Study Title: Extended Duration Varenicline for Smoking among Cancer Patients: A Clinical Trial

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PROTOCOL TITLE

1. Full Title

Extended Duration Varenicline for Smoking among Cancer Patients: A Clinical Trial

2. Brief Title

Varenicline for Smoking among Cancer Patients

STUDY SPONSORSHIP

1. Funding Sponsor

National Institutes of Health (National Cancer Institute)

2. Primary Sponsor

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PROTOCOL ABSTRACT

Upwards of 33-50% of cancer patients who smoked prior to diagnosis continue to smoke following diagnosis and treatment. Continued smoking by cancer patients reduces survival time, medical treatment efficacy, and quality of life (QOL). To date, studies of smoking cessation interventions for cancer patients have failed to yield significant treatment effects. As such, currently, there is no evidence-based treatment model for addressing tobacco use in this population. With medical advances in cancer care yielding a growing constituency of cancer survivors - close to 12 million today - addressing nicotine dependence in this population is a priority. A recent NCI meeting called for the evaluation of novel treatments for nicotine dependence among cancer patients which address the unique barriers to cessation evident in this population, including: a high level of nicotine dependence, high levels of psychological distress and cognitive impairment, and a protracted relapse timeline. While PHS guidelines recommend acute treatment durations with approved medications for tobacco use, we have shown that extending the duration of treatment beyond the standard treatment duration significantly increases quit rates, reduces the risk for a relapse, and promotes recovery to abstinence following a lapse. Extended duration treatment is particularly efficacious for smokers with high levels of nicotine dependence and cognitive impairment, vs. standard duration treatment, and increases quit rates for smokers with high levels of psychological distress. Varenicline, vs. other medications for smoking, may be particularly effective for cancer patients given the drug's beneficial effects on affect and cognition. Thus, using a double-blind placebo-

controlled design with 374 cancer patients, we will: 1) Compare standard varenicline treatment (12-weeks active + 12-weeks placebo) to extended varenicline treatment (24-weeks active) for increasing week 24 and week 52 biochemically-confirmed 7-day point prevalence abstinence; 2) Assess the effects of extended varenicline therapy on QOL, including varenicline side effects; and 3) Assess changes in affect and cognitive impairment as mediators of extended varenicline therapy's effect on quit rates. We will also explore potential moderators of the effect of extended varenicline treatment on quit rates (e.g., tumor site and stage, time since diagnosis, treatment history, level of nicotine dependence). This study is significant by addressing a population with high smoking rates, which has been under-studied in the area of nicotine dependence treatment, and is at risk for unique adverse tobacco-related health effects. This study is innovative by evaluating the efficacy of extended vs. standard duration varenicline treatment, which may more effectively address unique barriers to cessation in this population. This will also be the first study to use varenicline blood levels as a measure of adherence. There is widespread agreement that evidence-based treatment programs for nicotine dependence among cancer patients are needed. This study may help guide efforts to implement such programs and help determine the benefits of extended treatment duration for nicotine dependence more broadly.

OBJECTIVES

1. Overall Objectives

Aim 1: Compare standard varenicline therapy (12-weeks active then 12-weeks placebo) to extended varenicline therapy (24-weeks active) for treating nicotine dependence among cancer patients. Hypothesis: Extended varenicline therapy will increase 24- and 52-week biochemically-confirmed 7-day point prevalence abstinence, vs. standard varenicline treatment.

Aim 2: Assess effects of extended varenicline therapy on quality of life (QOL) and varenicline side effects. Hypothesis: QOL will be rated higher in the extended therapy group vs. the standard therapy group, and there will be no significant differences between groups in terms of severe side effects.

Aim 3: Assess changes in affect and cognitive impairment as mediators of extended varenicline therapy's effect on quit rates. Hypothesis: Improved affect and reduced cognitive impairment will mediate the effect of extended therapy on quit rates.

Exploratory Aim: Evaluate patient-related variables as moderators of extended varenicline therapy's effect on quit rates. To generate new hypotheses, we will explore patient-related moderators of extended varenicline therapy's effect on quit rates (e.g., nicotine dependence, depression, tumor site/stage). Variable selection was based on associations with cancer patient smoking (e.g., Cox et al., 2003; Morgan et al., 2011).

BACKGROUND

Prevalence of Smoking among Cancer Patients

The rate of smoking among individuals with cancer who are age 40 or under are substantially higher (38-40%) than rates of smoking in the comparable age group in the general population (~26%; Bellizzi et al., 2005; Coups & Ostroff, 2005). Studies with patients that have traditional tobacco-related cancers show extremely high rates of smoking; upwards of 50% of head and neck (Duffy et al., 2008) and lung (Cooley et al., 2009) cancer patients report current smoking. However, high rates of smoking are not unique to such traditional tobacco-related disease sites. Significant rates of current smoking have been reported among testicular (19%; Shinn et al., 2007), prostate (16-17%; Gong et al., 2008; Pantarotto et al., 2007), cervical (21%; Beesley et al., 2008), breast (19%; Li et al., 2009), bladder (18%; Blanchard et al., 2008), esophageal (39%; Sundelof et al., 2008), colorectal (22%; Vincenzi et al., 2009), and lymphoma (19%; Geyer et al., 2010) cancer patients. Overall, about one-third to one-half of cancer patients who were smokers prior to their diagnosis continue to smoke following diagnosis (Gritz et al., 2006).

Adverse Health Consequences of Smoking among Individuals with Cancer

Continued smoking by cancer patients has been associated with diminished QOL, reduced survival probability and duration, and increased risk for disease recurrence and a second primary tumor (Gritz et al., 2006; 2007). Continued smoking by cancer patients is associated with greater treatment side effects or diminished QOL among head and neck (Duffy et al., 2007; Zevallos et al., 2009), lung (Daniel et al., 2009), prostate (Ku et al., 2009), and a heterogeneous group of (Schnoll et al., 2010a) cancer patients. A recent meta-analysis of studies with lung cancer patients found that continued smoking was associated with an increased risk of death,

recurrence, and a second primary tumor (Parsons et al., 2010). Likewise, studies with head and neck cancer patients have reported that patients who continue to smoke following their diagnosis have a lower survival rate and an increased risk for a recurrence and a second primary tumor (Browman et al., 2002; Hilgert et al., 2009; Fortin et al., 2009; Leon et al., 2009). Continued smoking has also been associated with reduced survival among breast (Aksoy et al., 2007), lymphoma (Geyer et al., 2010), esophageal (Sundelof et al., 2008), prostate (Gong et al., 2008), cervical (Coker et al., 2009), and bladder (Aveyard et al., 2002) cancer patients and with an increased risk of recurrence or a second primary tumor among bladder (Fleshner et al., 1999), breast (Li et al., 2009), lymphoma (Moser et al., 2006), and colorectal (Jacobson et al., 1994) cancer patients. Continued smoking may worsen prognosis by reducing the effectiveness of chemotherapy (Duarte et al., 2008; van der Bol et al., 2007; Vincenzi et al., 2009; Hotta et al., 2008) and radiotherapy (Browman et al., 1993).

Nicotine Dependence Treatments for Those with Cancer

Very few smoking cessation trials have been conducted with this population (Gritz et al., 2006; 2007) and many of these past trials have used small samples and relied on self-report for smoking abstinence outcomes (de Moor et al., 2008). After nearly two decades of research in this area, not a single smoking cessation randomized clinical trial has yielded significant treatment effects (excluding Emmons et al., 2009, which studied adult survivors of childhood cancer; de Moor et al., 2008). Nurse-led (Griebel et al., 1998; Stanislaw & Wewers, 1994; Wewers et al., 1994), physician-led (Browning et al., 2000; Gritz et al., 1993; Schnoll et al., 2003b), and behavioral (Schnoll et al., 2005; Wakefield et al., 2004) smoking cessation trials have failed to yield treatment effects for cancer patients. Our recent clinical trial with bupropion (Schnoll et al., 2010a) found no main effect for the medication, but bupropion increased abstinence rates, reduced withdrawal symptoms, and improved QOL more for patients with depression, vs. those without depression. Lastly, a very recent varenicline study reported end-of-treatment quit rates of 34%, vs. 14% for the comparison group (OR = 3.14), and a side effect profile that mirrored the general population (Park et al., 2011). While these data are encouraging, as were reported feasibility data, the study was under-powered (n = 49) and did not use a randomized design. Thus, there is currently no empirically-based treatment model for addressing nicotine dependence in the oncologic context. As such, a recent NCI meeting, with representatives from NCI cancer centers, concluded that the evaluation of novel smoking cessation interventions for cancer patients is a critical priority (Morgan et al., 2010).

