smoking is scored as 1; the choice of the alternative reward is scored as 0. Scores range from 0 to 15, and the test has exhibited acceptable internal consistency (alpha=0.74) (Spring et al., 2003).

Reinforcing value of cigarettes versus money: The reinforcing value of cigarettes versus money will be measured using the Cigarette Purchase Task (CPT) (MacKillop et al., 2008). The CPT assesses estimated

consumption of cigarettes at escalating levels of price, ranging from no cost and very low prices to intermediate and very high prices. The resulting data is then modeled using demand curve analysis to generate multiple indices of the value of tobacco to the individual. The CPT takes approximately 2-3 minutes to complete.

Hedonic capacity: Hedonic capacity will be assessed with the 14-item Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995). The SHAPS has excellent psychometric properties in nonclinical and clinical samples (Franken, Rassin, & Muris, 2007; Leventhal, Chasson, Tapia, Miller, & Pettit, 2006; Snaith et al., 1995). High scores characterize someone who perceives a broad array of life experiences as rewarding and who experiences a high degree of pleasure in response to rewards; low scores characterize someone who does not respond fully to typical rewarding experiences.

Reward learning: A modified version of the Probabilistic Reward Task (PRT) will be used to measure hedonic capacity as indexed by reward learning (Liverant et al., 2014; Pizzagalli, Jahn, & O'Shea, 2005). The task comprises two 8-minute blocks of 100 trials administered using E-Prime 2.0 (Psychological Software Tools; http://www.pstnet.com/). Simple cartoon faces with two different mouth lengths, 11.5 mm (short) vs. 13.0 mm (long) are presented for 100 ms in the center of the computer screen. Participants are instructed to identify which mouth was shown (short or long) with a button press, and are told that the goal of the task is to win as much money as possible by choosing the correct mouth length. Correct responses for the "rich stimulus" are rewarded with money at three times the rate of correct responses for the "lean stimulus." A response bias is induced for the "rich stimulus" vs. "lean stimulus" via positive feedback for the correct answer ("Correct!! You win 5 cents."). Participants can earn up to $4.20 for completing the task. The designation of short vs. long mouth as the "rich stimulus" is counterbalanced across participants, with this assignment maintained across the three administrations. Outcome variables include response bias, discriminability, and response time.

Alternative reinforcers: A 45-item version of the Pleasant Events Schedule (PES)(MacPhillamy & Lewinsohn, 1982) will be used to measure traditionally rewarding activities that occur in a person's natural environment (Audrain-McGovern et al., 2011). The cross-product score of frequency (0=none to 2=often) and level of enjoyableness (0=none to 2=very) for each item provides a measure of activity reward. Participants are also asked whether they associate the activity with smoking or the urge to smoke. If the activity is associated with smoking, it is considered a complementary reinforcer. If the activity is not associated with smoking, it is considered a substitute reinforcer. The cross products of substitute reinforcers are summed to provide a score for substitute alternative reinforcers and those for complementary reinforcers are summed to provide a score for complementary alternative reinforcers. Scores have been associated with depression (Audrain-McGovern et al., 2011), discriminate between ex-smokers and current smokers, and predict smoking abstinence in cessation treatment (Audrain-McGovern et al., 2009; Goelz et al., 2014).

Cognitive function: Cognitive function will be assessed using the NIH Toolbox for the Assessment of Neurological and Behavioral Function (NIH-TB) (Weintraub et al., 2013) The NIH-TB was designed to provide a brief, convenient set of computerized measures for clinical trials involving a wide range of populations. The NIH-TB Flanker Inhibitory Control and Attention Test will be used to assess participants' ability to focus, sustain and shift their attention. Working memory, which refers to the ability to temporarily store and manipulate information for complex cognitive tasks, will be measured using the List Sorting task. Average total administration time for these two tasks is 11 minutes.

Mood induced tobacco choice task: The concurrent choice task developed by Hogarth and colleagues will be used to measure preferential choice of tobacco over natural rewards (i.e., chocolate) (Hogarth, 2012; Hogarth & Chase, 2012). This measure is sensitive to individual differences in nicotine dependence (Hogarth & Chase, 2012), nicotine replacement pharmacotherapy (Hogarth, 2012), and negative mood induction (Hogarth et al., Under review). The 10-minute test is administered using E-Prime 2.0 (Psychological Software Tools; http://www.pstnet.com/). The task provides a behavioral measure of background craving indexed by preferential tobacco choice, and the modulation of tobacco choice following induced negative and positive mood states. The task will test of whether varenicline and behavioral activation training reduce tobacco-choice overall, reduce negative mood induced increases in tobacco-choice, or increase positive mood induced decreases in tobacco choice. The outcome of this measure will provide insight into the affective mechanisms

by which the treatment manipulations influence smoking motivation.

Table 2. Measures/Events													
Week	**0[C]**	**1[C]**	**2**	**3[C]**	**4**	**6**	**7[C]**	**8**	**10**	**12**	**14[C]**	**27**	**27[C1]**
TREATMENT													
BASC or ST		X	X	X	X	X		X	X	X			
Varenicline or Placebo			X	X	X	X	X	X	X	X			
SCREENING/COVARIATES													
Urine Pregnancy Screen	X												
Medical Hx Form, MINI Psychiatric Interview	X												
Suicidality (C-SSRS)	X	X	X[2]	X	X	X	X	X	X	X	X	X	X
Depression Inventory (BDI-II)	X	X	X[2]	X	X	X	X	X	X	X	X	X	
Anxiety Symptoms (BAI)		X		X	X	X	X	X	X	X	X	X	
Demographics	X												
Smoking History, Nicotine Dependence (WISDM), Readiness Rulers	X												
Psychiatric History	X												
Outside Treatment					X	X		X	X	X	X	X	
Antidepressant Med Use		X		X	X	X	X	X	X	X	X	X	
Nicotine Metabolism	X												
Concomitant Medications	X	X		X	X	X	X	X	X	X	X	X	
Caffeine Consumption		X					X				X		
MEDIATORS													
Cigarette Reward Value (CRV)		X		X			X			X	X		
Reinforcing Value of Cigarettes Versus Money (CPT)		X		X			X				X		
Hedonic Capacity (SHAPS)		X		X			X			X	X		
Reward Learning (PRT)		X					X				X		
Alternative Reinforcers (PES)		X		X			X			X	X		
Cognitive Function (Flanker & List Sort)		X					X				X		
Mood Induced Tobacco Choice Task		X					X				X		
Craving (QSU) and Withdrawal (MNWS)		X		X			X			X	X		
HEALTH DATA													
Cholesterol, Glucose	X										X		
Sleep, Diet, Alcohol, Physical Activity (Health Behavior Assessment)	X						X[3]				X	X	
Height/Weight	X	X		X			X				X		X
TREATMENT DATA													
Adherence: Medication Accountability				X			X				X		
Adherence: Self Report Pill Count				X	X	X	X	X	X	X	X		
Side Effects Checklist & Adverse Events		X		X	X	X	X	X	X	X	X	X	
Recent Medical Hx	X	X		X			X				X	X	
Blood Pressure/Heart Rate	X	X		X			X				X		X
Integrity of the Blind and Satisfaction											X		
Brief Mood Assessment			X										X
OUTCOME													
Smoking Status, Cigarettes/Day	X	X		X	X	X	X	X	X	X	X	X	X
Carbon Monoxide (CO)	X	X		X			X				X		X

Target Quit Date = Week 3 (Day 8 of study medication); End of treatment = Week 14

C = clinic visit (in-person session)

[1] Week 27 is conducted by telephone with self reported abstainers to complete a clinic visit for expired CO verification

[2] BDI-II and C-SSSRS are only administered if the participant endorses a mood change

[3] Parts IV and V only (page 5).

Subjective cigarette craving: Craving will be measured using the Questionnaire of Smoking Urges-Brief version (QSU-Brief) (Cox, Tiffany, & Christen, 2001). The QSU-Brief is a widely used scale that yields an overall measure of cigarette craving (or urge to smoke) and two subscale scores: positive reinforcement and negative reinforcement. The full-scale score is computed by summing the 10 items. Higher scores indicate greater urges to smoke.

Nicotine withdrawal symptoms: Withdrawal will be measured with the Minnesota Nicotine Withdrawal Scale (MNWS) (Hughes & Hatsukami, 1986), which comprises nine questions: urge to smoke, depressed mood, irritability, anxiety, difficulty concentrating, restlessness, increased appetite, and two sleep questions, each rated from 0 to 4 (0 not at all, 1 slight, 2 moderate, 3 quite a bit, 4 extreme). A composite withdrawal score is computed by summing the nine items.

Health Data

Objective measures: Non-fasting blood plasma at weeks 0 and 14 will be tested for cholesterol and glucose levels as indices of cardiovascular health. Blood pressure and height/weight to determine body mass index will be measured at all in-person study visits (weeks 0, 1, 3, 7, 14, and 27)

Self-report measures of behavioral risk factors for cardiovascular disease: At weeks 0, 14, and 27, participants will complete questionnaires that assess sleep, diet, physical activity, and alcohol use. Past week sleep will be assessed using the PROMIS short-form sleep disturbance (4 items) and sleep-related impairment (8 items) scales (Buysse et al., 2010). Past week physical activity will be measured using 3 items the Godin Leisure Time Exercise Questionnaire (Godin & Shephard, 1985). Past week sedentary behavior will be measured will be measured using one item from the International Physical Activity Questionnaire (Craig et al., 2003). The Health Information National Trends Survey (HINTS)(Thompson et al., 2011) and Coronary Artery Risk Development in Young Adults (CARDIA) study (Lloyd-Jones, 2010; Lloyd-Jones et al., 2010) items were used as a basis to assess average consumption of fruits, vegetables, whole grains, sugar-sweetened beverages, and sodium (7 items). Alcohol consumption will be assessed using the 3-item AUDIT Alcohol Consumption (AUDIT-C) scale (Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998). Marijuana use over the past 30 days will be assessed using one item regarding frequency adapted from the AUDIT-C scale and one item regarding timing of most recent use. These health behavior questions will take about 7-8 minutes to complete.

Treatment Measures

Medication adherence: Medication adherence will be assessed at each session by self-report using the same timeline follow-back (TLFB) interview and by pill count via collection of used blister packs (clinic visits only) as done in past varenicline trials (Ebbert et al., 2009; Gonzales et al., 2006; Jorenby et al., 2006; Niaura et al., 2008) and in our current varenicline trial (**STU00064871**). Self-reported pill count has adequate sensitivity and specificity compared to plasma varenicline concentration (Buchanan et al., 2012). Adherence to BASC and ST will also be tracked.

Adverse events (AEs) and suicidality: As done in our ongoing varenicline trial (R01CA165001/ **STU00064871**), we will use a structured checklist followed by open-ended questions to assess for incidence and severity of varenicline-related adverse events, including neuropsychiatric AEs. These assessments will be used to monitor safety and enable dose reductions or suspension as needed during the trial. Dose reductions or suspension of drug may be considered if the study physician has determined that the endorsed symptom(s) are "likely" or "definitely" related to taking the study drug, the symptom(s) cause the participant moderate or severe distress, and the participant expresses concern about continuing on the study drug at the FDA-recommended dose. If this is the case, a reduction to 1mg daily or 0.5mg twice daily will be the initial reduced dose recommended, with close monitoring of the participant's side effect profile. If the endorsed side effect(s) continue to cause the participant moderate to severe distress at the reduced dose, stopping of the study drug may be considered and the participant will be invited to proceed in the trial completing therapy treatment and assessments only. We will administer the Columbia Suicidality Severity Rating Scale (C-SSRS) at each session to assess for suicidality. Recent history of cardiovascular symptoms (e.g., angina) or hospitalization/emergency department visit will be assessed at each session to monitor any cardiovascular events associated with varenicline. Blood pressure and heart rate will be measured at every clinic visit.

Integrity of the blind: Participants' perception of drug treatment assignment may influence their treatment adherence. This question is the one used by Schnoll and colleagues (Schnoll et al., 2008).

Satisfaction with the program (3 questions): Given the negative perception that many individuals have of varenicline, understanding patient's satisfaction with the program may be useful information to evaluate in the outcome analyses and can provide a basis for clinical relevance. These questions were modeled after patient satisfaction questionnaires used in a variety of smoking cessation programs. The four questions will be administered at the Week 14 (end of treatment) visit and take about 2 minutes for the participant to complete.

Outcomes Measures

Abstinence (primary outcome): Smoking will be assessed using a TLFB interview (Brown et al., 1998), and by breath carbon monoxide (CO) to verify self-report. Participants will be considered abstinent if they report abstinence (not even a puff of a cigarette) for ≥7 days prior to week 27 (24-weeks post-TQD) and have a CO ≤8 ppm at the time-point (Hughes et al., 2003). As per convention, participants are assumed to be smoking if they report smoking at the time-point, cannot be reached to provide data at the time-point, fail to provide a breath sample at the time-point, or provide a breath sample at the time-point that is >8 ppm (Hughes et al., 2003). Daily smoking will be assessed at each session using the TLFB. The TLFB interview provides data that can be used to assess the timing and rates of lapses (smoking episodes not lasting 7 days), recovery events (return to abstinence), and relapse events, as well as to monitor changes in cigarettes smoked per day. These data will also be used to compute and assess secondary measures of smoking cessation (below). CO will be measured at each in-person visit to confirm smoking status. To obtain participants' CO value, the participant takes 3 deep breaths. On the third deep breath, participants are instructed to inhale and hold their breath for 10 seconds, then place their mouth securely around the disposable mouthpiece on the handheld CO monitor and to blow through the tube until they have completely expelled all of the air in their lungs.

Smoking behaviors (secondary outcome): CO-verified 7-day point prevalence abstinence at weeks 7 and 14 (4- and 10-weeks post-TQD, respectively) will be secondary measures. As per guidelines (Hughes et al., 2003), secondary outcomes at 24-weeks post-TQD will include: prolonged abstinence (relapse defined as 7 consecutive days of self-reported smoking after a 2-week grace period), continuous abstinence (no smoking between TQD and follow-up), and time to 7-day relapse (no grace period).

RETAIN Sub-Study Measures

Mediators/ moderators: 1) *Income and personal financial wellbeing.* Annual household income will be assessed using a 6-level variable. Participants' economic wellbeing (e.g., whether participants have recently borrowed money to "make ends meet") will also be assessed. 2) *Participant characteristics.* Other factors that may influence response to financial assessments will be assessed; including prior research participation, age, race, gender, ethnicity, education, and marital status; with items taken from main trial demographic forms where possible.

Main outcome: Proportion of participants assigned to each incentive amount who consent to participate in the main trial.

Secondary outcomes: 1) Attention to Informed Consent Document (i.e., time spent reading each section, as described in Procedures above). 2) Research Attitudes Questionnaire (Kim, Kim, McCallum, & Tariot, 2005). 3) Perceived research risk (Cryder, London, Volpp, & Loewenstein, 2010). 4) Therapeutic misconceptions (S. L. Kim SH, Wilson RM, Frank SA, Holloway RG, Keiburtz K, De Vries RG, 2009; W. R. Kim SH, De Vries R, Kim H, Holloway R, Kieburtz K, 2015; Pentz et al., 2012). 5) Trial Elements Quiz (S D Halpern, 2002; S D Halpern, Karlawish, Casarett, Berlin, & Asch, 2004). 6) Perceived Coercion Scale (Gardner W et al., 1993). 7) Study retention (i.e., proportion of participants assigned to each incentive amount who complete study procedures through week 27).

RISK/BENEFIT ASSESSMENT

Potential Study Risks

A detailed description of the study will be given to all participants, which will include the risks of participation, assurance of full confidentiality, and the knowledge that their freedom to refuse participation or withdraw from the project will not affect the availability of treatment at Northwestern or PENN. Informed consent procedures will comply with current standards of the IRBs at Northwestern and PENN. Participants can choose, as an

alternative, to not enroll in this study. Adverse reactions will be assessed and reported as required by Federal law and the regulations of Northwestern and PENN. Potential study-related risks are listed below.

Mild Emotional Distress in Response to Assessments or Therapy

Participants may experience emotional distress during assessments from receiving information about mental health diagnostic status based on the clinical interview (i.e., new diagnosis of Major Depressive Disorder), discussing feelings and attitudes about smoking, or from learning about the risks from smoking. Study personnel will be alerted to expect some level of emotional distress from a small number of participants and will be trained to respond appropriately, maintain rapport with participants, and effectively utilize supervision from study physicians and psychologists. In addition, measures of depression, anxiety, and suicidality will be administered throughout the trial to detect acute changes in psychiatric status and provide appropriate referrals if requested. Northwestern and PENN have developed a protocol to monitor, assess, and refer for treatment any serious psychiatric concern that emerges within our trials (please see Safety Monitoring and Reporting Protocol).

Nicotine Withdrawal

Most individuals who stop smoking exhibit nicotine withdrawal symptomatology. These symptoms can include: sadness and anxiety, irritability, difficulty concentrating, anger, appetite change and weight gain, insomnia, and decreased heart rate. Eliminating the risk for these would not be possible, although in most cases these events are short-lived and have low intensity, lasting for 2-3 weeks. Use of varenicline should minimize the severity of withdrawal symptoms and the psychological treatments will offer strategies for reducing withdrawal. The study personnel will be trained to recognize these symptoms and to educate participants about them (e.g., their duration, their time-limited nature, methods for reducing them).