Barriers to Quitting Smoking Among Cancer Patients

Few of the randomized clinical trials of treatments for nicotine dependence among cancer patients have addressed important barriers to smoking cessation evident in this sub-group of smokers vs. the general population of smokers (Gritz et al., 2006). First, the need to address the high level of nicotine dependence exhibited by cancer patients has been widely noted (Cataldo et al., 2010; de Moor et al., 2008; Gritz et al., 2006). Indeed, continuing to smoke after experiencing such a serious health problem that is so centrally linked to their smoking behavior is a hallmark of psychiatric definitions of nicotine dependence (APA, 2000). Further, while studies with the general population of smokers show that 35-54% of participants report smoking their first cigarette within 30 minutes after waking (Huh & Timberlake, 2009; Messer et al., 2008), a well-regarded measure of nicotine dependence (Baker et al., 2007), studies with cancer patients indicate that this rate is 69-81% (Cooley et al., 2009; Schnoll et al., 2005; 2010; Gritz et al., 1993; 1999; Wakefield et al., 2004). Mean Fagerstrom Test for Nicotine Dependence (FTND; Heatherton et al., 1991) scores in the general population of smokers are 4.0-4.3 (Fagerstrom et al., 1996; Graham et al., 2008), versus 5.3 among cancer patients who smoke (Schnoll et al., 2010a). A higher level of nicotine dependence has been consistently associated with a poorer response to smoking cessation treatments in the general population (Bolt et al., 2009; Baker et al., 2007) and among cancer patients (Schnoll et al., 2002) and with relapse to smoking among cancer patients (Cooley et al., 2009; Walker et al., 2006).

Smoking cessation interventions for cancer patients also need to address psychological distress (Cataldo et al., 2010; de Moor et al., 2008; Gritz et al., 2006; 2007) and cognitive impairment (Cox et al., 2003). A cancer diagnosis and its medical treatment can lead to clinically significant and protracted symptoms of psychological distress and cognitive impairment (Biegler et al., 2009; Pirl et al., 2004). Psychological distress among cancer patients typically involves symptoms of depression and anxiety (Kash et al., 2005; Holland & Alici, 2010), while cognitive impairment typically includes difficulties with memory, attention/concentration, and executive function (Biegler et al., 2009). Symptoms of psychological distress have been shown to be a strong risk factor for relapse following successful smoking cessation in the general population (Zvolensky et al., 2009) and among cancer patients (Schnoll et al., 2010a). Likewise, in the general population, smokers use nicotine to enhance

cognitive function, nicotine withdrawal increases cognitive impairment which predicts relapse, and resuming smoking ameliorates abstinence-induced cognitive impairment (Heishman, 1999; Evans & Drobes, 2009; Rukstalis et al., 2005). A higher level of cognitive impairment among cancer patients has also been associated with a greater likelihood of smoking (Kahalley et al., 2010).

Lastly, to date, smoking cessation clinical trials for cancer patients have inadequately considered the protracted time-line for smoking relapse exhibited by cancer patients relative to the general population of smokers (Gritz et al., 2006; 2007). In the general population of smokers, the large majority of smokers who achieve abstinence and relapse do so within 1-2 weeks (Shiffman, 2006). A meta-analysis of studies with the general population of smokers showed that, after abstinence, upwards of three-quarters of individuals relapse within 8 days from abstinence (Hughes et al., 2004). In contrast, studies with cancer patients illustrate a delayed or protracted relapse process. A prospective study of smoking behavior among head and neck cancer patients showed that the majority of relapse to smoking occurs within 6 months following initial abstinence (Gritz et al., 1999). Likewise, prospective studies with lung cancer patients reported that the majority of smoking relapse did not occur until 2 months after initial abstinence (Cooley et al., 2009; Walker et al., 2006).

A Novel Treatment for Cancer Patients who Smoke: Extended Duration Varenicline

Thus, nicotine dependence treatments for cancer patients may show greater efficacy if they adequately address the patient's relatively high level of nicotine dependence, risk for psychological distress and cognitive impairment, and delayed relapse process. We hypothesize that extended duration varenicline (24-weeks) will address these barriers to cessation and significantly increase quit rates, vs. standard varenicline treatment (12 weeks).

Our rationale for selecting varenicline is as follows. First, the high rate of nicotine dependence among cancer patients underscores the need to include a pharmacotherapy as part of treatment. Varenicline is currently the most efficacious FDA-approved medication for nicotine dependence, yielding quit rates that significantly exceed those produced by bupropion (Gonzales et al., 2006; Jorenby et al., 2006) and nicotine patch (Aubin et al., 2008; Biazzo et al., 2010; Stapleton et al., 2008). Second, varenicline mitigates adverse psychological effects and cognitive impairment associated with quitting smoking (Patterson et al., 2009; Smith et al., 2009; Philip et al., 2009; Rollema et al., 2009; Sofuoglu et al., 2009). The anti-depressant-like (Rollema et al., 2009) and cognitive enhancing (Loughead et al., 2010) effects of varenicline is consistent with what we know about how varenicline works. As a nicotinic acetylcholine receptor (nAChRs) partial agonist, varenicline binds to nAChRs and blocks the entry of nicotine (from smoking) into the receptor and stimulates a moderate release of dopamine. This reduces the rewarding effects of smoking and reduces withdrawal symptoms (Rollema et al., 2009). Preclinical studies also indicate that α4β2 nAChRs subtypes are critical for cognition (Levin et al., 2006) and stimulation of these receptors by varenicline yields improved cognitive function (Loughead et al., 2010). Likewise, animal studies indicate that the simultaneous activation and desensitization of nAChRs receptors produced by nicotinic partial agonists like varenicline can yield antidepressant-like effects (Mineur & Picciotto, 2010), which underlies current evaluations of varenicline as a treatment for major depression. Third, varenicline is efficacious and safe for treating nicotine dependence among various clinical populations, including: cardiovascular disease patients (Rigotti et al., 2010), COPD patients (Tashkin et al., 2010), smokers with comorbid alcohol (Hays et al., 2010) and cocaine (Poling et al., 2010) dependence, and smokers with comorbid affective or psychotic disorders (McClure et al., 2010; Smith et al., 2009; Philip et al., 2009). It has been shown to be safe when taken over 52 weeks (Williams et al., 2007). Although there have been reports of adverse psychiatric events following varenicline use, leading the FDA to mandate a boxed warning for varenicline, pooled data from controlled efficacy trials (Cahill et al., 2009; Tonstad et al., 2010), effectiveness trials (McClure et al., 2010), and large cohort studies (Gunnell et al., 2009; Kasliwal et al., 2009) demonstrate that varenicline is safe for treating nicotine dependence, even among smokers with psychiatric comorbidity, including depression (Stapleton et al., 2008; McClure et al., 2010; Steinberg et al., 2010).

Our rationale for selecting an extended duration treatment is as follows. First, we have shown, in a placebo-controlled randomized trial with general population smokers, that 24-weeks of transdermal nicotine, vs. the standard 8-weeks, increases 6-month quit rates by an OR of 1.81 (32% vs. 20%; Schnoll et al., 2010b). Second, and importantly, extending treatment with the nicotine patch to 24-weeks significantly helps smokers with high levels of nicotine dependence and cognitive impairment, in particular, to overcome their liability to relapse (see below). While extended therapy with transdermal nicotine did not offset the effect of depression symptoms on relapse rates, the quit rate among depressed smokers in extended treatment was almost 2-times

higher than it was for depressed smokers in standard treatment (see below). Third, we showed in our placebo-controlled randomized clinical trial with general population smokers (Schnoll et al., 2010b) that extending treatment with transdermal nicotine to 24-weeks (vs. 8-weeks) significantly reduced the probability that smokers would experience a lapse and, importantly, increased the likelihood that smokers would recover to abstinence following a lapse. Extended duration treatment offered smokers who lapsed the opportunity to re-start their quit attempt and eventually achieve abstinence. Thus, extended duration varenicline may be particularly efficacious at addressing the barriers to cessation that are evident among cancer patients.

CHARACTERISTICS OF THE STUDY POPULATION

1. Target Population

Three hundred seventy-four adult male and female smokers 18 years of age or older who have been diagnosed with cancer (all sites) within the past 5 years will complete the study.

At PENN, a previous extended nicotine patch trial recruited a sample comprised of 45% women and 16% racial/ethnic minorities (Schnoll et al., 2010b); a separate PENN smoking cessation trial that used targeted efforts to recruit minority smokers had a sample comprised of 55% women and 52% racial/ethnic minorities (Schnoll et al., 2011). Further, 29% of the sample of cancer patients in Dr. Schnoll's bupropion trial was African American and 48% were female (Schnoll et al., 2010a). At NU, a smoking cessation trial with fluoxetine recruited a sample comprised of 54% women and 38% ethnic/racial minorities (Spring et al., 2007). Lastly, 53% of cancer patients at PENN are women and 24% are from ethnic/racial minority groups and 54% of cancer patients at NU are women and 48% are from ethnic/racial minority groups.