Varenicline

Some individuals who take varenicline may experience nausea, sleep disturbance, constipation, flatulence, and vomiting. These are the most common side effects and are experienced by 5- 25% of patients. However, these symptoms are usually mild and temporary, and do not lead to treatment discontinuation in most cases. There have been rare reports of allergic and skin reactions, including swelling of the face, mouth (tongue, lips, and gums), extremities, and neck (throat and larynx). The risk for these reactions is low (0.01%). Participants will be instructed to discontinue medication and seek medical help immediately if they experience any difficulty breathing or any of the noted allergic reactions, and then follow-up with research study staff once their symptoms have stabilized. Participants will be told that varenicline may impair their ability to perform tasks that require judgment or motor skills and that they should proceed with caution in this regard until they are certain that varenicline is not affecting their performance. Participants will also be told that varenicline may lower their tolerance to alcohol and that there have been rare reports of aggressive behavior and/or impaired memory following the consumption of alcohol while taking varenicline. In these cases, which number less than 30 across the United States, the amount of alcohol consumed was not sufficient to explain the symptoms. Therapists will instruct participants to restrict their alcohol intake while taking the study drug or until they know how varenicline affects their alcohol tolerance. Participants will be advised to inform the study staff if they are taking or plan to take any prescription or over-the-counter drugs.

Varenicline may be associated with new or worsening seizures during the first month of treatment. Some patients had no history of seizures, whereas others had a history of seizure disorder that was remote or well-controlled. We will screen for and exclude people who have an unstable, untreated history of seizures.

There have been reports, though rare, of suicidal thoughts, aggression, and changes in emotional functioning and behavior while taking varenicline. To minimize the likelihood of participants experiencing these adverse events we will:

1. Employ a stringent list of exclusionary criteria to limit the chance of adverse events occurring;
2. Administer the standard and recommended dose run-up to the 1mg BID dose;
3. Monitor self-reported adverse events at each session; and
4. Conduct open-ended evaluation of any potential adverse events at each session.

The U.S. FDA recommends that patients taking varenicline should contact their healthcare provider if they experience mood or behavior changes. Participants will be asked to notify the research staff as soon as possible if these changes do occur (if not already determined by formal study assessments), and will be reminded that they have a medical contact card with information about how to contact the study physician 24 hours per day. Varenicline trials of smokers with and without mental health disorders have provided evidence of safety (Gibbons & Mann, 2013; Hays et al., 2011; J. B. McClure et al., 2009; Meyer et al., 2013; Pachas et al., 2012; Philip et al., 2009; Spirling et al., 2008; Stapleton et al., 2008; Wu et al., 2012). In the only RCT of varenicline to target smokers with current or recent (past two years) MDD (Anthenelli et al., 2013), there were no suicidal ideation or self-injurious behavior events in the varenicline treated group (2mg/day for 12 weeks; N=256). In the placebo condition (N=269), there were three cases of suicidal ideation and one case of self-injurious behavior. Further, a recent trial including smokers both with and without psychiatric disorders did not find any varenicline treatment-associated changes on either suicidality or other neuropsychiatric adverse events (Anthenelli et al., 2016). Varenicline has no known pharmacokinetic interactions (Faessel et al., 2010; Rollema et al., 2011) or clinically meaningful interactions with other medications that are renally cleared, such as antidepressants ("Clinical Pharmacology [database online]," 2014).

Varenicline may be associated with an increased risk of certain cardiac and vascular AEs, including chest pain, heart attack, and stroke. These risks are rare and are still being studied to determine their validity. However, our study staff follows strict procedures to monitor for the presence of these adverse events, including monitoring blood pressure and heart rate at each in person visit and asking specific side effect questions related to cardiovascular events (e.g. chest pain, weakness on one side, etc.) during each session. Cases of somnambulism have been reported in patients taking varenicline. Participants will be asked to notify research staff as soon as possible if they experience somnambulism

Study physicians and psychologists will be alerted to any reported AEs that are coded as requiring further review (see Safety Monitoring and Reporting Protocol for coding definitions and corresponding severity ratings by symptom). They will review the information provided by research staff and, if applicable, contact the participant to gather more information and determine the appropriate course of action. Ultimately, the study physician, with the help of the study psychologists as necessary, will decide if the AE is related to study medication and whether or not the participant should discontinue taking study medication. Dose reductions, which will be tracked, may also be employed to minimize any side effects.

Blood Draw

The blood draws may result in bruising and/or slight bleeding at the needle site and, occasionally, may result in a feeling of faintness. These side effects are rare, so the chances of these discomforts are minimal. Sample collection will be conducted by study personnel trained in phlebotomy to minimize risk of discomfort.

Reproductive Risks

The safety of varenicline for an unborn baby is unknown, therefore participants will be told that they should not become pregnant or breast-feed a baby while in this study. Women will be asked to take a pregnancy test before starting the study. If the woman is of childbearing potential, she must agree to use an adequate form of contraception for at least one month prior to initiation of the study drug, while study medication is taken, and for at least one month after the end of the trial. Women who are pregnant, breast-feeding or planning to become pregnant will be excluded from the trial, and if an enrolled participant becomes pregnant during the study, she will be discontinued from the study medication but allowed to continue with psychological therapy and assessments.

Threats to Privacy/Confidentiality

Because self-report and medical data will be collected and stored as part of this study, it is possible that participant privacy or confidentiality could be threatened. To address this concern, the Data Management System (DMS) has established safeguards to prevent unauthorized access to study data. An automatically generated index number is assigned to a participant’s study identification number. A linked participant identification table is created for the storing of participant name, address and telephone contact information. This table uses the automatically generated index number rather than the study identification number. The

master participant map and participant identification information tables are maintained in a separate database. Using this method, no identifying information is directly linked to medical information or other study data. Northwestern and PENN have long-established protocols to guard against improper use of hard copies of data (e.g., locked files, numeric coding procedures). Neither of our two research teams has experienced the unauthorized use of study data. All electronic data (including any audio files) are kept on secure servers, behind a firewall within the Northwestern Department of Preventive Medicine, and will require a Northwestern network ID (NetID) and password for access and data entry. Any electronic communication with participants for the purposes of assessment and treatment are conducted using best practice data encryption and transmission standards. All electronic data collected as a part of psychological treatment (i.e., between-session practice or "homework" forms) will be transmitted using Transport Layer Security (TLS) encryption to prevent eavesdropping on and tampering while it is in the transmission pipeline.

Potential Risks of RETAIN Sub-Study

Coercion

There is a risk that the incentives used in the RETAIN-related procedures for this study may unfairly coerce participants to participate in a trial that they would not otherwise participate in. This is a primary question of the RETAIN sub-study. The RETAIN PENN PI has convened a study-specific data and safety monitoring board (DSMB) in conjunction with NIH to monitor any indication that this is occurring. Our hypothesis is that no population will be unfairly manipulated into participating in a trial that they would not otherwise participate in, and that financial incentives may lead to participants examining the potential risks of a study more closely than they would have otherwise.

Supporting Research

A study led by RETAIN PENN PI Halpern and RETAIN Co-I Karlawish assessed 126 hypertensive patients' willingness to participate in RCTs of experimental antihypertensive drugs(S D Halpern et al., 2004). We used a 3 x 3 within-subjects factorial design in which hypertensive patients were administered, in random sequence, 9 hypothetical RCTs which differed in their risk level (10%, 20%, or 30% chance of drug-related adverse events) and payment ($100, $1,000, or $2,000 for a 10-week trial). We found that increasing payments motivated greater RCT participation, and that increasing risk levels reduced participation levels ($p < 0.001$ for each). Importantly, patients' participation rates declined equivalently with increasing risk levels across all payment levels studied, and the statistical interaction between risk and payment was not statistically significant ($p=0.30$). This shows that patients were equally sensitive to risk despite very different payment amounts, suggesting that research incentives are not undue inducements.

Furthermore, this study of payments for RCT enrollment(S D Halpern et al., 2004), as well as another study by PI Halpern of payments for living kidney donation(S. D. Halpern et al., 2010), counter the notion that payments are unjust inducements. Specifically, in both studies, increasing payment levels were similarly motivating among patients with higher and lower incomes. Indeed, in the RCT participation study(S D Halpern et al., 2004), there was an indication that larger payments may preferentially motivate wealthier people to participate (payment-by-income interaction $p=0.09$). The validity of these results is enhanced by the income diversity among the study samples and the substantial statistical power to identify such income-by-payment interactions if they existed.

RETAIN Co-I Volpp and colleagues asked participants to rate the riskiness of a new technology (transcranial magnetic stimulation) being tested in RCTs after being told they would receive $25 or $1,000 for trial participation (Cryder et al., 2010). Participants assigned to review the trials offering $1,000 spent more time reading about study risks and other research aspects (mean = 3.7 minutes) than did patients assigned to trials offering $25 (mean = 1.0 minutes) ($p < 0.01$). Larger incentives also decreased the odds that participants would skip the page of the informed consent form that described study contraindications ($p < 0.05$). These findings suggest that payments alert people to the possibility of risk, and encourage them to learn more about the study (Cryder et al., 2010), rather than contravening the goals of informed consent, incentives may actually promote informed decision-making.