2. Accrual

At PENN, the trial will be primarily implemented at the Abramson Cancer Center (ACC). Dr. Lerman, ACC Deputy Director, will ensure study integration within oncology clinics. ACC data indicate that the clinics to be used to recruit for this study saw ~3200 new patients in 2009. Preliminary data ascertained as part of an ongoing smoking cessation project for relatives of cancer patients (R01 CA126969) showed that, among 517 eligible cancer patients screened, 150 were currently smoking (29%) and 78 (52%) agreed to enroll in a smoking cessation program. Thus, based on ~3200 patients available for screening/year, we expect that ~925 will be smokers and ~480 will be interested in a smoking cessation program. Given the trial requirements and inclusion/exclusion criteria, we estimate that we can enroll ~10% of these patients for this trial (Martinez et al., 2009) or ~48 patients/year at PENN (total sample at PENN = 187 over 4 years).

At NU, the trial will be primarily implemented at the Robert H. Lurie Comprehensive Cancer Center. Dr. Steven Rosen is Director of the cancer center and will ensure that this trial is integrated into the cancer center clinics to facilitate recruitment. Cancer Center data indicate that ~6000 new patients/year are seen at the NU cancer center. Preliminary data ascertained for this proposal showed that, among 127 eligible cancer patients screened, 17 were smokers (13%) and 12 (71%) agreed to enroll in a smoking cessation program. Thus, based on ~6000 patients available for screening/year, we expect that ~780 will be smokers and ~546 will be interested in this study. Given the trial requirements and inclusion/exclusion criteria, we estimate that we can enroll ~10% of these patients for this trial (Martinez et al., 2009) or ~55 patients/year at NU (total sample at NU = 187 over 4 years).

Both PENN and NU will supplement recruitment with referrals from physicians and other cancer care providers at various cancer treatment centers within the Philadelphia and Chicago metropolitan areas.

Based on our extended therapy and bupropion trial with cancer patients (Schnoll et al., 2010a, 2010b), we expect that <20% of participants will withdraw from the trial and ~70% of participants will complete follow-up evaluations, which will exceed rates in varenicline trials (Jorenby et al., 2006). As is advised in smoking cessation trials (Hughes et al., 2003), intent-to-treat will be used for primary analyses, with missing outcome data coded as smokers (even due to death).

3. Key Inclusion Criteria

Eligible subjects will be males and females:

1. 18 years of age or older who self-report smoking at least 5 cigarettes per week, almost every week (menthol and non-menthol) on average, for the last 6 months.
2. Who have been diagnosed with a primary or secondary cancer (all sites) or have experienced a recurrence of a previously diagnosed cancer within the past 5 years. Those diagnosed >5 years ago without remission will also be eligible.
3. With a Karnofsky Score of ≥50 or ECOG Performance Status score of ≤2 within 6 months of enrollment.
4. Able to use varenicline safely, based on a medical evaluation including medical history and physical examination, and psychiatric evaluation.
5. Residing in the geographic area for at least 12 months.
6. Women of childbearing potential (based on medical history review) must consent to use a medically accepted method of birth control (e.g., condoms and spermicide, oral contraceptive, Depo-Provera 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.
7. Able to communicate fluently in English.
8. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the combined consent/HIPAA form.

4. Key Exclusion Criteria

Subjects who present with and/or self-report the following criteria will not be eligible to participate in the study.

Smoking Behavior

1. Current enrollment or plans to enroll in another smoking cessation program in the next 12 months.
2. Regular (daily) use of chewing tobacco, snuff, snus, cigars, cigarillos, or pipes.
3. Current use or plans to use nicotine substitutes (gum, patch, lozenge, e-cigarette) or smoking cessation treatments in the next 12 months.
    a. Note: Once participants are found eligible for the study, they are told they should refrain from using any nicotine replacement therapy (NRT) for the duration of the study. If a subject reports NRT use during the study, s/he may be permitted to continue pending Study Physician and PI approval.

Alcohol/Drug Exclusion Criteria

1. Diagnosis of substance abuse or dependence that has been unstable within the past year according to self-report or Mini International Neuropsychiatric Interview (MINI) assessment.
2. Breath Alcohol Concentration (BrAC) assessment greater than or equal to 0.01 at the Intake Session.
3. Current alcohol consumption that exceeds 25 standard alcoholic drinks/week.

Medication Exclusion Criteria

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

1. Other smoking cessation medications (e.g. Zyban, Wellbutrin, Wellbutrin SR, Chantix)
    a. Note: Once participants are found eligible for the study, they are instructed to only use the smoking cessation medication provided to them by the study staff. If a subject 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 subject to continue participation.
2. Anti-psychotic medications (if used to treat psychotic symptoms. Other uses may be eligible pending Study Physician approval).
3. Bipolar Disorder medications (if used to treat Bipolar Disorder or manic symptoms. Other uses may be eligible pending Study Physician approval).

Medical Exclusion Criteria

1. Women who are pregnant, planning a pregnancy within the next 12 months, or lactating.
2. History of epilepsy or seizure disorder (history of seizure requires Study Physician approval).
3. History of kidney disease, including transplant.
4. Uncontrolled hypertension (SBP >160 or DBP >100).
    a. Note: If a participant presents with blood pressure greater than 160/100 at sessions occurring on Week 0 (Pre-Quit) or at any other point during the treatment period, they will not be provided with/able to continue on medication unless the Study Physician grants approval.
5. History of unstable heart disease, stroke or myocardial infarction, angina, abnormal heart rhythms, or tachycardia (as determined by Study Physician review or self-report).
6. Any suicide risk score on MINI, current suicidal ideation on Columbia scale, or lifetime self-reported suicide attempt.
7. Current or past diagnosis of psychotic or bipolar disorder, as determined by self-report or MINI assessment.
8. Current diagnosis of unstable and untreated major depression, as determined by self-report or MINI assessment (eligible if stable for ≥30 days).
9. Previous allergic reaction to varenicline.

General Exclusion Criteria

1. Any medical condition or concomitant medication that could compromise subject safety or treatment, as determined by the Principal Investigator and/or Study Physician.
2. Inability to provide informed consent or complete any of the study tasks as determined by the Principal Investigator and/or Study Physician.

5. Vulnerable Populations

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

6. Populations vulnerable to undue influence or coercion

Educationally or economically disadvantaged persons are included but not solely targeted for recruitment. Cognitively impaired persons are not included in the current study. Because of our recruitment efforts for this study, it is possible that University of Pennsylvania employees and students may be invited to participate. Status of participation in the study will be independent of the subject's work or school activities.

7. Subject Recruitment

Subjects will be recruited from oncologic clinics located within 2 NCI-designated cancer centers (PENN and NU). As done successfully for our past smoking cessation trial with cancer patients (Schnoll et al., 2010a) and our ongoing smoking cessation clinical trial for family members of cancer patients (R01 CA126969), Research Assistants will attend oncology clinics and use electronic databases to identify potential subjects (each site has patient smoking status indicated on the electronic medical record). Daily clinic schedules will be ascertained and RAs will approach patients prior to or after consultation or treatment. In addition to in-clinic recruitment, introduction letters will be sent to subjects who meet initial eligibility criteria based on the electronic medical record review. These letters will provide an overview of the study and notify the patient that a member of the study team will follow up with him/her over the phone about the study. One week after the letter is sent the Research Assistant will call the participants to assess interest in the study and screen for initial eligibility. This recruitment strategy will allow Research Assistants to reach the patients who miss their cancer center appointments or who do not need to attend the cancer center on a regular basis.

Research Recruitment Best Practice Advisories (BPAs) will also be integrated into electronic medical record recruitment. 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 (Hem/Onc

at Perelman and RadOnc). 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.

In addition, we will post program flyers/brochures in clinics and at additional hospitals that are part of the PENN and NU health system, which provides a contact phone number to call to enroll in the study. We will contact local cancer support groups and provide them with recruitment materials. Information about the study will be available on the CIRNA and iConnect websites and Craigslist. We will also place recruitment data requests with electronic research data warehouses such as Penn DataStore and PennOmics. ResearchMatch, a national health volunteer registry that was created by several academic institutions and supported by the U.S. National Institutes of Health as part of the Clinical Translational Science Award (CTSA) program, will also be utilized. ResearchMatch has a large population of volunteers who have consented to be contacted by researchers about health studies for which they may be eligible.

Once potential subjects are identified by any of the means described above, an RA will contact these individuals by phone to provide more information about the trial and to assess basic eligibility and study interest. Participants who are eligible and interested in the study will be scheduled for an Intake session (Week -1). If willing to proceed, the participant will sign an informed consent and HIPAA form, complete eligibility and baseline assessments, and will be scheduled for Week 0. The participant's eligibility will be confirmed by site physicians and psychologists. To assess external validity, eligible patients who refuse entry will be compared to those who enroll in terms of available data (e.g., disease stage, cigarettes per day).

To ensure a high level of trial retention and adherence we will: 1) educate subjects about the benefits of treatment adherence as recommended by Ebbert et al. (2010); 2) schedule in-person sessions at convenient times (e.g., evenings); 3) incorporate a medication adherence component into the behavioral counseling protocol (Gariti et al., 2009; Schnoll et al., 2008), and 4) as is standard practice in smoking cessation trials (Schnoll et al., 2010b; Niaura et al., 2005), provide modest financial compensation for session completion and transportation costs.

STUDY DESIGN

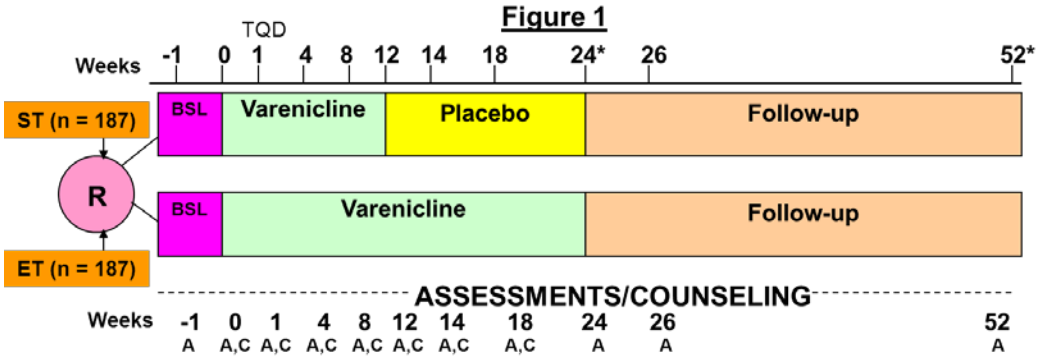
1. Phase

This study is a Phase III clinical trial.

2. Design

This is a randomized, between-subject, double-blind, placebo controlled study.

Figure 1. Study Overview



ST = Standard Treatment; ET = Extended Treatment; BSL = Baseline (Intake Session and Randomization); A = Assessment; C = Counseling; TQD = Target Quit Day; * = 6- and 12-months post-TQD and primary outcomes.

3. Study Duration

Length of Subject's Participation in Study

Subjects will participate in study related activities for approximately 12 months from initial eligibility assessment through follow-up. A subject's length of participation may be affected by center or subject scheduling conflicts.

Projected date of completion of the proposed study

We expect to complete accrual in approximately 48 months. We expect to obtain our numbers in this timeframe by enrolling approximately 8 subjects per month.

Table 1. Study Timeline

Tasks/Months	1	12	24	36	48	60
Refine and test DMS and Train Staff (1-3)	X—X					
Recruitment/baselines (3-48)		X----------X				
Treatment (3-54)		X----------X				
Outcome assessments (15-60)		X----------X				
Analysis/manuscripts (48-60)					X----------X	

DRUGS OR DEVICES

Study Medication

Dosing

Varenicline will be used in accordance with FDA approved labeling: Day 1-Day 3 (0.5mg once daily); Day 4-Day 7 (0.5mg twice daily); and Day 8-Day 84 (1.0mg twice daily). On Day 85, participants randomized to standard therapy will be given placebo pills (resembling the 1.0mg pills), while extended therapy participants will continue with active varenicline (1.0mg twice daily). Participants will take this medication until Day 168.

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

Varenicline and matching placebo will be provided at no-cost by Pfizer and packaged and stored at the Penn Investigational Drug Service (IDS). Penn IDS will oversee the randomization and labeling of all study medication, and will assign each kit, which contains 24 weeks of medication for one subject, a unique Pharmacy Randomization Number (PRN). Once a new subject is enrolled and eligible, Penn IDS will assign the subject the next available PRN. The research staff will then label the blister packs with the subject's study ID number. The PRN and study ID number must match for each blister pack a subject receives. A centralized system will help to preserve internal validity and maintain study blinding of clinical treatment site personnel.

The study coordinator at Penn will work with Penn IDS to ensure that an adequate supply of medication is available at all treatment sites. At NU, the study investigators will store the study drug in locked cabinets. Medication supply, in increments, will be given to participants at Pre-Quit, Weeks 4 and 12.

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 staff member who completed 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. Drug destroyed on site will be documented in the study files.

STUDY PROCEDURES

1. Procedures

Subjects
Subjects will be 374 adult smokers who have been diagnosed with cancer in the last 5 years, meet study eligibility criteria, and provide written consent to participate in this between-subject trial.

Study Procedures
Initial Eligibility Screening.
Recruited subjects will complete an initial eligibility assessment in the oncology clinic or over the telephone. This assessment reduces the likelihood that participants attend an Intake Session only to learn that they are ineligible or to allow us to ascertain physician's clearance should the participants have a medical condition that requires approval. Subjects who pass this pre-screening will be invited to attend an Intake Session.

Intake Session (Week -1): Consent, Eligibility Determination, Baseline Measures.
Subjects who pass the pre-screening will be invited to attend a 2.5-hour Intake Session where the following activities will occur:

1. Subjects will hear a study description where all study procedures, risks, and information about the study medication will be reviewed. Subject questions will be answered. Following this presentation, the combined informed consent and HIPAA form will be completed.
2. A urine pregnancy test (all female subjects) will be administered.
3. A breath alcohol concentration assessment (BrAC) to control for alcohol consumption. The handheld device uses a disposable mouthpiece, reports the concentration of alcohol in breath and takes about 2 minutes.
4. A carbon monoxide (CO) breath assessment to control for prior tobacco exposure. The handheld device uses a disposable mouthpiece, reports CO in parts per million (ppm), and takes about 3 minutes.
5. A mental status examination (Mini International Neuropsychiatric Interview, HADS, CSSRS) with a trained research staff member.
6. Complete routine medical history, including blood pressure assessment. If a participant has not received a Karnofsky or ECOG score within 6 months of enrollment the Karnofsky scale will also be administered.
7. A concomitant medication review.
8. Complete baseline paper and pencil measures to assess 1) background variables that may serve as covariates and will allow for assessment of external validity (e.g., smoking history, demographics); 2) mediators (e.g., affect), 3) moderators (e.g., disease-related information), and 4) baseline smoking behavior.

If eligible at this point, subjects will be scheduled for the first treatment session (Week 0). There must be no more than 60 days between the Intake Session and the first treatment session (Week 0, Pre-Quit). If 60 days elapses between these sessions, all intake measures must be re-administered and evaluated by the study physician before Pre-Quit can occur (both sessions may be completed on the same day pending study physician approval by phone).

Behavioral Counseling (Week 0-Week 18).
All subjects will receive manual-based counseling from a counselor trained and supervised by Dr. Hole. The counseling protocol is based on PHS guidelines for smoking cessation treatment (Fiore et al., 2008), used in our past studies with cancer patients (Schnoll et al., 2010a) and in our ongoing cessation trial at NU (R01 DA025078). Counseling is included given its efficacy at helping smokers quit (Fiore et al., 2008) and to increase study retention. Counseling is provided to both treatment arms through Week 18 to equate for time and attention across arms and since this method was used in varenicline clinical trials (Gonzales et al., 2006) and in our extended therapy trial (Schnoll et al., 2010b). In-person counseling was selected for most sessions to ensure adequate monitoring of participant safety and adherence throughout the trial. Sessions are arranged at convenient times for the participants, including evenings.

Pre-Quit Session (Week 0): The counseling program begins at Week 0 with a 1-hour in-person "pre-quit" counseling session to prepare for the target quit day. This session focuses on reviewing participant's history and experience with quitting, beliefs about smoking and quitting, and perceived barriers to cessation, and

initiates a quitting plan involving identifying smoking triggers and identifying strategies to increase the chance for success, including relying on social support and altering behaviors associated with smoking. Medication is dispensed at this session and will begin following the session.

Quit Day Session (Week 1): At Week 1, participants will receive a 30-minute in-person "quit-day" session to review the initial quit attempt, identify potential reasons for relapse, and review a plan for avoiding tempting situations.

Relapse Prevention Sessions (Weeks 4, 8, 12, 14, and 18): Participants will then receive 5 additional 20-minute sessions (in-person or over the telephone) at Weeks 4, 8, 12, 14, and 18 which either reinforce success and review the quit plan or reestablish a quit date and restart the cessation process. The sessions are designed to enhance awareness of the harmful effects of smoking, assist the person in developing skills to quit and avoid relapse, and instruct the smoker on varenicline use. All sessions may be audio-taped and a random 15% of sessions are assessed for protocol adherence. The counselor is blind to randomization.

Varenicline or Placebo Treatment (Weeks 0-24).
Varenicline will be used in accordance with FDA approved labeling: Day 1-Day 3 (0.5mg once daily); Day 4-Day 7 (0.5mg twice daily); and Day 8-Day 84 (1.0mg twice daily). On Day 85, participants randomized to standard therapy will be given placebo pills (resembling the 1.0mg pills), while extended therapy participants will continue with active varenicline (1.0mg twice daily). Participants will take this medication until Day 168. Extended therapy was defined as 24 weeks to be consistent with previous trials (Schnoll et al., 2010b).

If a participant is not able to attend a medication pick up visit (Week 4 or Week 12), the session will be completed over the phone and, if eligible, one week of study medication will be mailed to the participant from the research pharmacy. Participants will need to schedule a brief appointment in-center to complete a blood pressure evaluation before additional study medication is dispensed (session blood pressure procedures apply). If the Week 4 or Week 12 assessments cannot be completed over the phone within the session window, participants will be invited to a brief in-center appointment for a side effects assessment and blood pressure evaluation before additional study medication is dispensed (session side effects and blood pressure procedures apply).