Deception

The RETAIN sub-study involves an element of deception (i.e., participants are told that they are randomized to one of three financial incentive conditions, when in fact all participants receive the same amount of financial

compensation). We believe deception is an essential element of this sub-study, as it would not be feasible to address study aims without incomplete disclosure related to the random assignment of financial incentives. Adverse events from the incomplete disclosure will be minimized through the debriefing process. Participants will be debriefed at the end of the first in-person intake session. This debriefing will therefore happen within a few days of the deception, and will provide participants with full disclosure of the research and an opportunity to withdraw their participation or their data. We believe the value of the study is sufficient to warrant waiving some aspects of the requirement for full disclosure in the informed consent process.

Additional Ethical Considerations for RETAIN Sub-Study

Although some participants will enroll in the main trial without enrolling in the RETAIN sub-study, there are several reasons why these different paths to enrollment, and different associated incentives, do not unduly disadvantage participants who do not wish to participate in the RETAIN sub-study:

- The main trial was conceived independently from and prior to the RETAIN sub-study, and has commenced accrual without additional financial incentives. Participants who choose not to participate in the RETAIN sub-study are no worse off than if the RETAIN sub-study had never been proposed, or if the participants had been recruited prior to the RETAIN sub-study launching.

- Per available federal regulations, incentives for research participation ought not be construed as a benefit to research participation. While the Common Rule requires “risks to subjects [to be] minimized” (45 C.F.R. §46.111(a)) and requires that risks be “reasonable in relation to anticipated benefits, if any, to subjects and the importance to the knowledge that may reasonably result” (45 C.F.R. § 46.111(b)), it cautions that “[i]n evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the [specific] research.” Thus, federal regulations do not consider risks or benefits of opportunities (research or otherwise) external to the main trial as relevant in adjudicating the fairness of the trial.

- There is no regulatory requirement of equal treatment. Rather, the regulations incorporate the principle of justice by requiring the equitable selection of participants, which responds to historical abuses of vulnerable populations in research and seeks to achieve equitable distribution of benefits and burdens of research. This distinction between equal selection from among potential participants and equal treatment of enrolled participants is fundamental to RCTs.

- Finally, any difference in payment to individuals who do or do not participate in the RETAIN sub-study stems from participants’ choices. The most fundamental ethical principal in research, embodied in the federal regulations and international ethics guidelines, is that research participation must be voluntary. By extension, people have the right to refuse participation in any study. The federal regulations require researchers to provide specific information about study participation (45 C.F.R. § 46.116), but, after providing information and answering individuals’ questions, investigators must respect individual choice.

Potential Study Benefits

Participants in this study will have the opportunity to participate in a smoking cessation program at no cost. They will receive 12 weeks of psychological treatment and the opportunity to receive 12 weeks of varenicline, a medication with proven efficacy for treating tobacco dependence in the general population of smokers. Thus, participants will have the opportunity to stop smoking completely or reduce their amount of use. Participants may also benefit from the knowledge that they are contributing in an important way to potentially further scientific knowledge concerning ways to improve cessation treatment for smokers.

Alternatives to Study Participation

As an alternative to enrolling in this study, participants may choose to continue to smoke or to seek assistance with quitting smoking through other treatment programs located in their area, including contacting the national quitline. At any point in this trial, participants may decide not to continue in the study. Choosing not to participate or revoking informed consent once enrolled in the study will not negatively affect their right to any present or future treatment at Northwestern or PENN affiliated clinics, nor will it affect their class standing (Northwestern or PENN students) or current or future employment (Northwestern or PENN employees).

Risk/Benefit Assessment Summary
There is minimal risk for serious AEs. The treatments and procedures used in this study have been demonstrated to be safe. Varenicline has also been studied in several clinical trials and shown to be safe and effective, including in smokers with major depressive disorder (MDD). Nevertheless, there are some potential risks associated with participating in this trial, which are described above.

The potential benefits of this study far outweigh the potential risks. Nicotine dependence is a chronic condition that disproportionately affects people with mental health disorders like MDD. Smokers with MDD demonstrate greater nicotine dependence, suffer more severe nicotine withdrawal, and do not respond as well to evidence-based smoking cessation treatment versus smokers without MDD (Hitsman, Papandonatos, et al., 2013). Little is known about how to improve smoking cessation treatment in this population because smokers with MDD have been underrepresented in smoking cessation treatment research and underserved in clinical practice, despite substantial tobacco-related disease burden. Individuals will be screened prior to admission into the study and those at increased risk for adverse reactions will be excluded. Enrolled participants will be monitored closely for side effects and AEs. Another anticipated benefit of participation in the current research is that it will advance our understanding of the efficacy of targeted treatment for smokers with MDD. It will be the first trial to combine varenicline with behavioral activation integrated with standard behavioral cessation treatment. Study findings will have implications for national clinical practice guidelines.

While the RETAIN sub-study introduces some degree of additional risk to participants, we believe that the risk/ benefit ratio remains clearly in the favor of research participants. Further, importance of the information to be gained confers significant benefit. The RETAIN sub-study will be the first to explore how financial incentives impact actual decisions made by patients contemplating participation in a real trial, which will provide important information about the impact of financial incentives on decision-making, with implications for future conduct of clinical trials.

DATA AND SAFETY MONITORING
We will use established procedures and infrastructure for data and safety monitoring (e.g., **STU0064871**) and a protocol-specific DSMB. Safety and data quality monitoring will be performed on an ongoing basis by the investigators and study personnel. Study personnel will be responsible for collecting and recording all clinical data using a Manual of Operations (MOP) that will be developed for this study. This includes ensuring that source documents exist for all the data collected on the case report forms (CRFs), ensuring all fields are completed appropriately, and ensuring that all corrections are done according to Good Clinical Practice (GCP). Inconsistencies or deviations will be documented. The study physicians and psychologists at the two sites will review data for each participant on an ongoing basis and will document reviews by initialing and dating reports. Study personnel conduct 100% quality assurance (QA) on data, comparing all hard copy data to computer files.

Staff training will consist of a detailed explanation of the protocol and review of the CRFs. In addition, the duties of each research staffer will be outlined and all applicable regulations will be reviewed. Mock sessions with constructive critical feedback will be conducted. The MOP will be used for staff training and to guide procedures during the trial. Senior personnel will supervise junior staff and provide re-training as needed. Monitoring will be conducted in accordance with GCP and the U.S. Department of Health and Human Services Code of Federal Regulations Title 45, Part 46.a (http://www.hhs.gov/ohrp/policy/ohrpregulations.pdf). Recruitment and enrollment will stop when 576 participants are consented, randomized and complete the study. On average, about 12 participants will be enrolled per month across the two study sites.
Monitoring for AEs will be conducted in real-time by the study personnel and the site PI and study physician and psychologists. Research staff will complete thorough side effect assessments and send this information to the study physician and psychologists, who will determine the severity of the adverse events. The relationship of the event to the study drug and the course of action for the participant will be decided by the site physician and psychologists after reviewing the report. Participants will be monitored for the development of AEs by assessing side effects at each session between weeks 0 and 27 as well as through open-ended questions during assessments (at least 10 times during the trial). Monitoring may increase if required. Additionally, participants will be given a 24-hour emergency number they can call if necessary.

The PIs, study physicians, and psychologists will follow all participants who discontinue due to a serious AE until it resolves and becomes completely stable, unless a referral to another physician (i.e., specialist) is indicated or requested by the participant. All AEs and serious AEs will be documented in an Adverse Events CRF. This information will, in turn, be reported immediately to all necessary regulatory committees, including the FDA (see Data and Safety Monitoring Plan and Safety Monitoring and Reporting Protocol).

All serious AEs, as defined in the adverse event procedures in the Safety Monitoring and Reporting Protocol, will be reported within 24 hours to the PIs (lead and PENN PI). These events will be maintained in a unique database and reviewed monthly by senior study personnel. The site physician and psychologists will review all AE forms in “real-time” to ensure appropriateness of the data and timeliness of reporting. The Northwestern database manager and research assistants will be responsible for monitoring data integrity as data are collected. This includes ensuring that source documents exist for the data on the CRFs, ensuring all fields are completed appropriately, all corrections are done according to GCP and any inconsistencies and deviations are documented.

The study will be monitored by the PIs (lead and PENN site), co-investigators, and regulatory committees at Northwestern and PENN as well as by a study-specific DSMB. The following monitoring activities will be conducted according to standard operating procedures.

Initial Assessment Monitoring
The Northwestern database manager and site project directors will conduct a manual review of source documents and CRFs for a random 25% subset of participants enrolled in the study. This inspection is the visual comparison of source documents to CRFs in a quantitative assessment of accuracy based on the number of data fields. A brief, internal report will be generated to describe findings. If the data are less than acceptable (i.e., >1% discrepancy between data values from source documents compared to CRFs), additional cases are requested, with appropriate counseling/training for staff.