Participants who discontinue the study medication for 14 or more consecutive days will require approval from the Principal Investigator and Study Physician before restarting the study medication. Participants will also be required to sign a consent addendum acknowledging that re-starting medication at full dose without a dose run-up may result in increased side effects.

Varenicline Adherence.
At each session following Pre-Quit, medication adherence is evaluated by self-report and pill count. Specific strategies to address non-adherence will be used, if necessary. The varenicline adherence approach formally assesses participant reasons for non-adherence using scenarios and uses specific strategies to enhance compliance. At Week 4 (steady-state), all participants enrolled at Penn will be asked to provide a blood sample to evaluate varenicline levels as a measure of adherence. If a participant discontinues study medication for any reason for 14 or more consecutive days prior to an adherence blood draw, the blood draw will not be performed.

Mid-treatment Assessments.
Assessments will be conducted at Weeks 0, 1, 4, 8, 12, 14, 18, 24, 26, and 52 by trained RAs. These assessments will require ~30 minutes to complete and will be conducted in-person or over the telephone prior to counseling. Assessments include measures of mediating variables (e.g., affect), side-effects (including a suicidality scale), treatment adherence (pill count and collection of blister packs), concomitant medication review, carbon monoxide assessment, QOL, smoking behavior, and changes in cue-elicited smoking urges (via computer-based concurrent choice task; in-person visits only).

Side Effect Monitoring

The research team has clinical psychologists and physicians at each site to review initial eligibility and to monitor and address side effects during the trial. To reduce risk for adverse events, we carefully assess eligibility to ensure that individuals with certain pre-existing conditions that can increase adverse event risk are excluded.

We will also frequently assess participant treatment reactions with established varenicline symptom checklists and validated suicidality and depression scales. These assessments will be conducted at each visit before, during, and after the treatment phase. Also, given recent reports indicating the potential risk for adverse cardiovascular effects from varenicline (Singh et al., 2011 and www.fda.gov/Drugs/DrugSafety/ucm259161.htm), blood pressure will be assessed at each in-person visit to monitor cardiovascular reactions to study medication.

We will use an established coding and reporting system for side effects used in our ongoing multi-site varenicline trial (U01 DA020830). In this system, study personnel are trained by physicians and psychologists to administer established side effects measures, including validated scales of depression and suicidality. If a side effect report or a score on an established scale indicates a safety concern, site PIs and physicians/ psychologists are immediately notified and will determine a course of action (e.g., continue to monitor, stop medication). Participants are given contact information so that, if an adverse event occurs, they can contact study physicians 24-hours a day. These side effects are also coded and managed by PIs and site physicians/psychologists. All serious adverse events are reported to the IRB, NIH, FDA, and Pfizer in accordance with data safety and monitoring reporting procedures, and they may also be referred to an out-patient department at PENN/NU or to the ER. Lastly, a study-specific Data Safety and Monitoring Board will be convened for this trial to monitor side effects.

Outcome Assessments.

The primary outcome variable is 7-day point prevalence abstinence at Weeks 24 and 52, confirmed with CO (Hughes et al., 2003). All participants will be asked to attend the center at Weeks 24 and 52 and CO will be collected for all participants to avoid potential bias. Other outcomes include: 7-day point-prevalence abstinence (CO-verified) at Week 12 and 26, smoking rate, prolonged abstinence to Weeks 12, 24, 26, and 52 (relapse defined as 7 consecutive days of self-reported smoking, after a 2-week grace period), continuous abstinence at Week 12, 24, 26, and 52 (no smoking between the quit day and the follow-up measure), time to 7-day relapse (no grace period), lapse and recovery events, and QOL.

Note: If a participant is unable to complete a session in-person, assessments and counseling may be completed over the telephone. Every attempt will be made to accommodate participants' schedules & reduce the likelihood of missed sessions. Missed sessions will not be submitted as protocol deviations.

Table 2: Study Measures/Events

Study Week	-1	0	1	4	8	12	14	18	24	26	52
Session Name	Intake	Pre-Quit	TQD	W4	W8	W12	W14	W18	W24	W26	W52
Session Type	In Person	In Person	In Person	In Person	Phone	In Person	Phone	Phone	In Person	Phone	In Person
TREATMENT											
Standard Varenicline		X	X	X	X	X					
Extended Varenicline		X	X	X	X	X	X	X	X		
Counseling		X	X	X	X	X	X	X			
SCREENING/COVARIATES											
Urine Pregnancy Screen	X										
Breath Alcohol Concentration	X										
Blood Pressure	X	X	X	X		X			X		X
Psychiatric History (MINI)	X	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]
Medical History	X										
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Demographics	X										
Smoking History/FTND	X										
ETOH History	X										
Depression/Anxiety (HADS)	X	X	X	X	X	X	X	X	X	X	X
Lifetime MDE (Hitsman et al., 2011)	X										
MEDIATORS											
Withdrawal Symptoms (SJWF)		X	X	X		X	X		X	X	
Smoking Urges (QSU-B)		X	X	X		X	X		X	X	
Affect (PANAS)		X	X	X		X	X		X	X	
Cognitive Function (FACT-2)		X	X	X		X	X		X	X	
Cigarette Evaluation Scale (CES)[c]		X	X	X	X	X	X	X	X		
Cue-elicited smoking urges (Choice Performance Task)		X	X	X		X			X		X
Pearlin Mastery Scale (PMS)	X		X	X							
TREATMENT VARIABLES											
Adherence (Pill Count)			X	X	X	X	X	X	X	X	
Adherence (Blood)				X[b]							
Side Effects Checklist (SEC)		X	X	X	X	X	X	X	X	X	X
Side Effects (Open-Ended)			X	X	X	X	X	X	X	X	X
Suicidality (CSSRS)	X	X	X	X	X	X	X	X	X	X	X
Integrity of the Blind							X			X	
Program Satisfaction						X			X		
OUTCOMES											
Smoking Rate (TLFB)		X	X	X	X	X	X	X	X	X	X
Carbon Monoxide (CO) Test	X	X	X	X		X			X		X
Quality of Life (SF-12)		X	X	X	X	X	X	X	X	X	X

*TQD = Target Quit Day *W= Week

*Note: Target Quit Day visit may occur +3 days from target date; Week 4, 8, 12, 14, 18, 24, and 26 visits may occur +/- 1 week from target date. The Week 52 visit may occur +/- 2 weeks from target date. Window extensions are subject to PI approval.

[a] Administered only if HADS score exceeds borderline score for either anxiety or depression.

[b] Only completed in 50% of participants enrolled at Penn. Will not be administered if participant has discontinued study medication for 14 or more consecutive days prior to scheduled session.

[c] Administered only if participant has smoked a cigarette in the past 24 hours.

Screening/Covariate Measures.

Urine Pregnancy Screen
The urine pregnancy screen will assess for current pregnancy in all women and will be administered at the Intake Session.

Breath Alcohol Concentration/ETOH History
The breath alcohol concentration (BrAC) assessment will be administered at the Intake Session. The breath alcohol monitor assesses expired breath for alcohol content. Any reading >0.000 indicates alcohol consumption within the last 14 hours. The ETOH history form will be administered at the Intake Session visit and will ask subjects about their alcohol consumption over the past seven days.

Blood Pressure
Participants presenting at Intake with a blood pressure reading above 160 mmHg systolic and/or 100 mmHg diastolic will be ineligible for the study. Participants presenting at Intake with an elevated blood pressure reading between 150-160 mmHg systolic and/or 90-100 mmHg diastolic will have a second blood pressure reading taken after a ten minute period in which the participants will be instructed to sit comfortably. If, after the second reading:

- A participant has a blood pressure between 150-160 mmHg systolic and/or between 90-100 mmHg diastolic, the study physician will evaluate his/her situation and the participant may be withdrawn from the study.
- A participant has a blood pressure reading above 160 mmHg systolic and/or 100 mmHg diastolic, s/he will be ineligible for the study.

Blood pressure will be measured at each in-person visit. If participants present with elevated blood pressure (above 160 mmHg systolic and/or 100 mmHg diastolic) at any in-person visit following the Intake Session, a second blood pressure reading will be taken after a 10 minute rest period and the study physician will be notified to determine how to proceed.

Psychiatric History
Current and lifetime prevalence of major depression, suicidality, bipolar disorder, alcohol and substance abuse or dependence, psychosis, and generalized anxiety disorder will be determined using the Mini International Neuropsychiatric Interview (MINI). The MINI (Sheehan, Lecrubier et al. 1998) is a 10-15 minute structured interview developed by the World Health Organization to assess major DSM-IV Axis 1 psychiatric diagnoses. This instrument, completed by a research staff member at the Intake Session, permits both current (past 30 days) and lifetime assessments of psychiatric illness and data support its reliability and validity (Sheehan, Lecrubier et al. 1998). Suicidality will be further assessed at each visit through the Columbia Suicide Severity Rating Scale (**www.cssrs.columbia.edu**). The Brief MDE screen is a 4-item assessment of lifetime major depressive episode that takes a few minutes to administer and for which the positive predictive value has been evaluated among current, former and never smokers. Due to its length, ease of administration, and validation among a smoking population, it is a useful tool for assessing lifetime prevalence of major depression within a large scale clinical trial.

Medical History and Physical Examination
A medical history and a physical examination will be conducted at the Intake Session to review for any contraindications listed previously. The medical history will be completed by a research staff member. Current medication usage will be tracked at each time-point. Karnofsky and ECOG Performance Status scores will be ascertained from medical charts. If neither score is available, the Karnofsky scale will be administered by a staff member at the Intake Session to determine eligibility. Cancer site, stage, and time since diagnosis will be ascertained from medical charts and/or self-report.

Demographic and Smoking History

We will collect demographic (e.g., age, gender, race) and smoking history (e.g., age at initiation, prior abstinence periods, past use of nicotine treatments, current rate) data. The Fagerstrom Test for Nicotine Dependence, a validated 6-item measure of nicotine dependence, will be administered (Heatherton et al., 1991).

Depression and Anxiety
The Hospital Depression and Anxiety Scale (Zigmond & Snaith, 1983), a 14-item self-report measure, will assess depression and anxiety symptoms. This scale is widely used with cancer patients (Temel et al., 2010) and subscales correlate with clinical ratings of depression and anxiety (Zigmond & Snaith, 1983). This measure will be used as a mediator and a covariate.

Mediating Variables.

Mood: Positive and Negative Affect
The Positive and Negative Affect Schedule (PANAS; Watson et al., 1988), a 20-item self-report measure, assesses positive (PA; 10 items, e.g., enthusiastic) and negative (NA; 10 items, e.g., distressed) affect. The inclusion of PA is a strength since it is less frequently examined as a mediator of smoking cessation. The PANAS subscales are internally consistent (α = .84-.91) and exhibit good validity (Watson et al., 1988). The anxiety and depression scales described above will also be assessed as mediators. The PANAS will be administered at Pre-Quit, Target Quit Day, and Weeks 4, 12, 14, 24 and 26.

Cognitive Function
The FACT-Cog-Version 2 (Lai et al., 2009) is a 42-item measure of cognitive function designed for cancer patients. The scale measures mental acuity, concentration, and memory, and considers other people's perception of change and change from previous level of functioning. The FACT-2 will be administered at Pre-Quit, Target Quit Day, and Weeks 4, 12, 14, 24 and 26.

Withdrawal Symptoms
The Shiffman-Jarvik Withdrawal Form (Short-form) will measure withdrawal symptoms associated with quitting smoking (e.g., irritability; Shiffman & Jarvik, 1976). This scale was included since most trials examine changes in withdrawal as mediators of treatment efficacy. The Shiffman-Jarvik Withdrawal Form will be administered at Pre-Quit, Target Quit Day, and Weeks 4, 12, 14, 24 and 26.

Smoking Urges
Craving will be assessed by the well-validated Questionnaire of Smoking Urges (QSU-B). The QSU contains 10 items forming 2 subscales (anticipation of reward, relief from negative affect) with established reliability. Cravings to smoke following a quit attempt have been related to cessation. The QSU-B will be administered at Pre-Quit, Target Quit Day, and Weeks 4, 12, 14, 24 and 26.

Effects of Smoking
The Cigarette Evaluation Scale (CES), developed to assess subjective effects of smoking (Westman, Levin, et al., 1992), is an 11-item Likert-format measure. Questions include items for nausea and dizziness, craving relief, and enjoyment of airway sensations. This measure will only be administered to participants who self-report smoking within the past 24 hours.

Cue-elicited Urges
The 10-minute E-Prime choice task will provide a behavioral measure of cue-elicited and background craving (urges) to assess how acute versus chronic administration of varenicline affects these two types of craving differently, as has been previously demonstrated (Brandon et al., 2011; Hitsman et al., in press). The task also will provide a test regarding whether or not acute varenicline enhances cognitive function in patients who smoke. Cognitive functioning will be indexed by simple target reaction times, ability to withhold pre-emptive responses in a no-go situation (Mocking et. al., 2013), and by the ability to modify response choice based on

prevailing contextual cues (Elsner & Hommel, 2001). We plan to examine whether the effects of varenicline on either cue-elicited urges or certain aspects of cognitive functioning mediate treatment outcome.

Pearlin Mastery Scale
The Pearlin Mastery Scale (PMS; Pearlin & Schooler, 1978) is a 7-item Likert-format questionnaire that assesses feelings of mastery over oneself and one's circumstances. This scale will be included to examine participant feelings of mastery as a predictor of short-term smoking cessation outcomes. The measure will be administered at Intake, Target Quit Day, and Week 4.

Treatment Measures.

Side Effects
As in our past (Patterson et al., 2009; Schnoll et al., 2011) and ongoing (U01 DA020830) varenicline trials, a checklist and open-ended questions assess the incidence and severity of varenicline-related side effects at all time-points following the Intake Session. These assessments monitor safety, and dose reductions or suspension of medication may be indicated based on the side effect reporting. Side effects will be a study outcome and a covariate; overall frequency, changes from pre-treatment baseline (Pre-Quit) and the presence of specific side effects will all be tracked. This measure includes potential varenicline-related psychiatric events (Kuehn, 2008) and cardiovascular side effects.

Varenicline Adherence
Medication adherence will be assessed by self-report using a time-line follow-back method and by pill count and collection of used blister packs at each visit as in past varenicline trials (e.g., Gonzales et al., 2006; Jorenby et al., 2006; Ebbert et al., 2009; Niaura et al., 2008). We will also collect blood (10mL) from 50% of participants enrolled at Penn at Week 4 to assess varenicline levels as an adherence measure and to examine the validity of self-report and pill count data. An adherence measure will represent the proportion of total dose taken (adherence = > 80% of dose taken based on self-report, pill-count, and ng/ml for plasma varenicline; Catz et al., 2011).

Integrity of the Blind
Participants may be likely to notice a change in their physiological and/or psychological state that would be best noted following the two-week washout period (Week 14), and their perception may change after they experience the second potential washout period (Week 26). This follows the questions outlined by Schnoll et al. (2008).

Program Satisfaction
Given the negative perception that many individuals have of Chantix, understanding patient's satisfaction with the program, and how that might change between weeks 12 (standard duration) and 24 (extended duration), will provide a basis for clinical relevance. These questions were modeled after patient satisfaction questionnaires used for a variety of smoking cessation programs.

Outcomes Variables.

Abstinence (primary)
Smoking status is assessed using the timeline follow-back method (Brown et al., 1998) as done previously (Lerman et al., 2004; Schnoll et al., 2010b) and by using breath CO to verify self-report. Participants are considered abstinent if they self-report abstinence (not even a puff of a cigarette) for >7 days prior to the Week 24 and 52 assessment and have a breath CO of <10ppm at the time-point (SRNT, 2002; Hughes et al., 2003). As per convention, participants are assumed to be smoking if they self-report to be 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 >10ppm (SRNT, 2002).

Cessation/Smoking Rate: Daily smoking (presence and rate) will be assessed at each visit after Intake Session with the well validated timeline followback method (TLFB). These data 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 smoking rates (i.e., # cigarettes/day). These data will also be used to compute and assess secondary measures of smoking cessation (e.g., continuous and prolonged abstinence).

Carbon Monoxide (CO) Test: Carbon monoxide will be measured at each in-person visit to confirm smoking status.

Other Smoking Measures (secondary)
As per recommendations (Hughes et al., 2003), we will also assess: prolonged abstinence to Weeks 12, 24, and 52 (relapse is 7 consecutive days of self-reported smoking, after a 2-week grace period), continuous abstinence at Weeks 12, 24, and 52 (no smoking between the quit day and follow-up), time to 7-day relapse (no grace period), smoking rate, and lapse (smoking episodes < 7 days) and recovery (return to 24-hour abstinence) events.

Quality of Life (QOL)
The Short-Form Health Survey (SF-12) will assess QOL (Ware et al., 1996). This scale yields physical and mental subscales, has been used to assess cancer patient QOL (McCorkle et al., 2009), has demonstrated validity and reliability (Gandek et al., 1998), and has been used in smoking cessation trials with cancer patients (Schnoll et al., 2010a). The SF-12 will be administered at all visits following the Intake Session.

2. Statistical Analysis

Power
Power is provided for the primary aims since the exploratory aim is hypothesis generating. All comparisons are 2-sided.

Aim 1: The primary analysis is a comparison in Week 24 and Week 52 point prevalence quit rates between standard and extended therapy. For the week 24 comparison, we based our sample size on the expectation that the quit rate in the standard arm would be equal to the Week 24 quit rates reported in past clinical trials of varenicline for participants who received 12 weeks of treatment (i.e., 33%; Gonzales et al., 2006). We also expect to see at least the same effect on week 24 quit rates here as we saw in our past extended treatment trial (i.e., an OR of 1.81 or a difference of ~14%; Schnoll et al., 2010b). Thus, we have 80% power (alpha .05) with a sample of 374 if the difference between treatment arms in Week 24 quit rates is 14% (i.e., Week 24 quit rates for extended therapy is 47%). For the Week 52 comparison, we can expect a Week 52 quit rate for the extended arm of 56% (Tonstad et al., 2006), vs. 28% for standard treatment (Gonzales et al., 2006), for which we have 99% power (alpha = .05) with n = 374; we are powered to detect a difference at Week 52 of 14% if the present study yields a smaller effect than expected based on past studies.