Protocol Monitoring
Protocol monitoring includes a survey of those activities that are associated with protocol adherence such as study visit deviation and violation of inclusion/exclusion criteria. All accrued cases will be subjected to protocol monitoring throughout the duration of the trial.

Database Auditing
The Northwestern database manager and research assistants will review data entered into the database versus that recorded on the CRFs. All accrued cases will be subjected to database auditing throughout the duration of the trial. Re-training will be provided should problems, such as increased errors, be detected.

Data Auditing
The site physician and psychologists will review safety data recorded on the CRF versus that contained on the actual source document (patient chart, lab report, etc.). All accrued cases could potentially be subjected to auditing throughout the duration of the trial.

Data Security
Using network firewall technologies, the database will prevent the three major sources of data security problems: unauthorized internal access to data, external access to data, and malicious intent to destroy data and systems. Controlled user access will ensure that only appropriate and authorized personnel are able to view, access, and modify trial data. All modifications to data will document user access and data associated with the modification, as well as values prior to modification.

IRB Monitoring
As the official IRB of record indicated in the approved IRB authorization agreement (IAA, Federalwide Assurance #00004028), the protocol will be reviewed by the Northwestern IRB and will only be implemented after successful approval. Annual reporting and auditing will be conducted by the Northwestern IRB. All

procedures will be approved by the Northwestern IRB and monitored locally by both the Northwestern and PENN IRBs. A protocol-specific DSMB will be used for this trial (see below). The Northwestern and PENN IRBs will ensure participant safety and data integrity in collaboration with the DSMB.

Evidence of Training in Human Subject Research
All personnel working on the study will be required to review the protocol, complete training in the protection of human subjects (developed and implemented by the Northwestern and PENN IRBs), and undergo training.

The Data and Safety Monitoring Board (DSMB)
A DSMB will convene regularly for this study. The DSMB will consist of a physician (Michael Fleming, M.D., Department of Psychiatry and Behavioral Sciences), a behavioral scientist (Matthew Smith, Ph.D., Department of Psychiatry and Behavioral Sciences), and a biostatistician (Juned Siddique, DrPH., Department of Preventive Medicine). The primary concern of the DSMB will be the monitoring of side effects in placebo vs. varenicline groups. The DSMB will meet every 6 months to review accrual, retention, and side effect and AE reports. The study biostatistician (George Papandonatos, Ph.D.) will present unblinded data to the DSMB to determine if unacceptable side effects are occurring. The DSMB can request additional data or recommend trial suspension. We are using a DSMB and the current DSM plan in our ongoing varenicline trial (R01CA165001).

Details of the DSMB meetings are as follows:

- Data and safety monitoring will be performed on an ongoing basis by the DSMB led by a Northwestern biostatistician unaffiliated with the project and by study personnel and the site IRBs. The chair of the DSMB and the DSMB committee will review the trial data as described below. The DSMB will consist of three members: a biostatistician (Dr. Jovanovic), who will serve as DSMB chair, a physician (Dr. Fleming), and a behavioral scientist (Dr. Smith). The DSMB will meet twice per year to review data concerning recruitment, randomization, retention, compliance, form completion, gender and minority inclusion, intervention effects, and safety. In addition, the DSMB will: 1) identify specific safety concerns for participants and communicate these to the study PI; 2) consider the need for additional data concerning participant safety; 3) consider the rationale for the continuation of the study; 4) provide a written report concerning the protocol to the IRB and to the study PI; and 5) review manuscripts reporting study results prior to submission.

- The following will be reviewed at the DSMB meeting and included in the report which will be compiled following DSMB meetings and then updated at the trial's conclusion: 1) brief description of the trial; 2) baseline sociodemographic characteristics; 3) accrual, retention and disposition of study participants (recruitment versus goal, withdrawal rate); 4) quality control issues (assessment of randomization procedures, including stratification); 5) regulatory issues (review of protocol changes); 6) side effects by treatment arm (overall and by site); 7) serious adverse events by treatment arm (overall and by site); and 8) efficacy.

Structure of DSMB meeting. Each meeting will consist of three parts. First, an open session will occur in which the Dr. Hitsman and the DSMB will review the conduct of the trial (e.g., accrual, protocol compliance, general toxicity). Second, to maintain the study blind, a closed session involving only the DSMB and Dr. Papandonatos, the study biostatistician, will be held during which he will present side effect results to the DSMB as requested. A report of unblinded side effects results will be prepared; however, it will only be presented if specifically requested by the DSMB. This will focus on the presentation of the rate of increase in any side effect from baseline to a follow-up across treatment arms. Finally, an executive session involving only DSMB members will be held to allow the DSMB the opportunity to discuss the conduct of the trial and outcomes, including toxicities and adverse events, develop recommendations, and take votes as needed. The DSMB written recommendations will be provided to Dr. Hitsman and to the IRBs. The DSMB will summarize AE reports for Dr. Hitsman and the IRB chair, and Dr. Hitsman must implement any DSMB recommendations expeditiously. All DSMB recommendations will also be forwarded to the NIH and the FDA (where necessary).

RETAIN Sub-Study DSMB.

Ongoing oversight of the RETAIN sub-study is provided by a DSMB committee, whose members are: Jennifer S. Blumenthal-Barby, PhD (Chair, Associate Professor of Medicine and Medical Ethics, Baylor College of Medicine), Salma Jabbour, MD (Associate Professor, Department of Radiation Oncology, Robert Wood Johnson Medical School, Rutgers Cancer Institute of New Jersey), Brenda F. Kurland, PhD (Research Associate Professor, Biostatistics, University of Pittsburgh, Graduate School Public Health), Jeffrey M. Peppercorn, MD, MPH (Associate Professor, Medicine, Harvard Medical School), and Kim Vernick (Patient Advocate).

The RETAIN PI (Scott Halpern), assisted by the PENN project manager (Jackie McMahon), will be responsible for maintaining communication between the DSMB and the individual project staff for all RETAIN-related activities. The DSMB will be responsible for monitoring the trial and making decisions about the termination of individual study arms or the study itself. The DSMB will review and approve the research protocol. They will also assess the progress of the trial, including the assessment of data quality, participant recruitment, accrual and retention, participant risk versus benefit, and study outcomes.

Data Management System (DMS)
The Northwestern database manager will oversee the DMS for this trial and direct the Northwestern DMS to link with PENN. MS ACCESS permits real-time data entry, storage, and QA by NU secured network remote access and scannable forms, which increase standardization across personnel. This system is being used in our ongoing varenicline trial of smokers with cancer (R01CA165001/**STU00064871**). The DMS generates database tables in a NIH-compliant format, constructs semantic constraints on fields, and is used for data entry, storage, retrieval, and security. The DMS uses session dates to describe procedures and measures to be ascertained. The DMS mimics the appearance of CRFs completed at sessions. During data entry, validation occurs via the following procedures: 1) Variable type checks - variables defined as specific type, e.g., integer, and entry is restricted to type; 2) Range checks - entry of data outside a range is rejected; 3) List of possible values checks - value of data is checked against acceptable values; 4) Internal logical consistency checks - dependent fields are logical (e.g., study entry date occurs after birth date); 5) Data completeness checks - data inspected for completeness; and 6) Duplicate record checks - data are inspected to prevent duplication. Daily backups occur to protect against accidental corruption or deletion. We compare 100% of hard copy to computer data. Protection of participant privacy is accomplished by minimizing use of identifying information, use of ID numbers rather than participant names, keeping all data in locked files, and limiting access to the dataset that links participant names with ID numbers strictly to the study biostatistician.

RETAIN Sub-Study Data Management
All RETAIN survey data will be managed in REDCap (Research Electronic Data Capture), a secure data management system available at both PENN and NU. Questionnaire measures will either be entered into REDCap directly by participants (i.e., at the in-person intake session), or completed via pen and paper questionnaires and entered into REDCap by study staff. The RETAIN Project Data Managers will maintain the database with oversight from key study personnel.

All datasets and computer files and study ID numbers will be further secured as follows. We will implement multiple, redundant protective measures to guarantee the security of participant data. All data for this project will be stored on the secure/firewalled servers of the Center for Clinical Epidemiology and Biostatistics (CCEB). These data servers are maintained in a guarded facility behind several locked doors, with very limited physical access rights. They are also cyber-protected by extensive firewalls and multiple layers of communication encryption. Electronic access rights are carefully controlled by Penn system managers. We will use highly secure methods of data encryption for all transactions involving participants' financial information, such as W-9 forms, using a level of security comparable to what is used in commercial financial transactions. This multi-layer system of data security, identical to the system protecting the University of Pennsylvania Health System's medical records, greatly minimizes privacy risks.

Only authorized personnel will have access to the data. All of these personnel will have completed research and confidentiality training (specifically, CITI training). Through REDCap, each study subject will be given a

unique study identification number (ID). By default, all direct identifiers will be omitted from data extracts, and the study ID will be used exclusively in all analytical files.

STATISTICAL CONSIDERATIONS

Power

To address hypotheses related to Aims 1-3**,** we base our estimates upon the Anthenelli et al. trial (2013) and the study by MacPherson et al (2010) that randomized 68 smokers with elevated depressive symptoms (BDI-II scores ≥10) but no current MDD to 8 weeks of treatment with either behavioral activation (BA) or standard behavioral treatment (BT). At 26-weeks post-TQD, bioverified 7-day point-prevalence abstinence rates were 14.3% for BA (n=35) and 0% for BT (n=33). In the Anthenelli et al. trial (2013), smokers with current or past (≤2 years) MDD received 12 weeks of varenicline or placebo. Bioverified 7-day point-prevalence abstinence rates at 24 weeks were 31.3% for varenicline (n=256) and 18.2% for placebo (n=269). Based upon our conceptual model of the therapeutic targets of BASC and varenicline individually, we predict that there will be a synergistic effect of combination treatment with BASC and varenicline on abstinence (see Figure 2). Assumed 7-day point prevalence abstinence rates at 24-weeks post-TQD in our 2x2 design are presented in Table 3, under an ITT approach that considers participants lost to follow-up as treatment failures. A minimum of N=128 participants be assigned to each psychological treatment group (BASC, ST) receiving placebo, while a minimum of N=160 participants be assigned to each psychological treatment group (BASC, ST) receiving varenicline.

Such a sample configuration (N=576 total) guarantees at least 85% power for testing each of the three pairwise comparisons of interest in Primary Aim 3: BASC + varenicline vs. ST + varenicline (42% vs. 24% abstinence, power = 85%), BASC + varenicline vs. BASC + placebo (42% vs. 18% abstinence, power = 98%), and BASC + varenicline vs. ST + placebo (42% vs. 5% abstinence, power > 99%) at a multiplicity-adjusted significance level alpha=.053 =.0167. This equates to enrolling about 12 participants per month (6/month/site) over the 48 month recruitment period. Further, it guarantees 91% power for testing the efficacy of BASC vs. ST (18% vs. 5% abstinence) among the N=256 participants receiving placebo (Primary Aim 1), and power in excess of 99% for testing the efficacy of varenicline vs. placebo (24% vs. 5% abstinence) among the N=288 participants receiving ST (Primary Aim 2) when the significance level for these tests is fixed at alpha=0.05. Aim 2a will be tested based on a non-inferiority approach that seeks to establish the maximum increase in the moderate-to-severe AE rates (individual, total) in the varenicline arm relative to that in the placebo arm consistent with rejecting at alpha=.05 the one-sided null hypothesis that the true varenicline vs. placebo AE Rate Ratio (RR) exceeds 1.25 (Hauschke, Kieser, Diletti, & Burke, 1999). Assuming a 67% AE rate in the placebo arm, we have 84% power to establish non-inferiority, provided that the AE rate in the varenicline arm does not exceed 72%. That is, we need a true RR <1.075 (72% vs. 67%) to have an 84% chance of observing a sample RR small enough to lead to a rejection at alpha=.05 of the null hypothesis that the true RR>1.25.

Table 3. Assumed Abstinence Rates at 24-weeks Post-TQD

		Psychological Treatment	
		ST	BASC
Pharmacological Treatment	Placebo	5%	18%
	Varenicline	24%	42%

Regarding Secondary Aim 1 (Mediation), Fritz and MacKinnon (2007) present sample size requirements for a variety of mediation scenaria, assuming a continuous mediator (e.g., change in hedonic capacity) and a continuous dependent variable (e.g., change in cigarette reward value). With the exception of a rather unlikely complete mediation scenario, under which the entire effect of treatment assignment occurs through differences in hedonic capacity, the sample size required for 80% power at the 5% significance level was N=562 provided that 1) the main effect of treatment assignment on hedonic capacity, and 2) the effect of hedonic capacity on cigarette reward value each explain only 2% of the variance in the respective normal regression models, corresponding to “small” effects in Cohen’s nomenclature (Frandsen, Walters, & Ferguson, 2014). This is below N=576, suggesting adequate power for detecting mediation of proximal continuous outcomes. For the more distal outcome of abstinence (yes/no), the Fritz & MacKinnon (2007) method can still be used, provided our effective sample size is adjusted downwards to reflect loss of information due to dichotomization (Gibbons & Mann, 2013). Results suggests that detecting mediation of treatment effects on abstinence rates will be more

challenging, and will require effects of changes in cigarette reward value on smoking abstinence to be in the "medium-to-large" range instead.

Data Analysis

Preliminary analyses will assess sample characteristics by treatment with chi-square or logistic regression (tobacco dependence, use of antidepressant medication, number of past depressive episodes, and number of other Axis I disorders). These variables will also be examined for their relationship to completion of outcome assessments. Variables related to treatment arm and completion of follow-ups will be included as covariates in analyses of study aims. Treatment compliance measures (psychological treatment sessions, medication) will be evaluated across treatment arms, and controlled for in primary analyses.

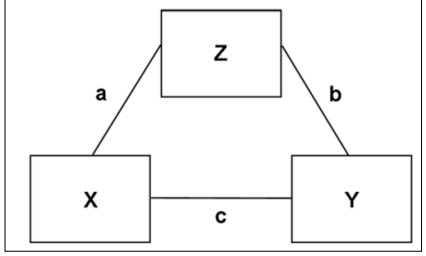
Primary Aims 1-3: Outcome Analyses

The primary outcomes will be 7-day point prevalence abstinence at week 27 (24-weeks post-TQD; self-reported abstinence for 7 days prior to the assessment and breath CO ≤8 ppm) and AE rates. CO-verified 7-day point prevalence abstinence at weeks 7 and 14 (4- and 10-weeks post-TQD, respectively) will be secondary measures. As per guidelines (Hughes et al., 2003), secondary outcomes at 24-weeks post-TQD will include: prolonged abstinence (relapse defined as 7 consecutive days of self-reported smoking after a 2-week grace period), continuous abstinence (no smoking between TQD and follow-up), and time to 7-day relapse. Other than time to relapse, all outcomes of interest are binary (abstinence and AE rates) and will be analyzed using logistic regression. The effect of varenicline on AE rates (Primary Aim 2a**)** will be based upon the union-intersection test arm for establishing non-inferiority in the proportion of participants experiencing moderate to severe AEs in the varenicline vs. the placebo arm (Hauschke et al., 1999). To ensure that tests on the overall sample do not mask differential effects by antidepressant medication use and type, these analyses will be preceded by a Breslow-Day for homogeneity across strata of interest. If no evidence of heterogeneity is found, stratum-specific estimates will be combined using a Cochran-Mantel-Haenszel weighing scheme (Wiens & Heyse, 2003).

Missing Data Approaches

Analyses of abstinence rates will be conducted first using an ITT principle, analyzing data from all participants randomized to treatment, counting those lost to follow-up as non-responders (missing=treatment failures). We will also conduct an adherence sample analysis that includes only participants reached at 24-weeks post-TQD (≥70% based on our experience). This approach addresses the question of efficacy more directly, but it is subject to more bias if attrition is large or differential by treatment arm. Consequently, we will complement it by analysis of non-response patterns using sociodemographic (gender, race, education), smoking (tobacco dependence), and psychiatric characteristics (number of lifetime MDEs, current use of psychotropic medication, presence of other Axis I diagnoses). These analyses will be used to create propensity scores that will allow for inverse-probability-weighing (IPW) of observed outcomes (Cole & Hernan, 2008; Robins, Rotnitzky, & Zhao, 1995) to achieve balance across potential confounders of the treatment-to-outcome relationship. The distribution of propensity scores should show large overlap across study arms. If not, that will be taken as evidence that study completers are not comparable on measured confounders, and that one should refrain from further treatment comparisons. Similar findings across all three approaches would increase confidence in the results overall. Both raw and adjusted rates will be presented for each outcome by study arm. Time to 7-day relapse will be evaluated using discrete-time survival models (Singer & Willett, 1993), as implemented in PROC LIFEREG of SAS/STAT 9.2 (SAS Institute, 2009).

Figure 5. Mediational Model



Secondary Aim 1: Mediator Analyses

Secondary Aim 1 hypothesizes that increases in hedonic capacity and cognition will mediate the effects of BA plus varenicline on bioverified 7-day point prevalence abstinence at 24-weeks post-TQD for participants assigned to the varenicline arm alone. This outcome is expected to be achieved via the individual and combined effects of BA and varenicline on lowering cigarette reward value, with additional effects on abstinence via reductions in cigarette craving and tobacco withdrawal, particularly the anhedonia, depressed mood, and cognitive impairment components. For simplicity

of exposition, we present only part of the full mediation model in Figure 4. Here **X** is the exogenous variable (treatment), **Z** is a putative mediator (e.g., hedonic capacity), and **Y** one of the two intermediate outcomes (e.g., cigarette reward value). To aid interpretation of the regression coefficients as partial correlations, both **Z** and **Y** (or any normalized transformations thereof) will be standardized to zero mean and unit variance.