Aim 2: The primary analysis is a comparison in Week 24 and Week 52 differences in QOL and severe side effects. For QOL, we have 80% power to detect a mean difference of 0.87 in physical QOL and a mean difference of 1.2 in mental QOL at any time-point, effects seen previously (Schnoll et al., 2010a). For side effects, the analyses will involve a test of non-inferiority since we cannot use standard statistical tests and conclude that a non-significant comparison means that the treatments are equal (i.e., "the absence of evidence is not evidence of absence"). In our past bupropion study (Schnoll et al., 2010a), 95% of placebo and 88% of bupropion participants reported no severe side effects. Assuming a similar difference, we have 90% power to detect equivalence with a floor of 80%, or an extended group that is 15% < the standard group.

Aim 3: The analyses will assess changes in affect and cognitive impairment as mediators of treatment arm effects at Week 24 and 52. These measures are continuous difference scores. Our sample of 374 is well above the minimum sample of 200 recommended for models of this size (Haduk, 1987; Boosma & Gabrielli, 1985). The mediation hypothesis will examine the proportion of treatment effect explained (Lin et al., 1997; Vittinghoff et al., 2009), and test with a z-score generated using the delta method. Our sample of 374 gives us 80% power to observe small effects in a 1-sample test (δ=0.20) when testing at α=0.05. There are two proposed mediating pathways between treatment and outcome, so our type-1 error will be corrected to 0.025. Our sample of 374 gives us 80% power to detect small to medium effects (δ=0.22) for changes in the proposed mediators.

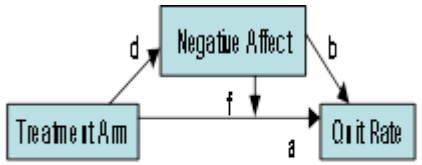
Data Analysis

Dr. Wileyto will oversee analyses. Preliminary analyses will assess sample characteristics by treatment with chi-square or logistic regression (e.g., gender, dependence, depression, disease site). 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. Compliance measures will be evaluated across treatment arms, and controlled for in primary analyses. Although we will use an intent-to-treat analysis as the primary method for evaluating study aims, we will conduct a completers only analysis of study aims and examine study aims with participants lost to follow-up due to death excluded as done previously (Schnoll et al., 2003).

Aim 1: Compare standard varenicline treatment (12-weeks active then 12-weeks placebo) to extended varenicline treatment (24-weeks active) for treating nicotine dependence among cancer patients. The hypothesized effect of treatment arm (i.e., the difference in quit rates between subjects receiving standard or extended treatment) will be tested by a treatment arm term in a binomial family with logit link (logistic regression) model that possibly includes terms for covariates. Outcomes of the logistic regression analyses will be characterized by odds ratios (e.g., odds of quitting smoking) and 95% confidence intervals. Although quit-rates at the end of 24 and 52 weeks will represent our primary outcome variables, similar logistic regression analyses will be performed for other assessments of quit rates (e.g., quit rates at Weeks 12 and 26). This model will be used for measures of prolonged and continuous abstinence as well. In addition, as many participants will fail to become completely abstinent, the negative binomial family log link for count data will used to examine the main effects of treatment arm on changes in smoking rate. Time to (recurrent) event models will be fitted using Cox regression, stratified by event sequence, as in Schnoll et al. (2010).

Aim 2: Assess effects of extended varenicline therapy on QOL and varenicline side effects. Repeated-measures MANOVA will examine differences across treatment arms in mental and physical QOL over the trial. Covariates will be included, such as medical treatment history. We will compare treatment arms in terms of the frequency of severe side effects (individual and total). Logistic regression will test against the lower boundary on percent reporting only mild-moderate (i.e., < severe) side effects. The hypothesis test for equivalence is whether the OR is out of the prescribed range for the difference between the treatment arms.

Aim 3: Assess changes in affect and cognitive impairment and cue-elicited urges as mediators of extended varenicline therapy's effect on quit rates. The effects of treatment arm on mediators will be assessed using linear regression. Structural equation modeling will be used to obtain a more comprehensive understanding of these mechanisms. It is hypothesized that treatment arm will yield significant differences in proposed mediators and that differences in mediators will predict week 24 and 52 outcomes. We will focus on changes in mediators from baseline to week 14, when the standard therapy participants transition to placebo and the extended therapy group stay on active treatment. After first demonstrating that treatment arm affects quit rates (Aim 1), these effects will be partitioned into mediated and unmediated effects, via path and structural equation models. For example, paths ***d*** and ***b*** represent the mediated effects of treatment arm on quit rates through changes in negative affect, and path ***a*** represents residual effect of treatment arm on quit rates not mediated by negative affect. Path ***f*** represents the hypothesis that the impact of treatment arm on quit rates will depend on negative affect. Specific hypotheses will be tested by using chi-square difference tests that contrast the overall fit of this full model with more parsimonious nested models in which specific predictive effects are fixed to zero (e.g., the unmediated path a). Model goodness-of-fit indices will be contrasted to guide interpretation of results and determine the practical significance of statistically significant differences. Modification indices will be examined to guide model interpretation and modification. Models will be tested through Mplus, which easily accommodates the combination of binary and continuous variables. This approach allows us, in principle, to test whether treatment effects on quitting are due to specific mechanisms (e.g., reduction in negative affect). Tests for mediation by positive affect, withdrawal, cognitive impairment, and cue-elicited urges will be conducted in this fashion.



Path Model of Treatment Arm, Negative Affect, & Quit Rate

Exploratory Aim: Evaluate patient-related variables as moderators of extended varenicline therapy's effect on quit rates. Variables associated previously with cancer patient smoking behavior will be selected for this aim (e.g., Cox et al., 2003). The significance of patient-related variables (e.g., time since diagnosis, stage of disease, nicotine dependence) as moderators of the treatment arm effect can be evaluated by fitting logistic regression models relating quit rates to treatment and covariates. The likelihood ratio test can determine whether including such variables in the model contributes significantly to model fit. Evaluating the effect of extended therapy on quit rates by stage 1 vs. 3 disease, for example, is essentially doing a subgroup

analysis of the interaction effect separately by disease stage. To test a moderator's significance, interaction terms (e.g., treatment x disease stage) are added in successively in a hierarchical logistic regression model.

3. Confidentiality

All subject information will be kept in a secure filing cabinet that is accessible only to authorized study personnel. All databases containing subject information will be password protected, and again, accessible only to authorized study personnel. Each subject will have a unique study ID number for all data collected. In all data sets we will use ID numbers, only. A separate data set linking names with ID numbers will be accessible only by the senior project staff. All communications about subjects 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 the study Principal Investigator, Co-Investigators, the Study Physician, other study staff and the UPenn and NU IRBs and Offices of Human Research.

How will confidentiality of data be maintained? Check all that apply.

☒ Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.
☒ Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.
☒ 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.
☒ Whenever feasible, identifiers will be removed from study-related information.
☐ A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.
☐ A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)
☐ Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.
☒ Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.
☐ Other (specify):

4. Subject Privacy/Protected Health Information

The following personal health information will be collected as part of this study:

- Name, address, telephone number
- Date of birth
- Social Security Number (W-9 form)
- Some personal information that may be considered sensitive, such as medical history, psychological history, alcohol use history, etc.
- Results from physical examinations, tests or procedures
- Information on medication adherence from the blood sample at the Week 4 visit
- Medical Record Number

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

5. Tissue Specimens

Blood. One 10ml sample of blood will be drawn at Week 4 to evaluate varenicline adherence in 50% of participants enrolled at Penn.

Urine. A urine sample will be required at the Intake Session for pregnancy screenings. Women who test positive for pregnancy will be deemed ineligible

RISK/BENEFIT ASSESSMENT

1. Potential Study Risks

A detailed description of the study will be given to all subjects, 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 the University of Pennsylvania. Informed consent procedures will comply with current standards of the IRBs at the University of Pennsylvania and Northwestern University. Subjects 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 PENN and NU.

Assessments and Counseling. Some subjects may experience some emotional distress during the assessments and counseling sessions from discussing feelings about quitting smoking, from learning about the risks from smoking, or from contemplating and attempting tobacco cessation. These events happen very rarely and in almost all cases are short-lived and of low intensity, lasting for 1-2 weeks. Study personnel, who have a great deal of experience working with people attempting to address nicotine dependence, can make referrals for mental health services as needed (within PENN and NU). The research staff will be trained to query for adverse emotional reactions during the assessments and counseling sessions and will be trained to deal with such reactions and to provide referrals if needed. In addition, measures of depression and anxiety will be administered throughout the trial to detect psychological concerns and provide appropriate referrals if requested. PENN and NU have developed a protocol to monitor, assess, and refer for treatment any serious psychological concern that emerges within our trials. This involves identifying participants who score over the diagnostic threshold on scales of depression and anxiety, contacting these patients for a more formal psychiatric evaluation, and providing referrals for formal psychiatric treatment if requested.