We will establish mediation of treatment effects on this intermediate outcome (e.g., cigarette reward value) using MacKinnon's (2008) approach which is more powerful than Baron and Kenny's causal-steps method (Baron & Kenny, 1986). As explained in Cerin and MacKinnon (2009) and successfully implemented by Papandonatos et al. (2012) researchers ought to determine whether: 1) the intervention successfully acted upon the putative mediator (i.e., "Action Theory test"); 2) changes in the mediator were predictive of changes in the target construct/behavior suggested by the conceptual framework underpinning the intervention (i.e., "Conceptual Theory test") over and above any direct treatment effects; and 3) these conditions held simultaneously for the putative mediator of interest (i.e., "Mediation test"). Let the regression path coefficients between treatment and mediator (action path), mediator and outcome (theory path), and treatment and outcome controlling for the effect of the mediator (outcome path) be denoted by **a, b, c'** respectively. Successful mediation through changes in hedonic capacity requires that the 95% confidence interval for the **a*b** product of path coefficients (which equals **c-c'** for continuous outcomes) includes zero. To accommodate skewness and kurtosis, interval estimation will be based upon bias-corrected and accelerated (BCA) bootstrap confidence intervals (Preacher & Hayes, 2008).

Figure 4 is based upon a simplified 2-group comparison (e.g., with **X** as an indicator of treatment assignment to BA over ST). In reality, treatment assignment will be coded using three contrasts corresponding to the main effects of the psychological and pharmacological treatment components and their interaction, so as to accommodate the hypothesized moderation of the path between hedonic capacity and cigarette reward value by varenicline (Preacher, Rucker, & Hayes, 2007). Simultaneous estimation of the effect of multiple mediators (e.g., hedonic capacity and cognition) will be conducted as in Napolitano et al (2008). Once mediation of the intermediate outcome (cigarette reward value) has been modeled as described above, we will estimate the remaining paths linking intermediate outcomes (cigarette reward value, craving/withdrawal) to the distal outcome (abstinence) via logistic regression. Although we see value in building the model in a piecewise fashion (e.g., in terms of evaluating the need to adjust for potential confounders of the treatment to outcome relationship), we will also estimate the full model in Figure 2 in a single step using the structural equation modeling (SEM) package Mplus 6.0 (Muthén & Muthén, 1998-2010), which allows the user to assess the statistical significance of any complete mediation path via bootstrapping. One important consideration is the choice of measurement points at which to assess the mediators to maximize intervention effects while also preserving the temporal precedence between mediator and outcome. Because all putative mediators follow an intensive measurement schedule, we will be able to estimate their longitudinal trajectories precisely, and will identify appropriate turning points at which the treatment effect is maximized.

RETAIN Sub-Study Analyses

Randomization

Participants will be randomized to the 3 experimental arms ($0, $200, $500) in equal, 33.3% probabilities. A Penn analyst will use the REDCap randomization module to implement block randomization stratified by phone screeners across the two sites. The trial's primary statistician on the Penn research staff will create a block randomization scheme for each screener and will upload a CSV file of each block assignment to the REDCap randomization module. The screener will select his or her name via the REDCap software through an initialization step and will immediately receive the randomization assignment for that participant. This will allow the screener to immediately present the participant with the correct incentive amount, and subsequently present the correct paper informed consent form at the intake visit.

Analytic Strategy

In Secondary Aims 2 and 2a of the trial, we will assess bivariate relationships of incentives with the outcomes described above using t-tests or Wilcoxon rank-sum tests for normally and non-normally distributed continuous variables, and chi-square tests for comparisons of proportions. To examine the hypothesized statistical interactions, we will use logistic, linear, or quantile regression, as appropriate based on outcome

parameterizations and distributions. For all outcomes other than tests for undue or unjust inducement, we will adjust significance levels for multiple comparisons using the Sidak-Holm method.

In all analyses, we will model the center from which patients are recruited as a fixed effect, thereby mitigating confounding by center and adjusting variance estimates for clustering of participants within centers. To adjust for chance covariate imbalance among arms, we will include covariates in multivariable models if they are significantly associated with the intervention arm and predictive of enrollment in the smoking cessation study in bivariate analyses. We will explore temporal trends in incentives' effects over the study period using stratified analyses. If temporal trends are noted, as may occur if prospective patients learn of the incentives study, we will adjust for their influence by entering time as a covariate, modeled as a spline.

Our analyses to rule out undue and unjust inducements entail three primary covariates. All models will have the primary outcome of enrollment in the parent RCT as the outcome. First, to determine whether incentives represent undue inducements for research participation, we will test the statistical interaction between incentive size and the primary covariate of risk perception on the outcome of enrollment in the parent RCT. Second, to determine whether incentives represent unjust inducements for research participation, we will test two interactions, each in a separate model to avoid collinearity: that between incentive size and the primary covariate of annual household income, and that between incentive size and the primary covariate of economic well-being.

Analyses of these interaction terms will be structured as tests of non-inferiority, such that the null hypotheses are that incentives do meet criteria for undue or unjust inducement, and we reject the null, and conclude the absence of undue or unjust inducement, if the interaction terms are "small" according to pre-specified criteria (in technical terms, the inferiority margin). Said a different way, our analyses our designed to determine whether we can exclude the possibility that incentives represent undue or unjust inducements if the resulting interaction terms are sufficiently small. Specifically, we will use one-sided alpha levels of 0.05 to exclude, with 95% confidence, the possibility that any of these interaction odds ratios are >2.0.

Secondary Aim 2b explores the incremental cost-effectiveness of using research incentives to recruit a fixed sample size from the perspective of the research sponsor and investigators. We define the incremental cost-effectiveness ratio (ICER) as the incremental costs of conducting the trial with vs. without a given incentive (or with one incentive vs. another), divided by the time saved in the presence of the incentive or larger incentive. We will evaluate 3 specific ICERs: (i) $500 vs. $0, (ii) $200 vs. $0, and $200 vs. $500. Relevant costs to be analyzed include the total costs of the incentives themselves (the incentive amount multiplied by the number of patients receiving it) and the costs of conducting the RCT for sufficiently long to recruit that number of patients. These latter costs include, for example, the costs of direct recruitment activities such as mailings, advertisements, and phone charges, and the duration of salary and benefits support needed for relevant study personnel.

CONFIDENTIALITY

All participant information will be kept in a secure filing cabinet that is accessible only to authorized study personnel. All databases containing participant information will be password protected, and again, accessible only to authorized study personnel on NU's password-protected and encrypted network. Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information. Each participant will have a unique study ID number for all data collected. In all datasets, we will use ID numbers only. A separate data set linking names with ID numbers will be accessible only by the study biostatistician. All communications about participants will use the ID number only and never include names or other personal information. All data will be stored until all analyses are completed. No data will be shared with any unauthorized party (i.e., aside from study personnel and regulatory officials). Any publication of data will not identify subjects by name or with an identifier that could be used to reveal identity. Data will be accessible to the study PIs (lead and PENN site PI), co-investigators, the study physician, other study staff, and the Northwestern and PENN IRBs and their Offices of Human Research.

Protected Health Information (PHI)

The following PHI will be collected as part of this study:

- Name, address, telephone number
- Email address
- Date of birth
- Social Security Number (PENN site only)
- Some personal information that may be considered sensitive, such as medical history, psychological history, alcohol and other substance use history, etc.
- Results from physical examinations, tests or procedures
- Medical record number

Precautions, as described above, will be taken to ensure that the privacy of subjects' personal health information will be maintained.

PARTICIPANT COMPENSATION

Main Trial

Participants will be compensated for their time up to a maximum of $140 (see Table 5). Participants will also be reimbursed for transportation expenses related to their participation in the study with $10 for each clinic visit (up to $60). The Northwestern site will provide compensation in cash for all sessions (except the Week 27 phone session). The PENN site will provide compensation in cash at the intake visit, but all other visits will be compensated using a Greenphire ClinCard, which is a reloadable, pre-paid card. Compensation will be loaded onto the ClinCard at the end of successfully completed visits. Participants will be issued the ClinCard at Pre-Quit 1. Participants at the Northwestern site will receive compensation for achieved phone sessions at the next clinic visit , and participants at the PENN site will receive compensation within 24 hours of an achieved phone session on the ClinCard. Participants who complete the week 27 phone session but report that they are currently smoking will not be eligible to come in for the week 27 clinic visit. To reimburse these participants for completing the week 27 phone session at the Northwestern site, an electronic gift card to the retailer of their choice (e.g., Target, Walmart, Amazon.com) will be sent to the participant's email and activated through the e-voucher link provided in the email. To reimburse these participants at the PENN site, $10 will be loaded onto the ClinCard.

Table 4. Participant Compensation

Study Session	Session	Travel/Parking
Intake Session (Week 0)	$15	$10
Week 1 (Pre-Quit 1; Clinic)	$15	$10
Week 2 (Pre-Quit 2; Phone)	- (No assessment)	-
Week 3 (Target Quit Day)	$10	$10
Week 4 (Phone)	$10	-
Week 6 (Phone)	$10	-
Week 7 (Clinic)	$15	$10
Week 8 (Phone)	$10	-
Week 10 (Phone)	$10	-
Week 12 (Phone)	$10	-
Week 14 (Clinic)	$15	$10
Week 27 (Phone)	$10	
Week 27 (Clinic)	$10	$10
	$140	**$60**

Total: $ 200

RETAIN Sub-Study

Participants who are eligible for the RETAIN sub-study at phone screen but are not enrolled in the main trial will not receive any RETAIN sub-study compensation. Participants who complete all RETAIN sub-study

procedures will receive two installments of $150 each following the Intake and Week 27 study sessions, for a total payment of $300. This payment will be made in the form of a stored value payment card, with oversight from the Penn RETAIN study team. During the debriefing session, research staff will explain that all RETAIN sub-study participants receive a $300 payment, regardless of what was stated in the Informed Consent Form.

INFORMED CONSENT

Main Trial

Fully trained research personnel will obtain informed consent using the combined consent and HIPAA form approved by the Northwestern and PENN IRBs. The consent process will take place before study data are collected and prior to any treatment. Consenting will occur in person at the start of the intake session and will involve a one-on-one discussion of the study requirements and procedures and an opportunity for participants to ask questions and express concerns. The participants will receive a copy of the combined consent and HIPAA form for their records. In addition, the participants will be given the PI and study physician's contact information should they wish to speak to either of them during the course of the study regarding their consent or the study procedures. The consent process will take place in English, there will be no waiting period, no coercion to participate, and all participants will be considered competent to provide informed consent (i.e., they will be asked if they understand to what they are consenting).

RESOURCES AND STUDY MANAGEMENT FOR HUMAN SUBJECTS PROTECTION

Qualifications of PIs

Brian Hitsman, Ph.D. (Lead PI, Northwestern University)

Dr. Hitsman is a clinical psychologist and assistant professor in the Departments of Preventive Medicine and Psychiatry and Behavioral Sciences. His research focuses on the causes and treatment of tobacco dependence in underserved populations, especially among persons with mental health disorders. Dr. Hitsman has been involved in clinical trial research since 1993 in large efficacy and effectiveness studies of combination behavioral therapy and pharmacotherapy (fluoxetine, bupropion, varenicline, nicotine patch). An ongoing NCI-funded trial being conducted in collaboration with Dr. Schnoll involves extended duration treatment with telephone-based behavioral therapy and nicotine patch or varenicline. Dr. Hitsman served on the 2005 NIMH Tobacco Use and Cessation in Psychiatric Disorders Workgroup that led to a comprehensive review of smoking behavior and tobacco dependence in persons with mental health disorders, including major depressive disorder (MDD), and established a comprehensive research agenda that continues to be highly relevant today. Finally, Dr. Hitsman was a contributing author of the 2010 Surgeon General's Report on *How Smoking Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease* (*Nicotine Addiction: Past and Present)* and serves as a Deputy Editor of *Nicotine & Tobacco Research*.

Robert Schnoll, Ph.D. (Clinical Site PI, University of Pennsylvania)

Dr. Schnoll has conducted numerous randomized clinical trials of treatments for nicotine dependence and co-directed a career development core facility for the NIH-funded Center for Interdisciplinary Research on Nicotine Addiction (CIRNA). Over the past decade, Dr. Schnoll has developed behavioral interventions for nicotine dependence and completed randomized clinical trials of behavioral and pharmacological interventions for nicotine dependence among the general population of smokers and among cancer patients, many times in collaboration with Dr. Hitsman. Dr. Schnoll has served as a co-investigator on an American Cancer Society-funded randomized clinical trial of a behavioral intervention for nicotine dependence among pregnant smokers and completed a bupropion clinical trial, stratified by depression, for nicotine dependence among cancer patients. Dr. Schnoll has ongoing varenicline trials with cancer patients and smokers with HIV/AIDS. Dr. Schnoll has served as Program Chair for the Society of Research on Nicotine and Tobacco annual meeting and as Chairperson for the Risk, Prevention, and Intervention for Addiction NIH Study Section.

Other Members of the Research Team

The following people will be directly involved with study implementation and execution:

Northwestern

1. Mark Huffman, M.D., Lead study physician and co-investigator

2. Jacqueline Gollan, Ph.D., Lead psychologist and co-investigator
3. David Mohr, Ph.D., Co-investigator
4. Nancy Jao, M.S., Graduate research assistant
5. Allison Carroll, M.S., Graduate research assistant
6. Celine Reyes, M.A., Research Study Coordinator
7. Erica Fox, B.S., Research Assistant
8. Sue Giovanazzi, Research clinic manager
9. Ravi Kalhan, M.D., alternate study physician when Dr. Huffman is unavailable
10. Charles Culpepper, M.S., Study Therapist
11. Matthew Olonoff M.A., Graduate Research Assistant
14. Amanda Mathew, Ph.D., Research Assistant Professor
15. Sadiya Khan, M.D., MSc, Study Physician

PENN

1. Scott Halpern, M.D., Ph.D., Co-investigator and PI, RETAIN Sub-Study
2. Frank Leone, M.D., Site physician and co-investigator
3. Anita (Annie) Hole, Ph.D., Site psychologist and co-investigator
4. Janet Audrain-McGovern, Ph.D., Co-investigator
5. Michael Thase, M.D., Site physician
6. Su Fen Lubitz, B.A., Clinical Research Coordinator
7. Alex Flitter, M.A., Clinical Research Coordinator
8. Joseph Bastian, B.A., Research Assistant
9. Anna-Marika Bauer, B.A., Research Assistant
10. Nathaniel Stevens, Research Assistant
11. Mackenzie Quinn, B.A., Research Assistant
12. Sue Ware, B.S., Database Manager
13. Paul Sanborn, M.S., Samples Manager
14. Tierney Fisher, N.P., Site Nurse Practitioner
15. Elizabeth Cooney-Zingman, M.P.H, RETAIN, Chief of Staff
16. Brian Bayes, M.S., Sc.B., RETAIN Study Data Manager
17. Marzana Chowdhury, Ph.D., RETAIN Statistical Analyst
18. Dominique Spence, Phlebotomist
19. Morgan Thompson, B.A., Phlebotomist
20. Katrina Serrano, B.A., Phlebotomist
21. Molly Ruben, M.P.H, Phlebotomist
22. Erin Louge-Chamberlain, B.A., Phlebotomist

Brown University
George Papandonatos, Ph.D., Biostatistician and co-investigator

Legacy Foundation
Raymond Niaura, Ph.D., Co-investigator

Training and Quality Assurance
Drs. Hitsman and Schnoll currently collaborate on an ongoing efficacy trial of extended duration varenicline with cancer patients (R01CA165001) and a recently completed effectiveness trial of long-term nicotine patch therapy (R01DA025078). The PIs have >15 years of experience coordinating multi-site smoking cessation trials involving extensive data collection, counseling, and pharmacotherapy. Thus, systems for training and QA are established to ensure accurate eligibility screening and recruitment, accurate data collection, entry, and management, and optimal protocol delivery. A new Manual of Operations (MOP) will be developed. Training sessions will occur at both sites and annually as needed. Monthly conference calls will review progress, assess adherence, and determine the need for protocol changes or additional training and QA. The MOP will ensure that the trial is conducted uniformly across sites. The MOP will describe responsibilities for all personnel and provide a detailed description of procedures for each point of contact with participants (i.e., for each Week in

Table 1). For each visit/week, a checklist of events (e.g., each measure, therapy) will be created that will be completed by personnel. CRFs will be created for each measure at each week, and every participant will have a study chart, with sections for every visit/week. Every visit is "milestoned" (e.g., attended, missed, scheduled) in the trial database to ensure subject tracking through the trial. Drs. Hitsman, Schnoll, Gollan and Hole have developed the BASC and ST therapy manuals for training. Lastly, a manual for data collection and entry is developed. We will use a server-based DMS, already in use at Northwestern, which allows for real-time, remote data entry using scannable forms. All training will involve didactic instruction, mock sessions, and feedback in the MOP, assessment of eligibility and side effects, therapy, and the DMS by Drs. Hitsman, Schnoll, Gollan, Hole, Huffman, Thase, and Leone. QA focuses on protocol adherence and data validity. We will conduct 100% QA by comparing all hard copy and computer data. We also will audio-record all therapy sessions and assess protocol adherence by selecting a random 15% of sessions for review.

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