Varenicline. Some people who take varenicline may experience nausea, sleep disturbance, constipation, flatulence, and vomiting; however, these symptoms are usually mild and temporary. There have also been rare reports of erratic behavior, aggressive behavior, depressed mood, and suicidal thoughts/behavior. To minimize the likelihood of participants experiencing these side effects we will:

- Employ a stringent list of exclusionary criteria
- Administer the standard and recommended dose run-up to the 1mg B.I.D. dose
- Monitor self-reported side effects at each assessment time-point.
- Open-ended evaluation of any potential adverse events.

Study Physicians will be alerted to any severe side effects or any reported adverse events. The Study MD will review the information provided by the research staff and if applicable, will contact the study participant to gather more information and determine the appropriate course of action for the subject. Ultimately, the Study Physician will decide if the AE is related to study medication and whether the subject should discontinue taking study medication. Dose reductions, which will be tracked, may also be employed to minimize any side effect.

Varenicline may be associated with an increased risk of certain cardiac and vascular side effects, including chest pain, heart attack, and stroke. These risks are rare and are still being studied to determine how real they are. However, our study staff follows strict procedures to monitor for the presence of these side effects, including monitoring blood pressure 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.

Varenicline may also 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. Participants will be advised not to take Chantix if they have an unstable, untreated history of seizures.

Participants will also be told that varenicline may impair their ability to perform tasks requiring judgment or motor and cognitive skills and that they should proceed with caution in this regard until they are certain that varenicline does not affect their performance. Participants will be told that varenicline may be associated with somnambulism (sleep walking) that may result in harmful behavior to self, others, or property, and if they notice such behaviors that they should discontinue varenicline and notify the study staff after seeing their medical provider. Participants will also be advised that Chantix may affect their response to alcohol including lower alcohol tolerance, aggressive behavior, or impaired memory following consumption of alcohol. Participants will be instructed to minimize alcohol intake (no more than 3 drinks per occasion or within a 24-hour time period) while taking varenicline. Participants will be advised to inform the study staff if they are taking or plan to take any prescription or over-the-counter drugs. Women will be advised to notify the study staff if they become or intend to become pregnant during the study period. The research team has extensive prior experience conducting smoking cessation trials with varenicline.

Withdrawal. Many individuals who quit tobacco use exhibit a pattern of symptoms associated with withdrawal from tobacco use. 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 1-2 weeks. Use of varenicline (by all participants for the first 12 weeks of the study) will also minimize the severity of withdrawal symptoms and behavioral counseling will also offer strategies for reducing withdrawal. The study personnel will be trained to recognize these symptoms and educate the participants about them (e.g., their duration, methods for reducing them).

Blood Draws. Blood draws may result in bruising and/or slight bleeding at the needle site. This is rare and happens infrequently. Occasionally, blood drawing results in a feeling of faintness. This too is rare. A trained professional will draw blood, so the chances of these discomforts are minimal. Procedures are in place to ensure that PHI is not linked with the results of this research.

Reproductive Risks. Because varenicline safety for an unborn baby is unknown, participants will be told that they should not become pregnant while on this study. Women taking the study medication should not nurse a baby. If the woman is of childbearing potential, she must use an adequate form of contraception while study medication is being taken and for at least one month after the end of the medication period. If the woman is pregnant or breast feeding, she may not participate in this study, and if she becomes pregnant during the study, study medication will be immediately discontinued and the woman will be permitted to continue with counseling and assessments only. Women will be asked to take a pregnancy test before starting the study.

Threats to Privacy/Confidentiality. Since self-report and medical data will be collected and stored as part of this study, it is possible that subject privacy or confidentiality can be threatened. To address this concern, the Data Management System has set up several safeguards to prevent unauthorized access to study data. An automatically generated index number is assigned to a subject's study identification number. A linked subject identification table is created for the storing of subject name, address and telephone contact information. This table uses the automatically generated index number rather than the study identification number. The master subject map and subject identification information tables are maintained in a separate database. Using this method, no identifying subject information is directly linked to medical information or other study data. The two clinical sites have long-established protocols to guard against improper use of hard copies of data (e.g., locked files, numeric coding procedures). The present research team has not experienced the unauthorized use of study data. A server-based data collection procedure will minimize the possibility of loss of privacy or confidentiality.

2. Potential Study Benefits

Participants in this study will have the opportunity to participate in a smoking cessation program at no cost. Participants will have behavioral counseling and the opportunity to receive 12 weeks or 24 weeks of

varenicline, a medication with proven efficacy for smoking cessation in the general population of smokers. Consequently, participants will have the opportunity to quit 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 furthering scientific knowledge concerning ways to improve cessation treatment for smokers.

3. Alternatives to 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 quit-line. At any point in this trial, subjects may decide not to continue in their participation.

4. Data and Safety Monitoring

Who will monitor this study? Check all that apply.

☒ Principal Investigator
☐ Sponsor or contract research organization
☐ NCI sponsored cooperative group
☒ Cancer Center (if mandated by CTSMRC)
☐ Medical monitor
☒ Data and safety monitoring board

For this study, we will use established UPENN procedures and infrastructure for data and safety monitoring and we will use a protocol-specific Data Safety Monitoring Board. During the course of the study, safety and data quality monitoring will be performed on an ongoing basis by the Principal Investigators and the study personnel. Study personnel are responsible for collecting and recording all clinical data using the established MOP. This includes ensuring that all source documents exist for the data on the case report forms, ensuring all fields are completed appropriately, and ensuring that all corrections are done according to Good Clinical Practice (GCP). Any inconsistencies/deviations will be documented. The study physicians and psychologists at PENN and NU 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 on data, comparing all hard copy data to computer files.

Staff training will consist of an explanation of the protocol and review of the Case Report Forms. In addition, the duties of each staff person will be outlined and all applicable regulations will be reviewed. Mock sessions with critical feedback will be conducted. The MOP will be used for staff training and to guide procedures throughout the trial. Senior personnel will supervise junior staff and provide re-training in the study protocol as needed.

Monitoring will be conducted in accordance with the University of Pennsylvania Sponsor-Investigator Standard Operating Procedure PM 504. Monitoring days will be conducted periodically throughout the study. The first monitoring day will occur no more than two weeks after the first subject is entered. Subsequent monitoring meetings will be quarterly. The monitoring is conducted by the site IRBs and the PENN Office of Human Research (see www.med.upenn.edu/ohr). Audits are conducted bi-annually or annually and involve the review of regulatory documents, the ascertainment and documentation of informed consent, the compliance with the study protocols, and the completion of CRFs.

Monitoring for Adverse Events (AE) will be conducted in real-time by the study personnel and the on-site Principal Investigators and the study physicians and psychologists. Research staff member will complete side effect assessments and will determine the severity of the adverse events; the relationship of the event to the study drug and the decision on the course of action for the participant will be decided by the site physicians and psychologists after review of the report. Participants will be monitored for the development of adverse events by assessing side effects at each assessment time-point between weeks -1 and 52 as well as through open-ended questions during assessments. Monitoring may increase if required.

Subjects will also be given a 24-hour emergency number they can call if necessary. The PIs and study physicians and psychologists will clinically follow all subjects who are discontinued due to a serious adverse event until it resolves and becomes completely stable, unless a referral to another physician (i.e., specialist) is clinically indicated or requested by the subject. All AEs and SAEs will be documented on an Adverse Events Case Report Form. This information will, in turn, be reported immediately to all necessary regulatory committees, including the FDA.

All serious adverse events, as defined in the AE procedures, will be reported within 24 hours to senior study personnel. These events will be maintained in a unique data base and reviewed monthly by senior study personnel. Site physicians and psychologists will review all Adverse Event forms in "real-time" to ensure appropriateness of the data and timeliness of reporting.

Ms. Ware and staff RAs will be responsible for monitoring data integrity as data are collected. This includes ensuring that source documents exist for the data on the case report forms, ensuring all fields are completed appropriately, all corrections are done according to GCPs and any inconsistencies/deviations are documented.

The study will be monitored by the PIs and co-investigators, and regulatory committees at PENN and NU (i.e., IRBs, OHR) as well as by a study specific DSM Board. The following monitoring activities will be conducted according to standard operating procedures. These activities will be performed in association with database auditing and facilities monitoring by the PENN OHR and/or study personnel.

Initial Assessment Monitoring: OHR may conduct a manual review of source documents and Case Report Forms (CRFs) for a random 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, 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. A specific protocol monitoring plan will be used. All accrued cases will be subjected to protocol monitoring throughout the duration of the trial.

Database Auditing: Ms. Ware and RAs 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. Depending on the data management findings, re-training will be provided should problems such as increased errors be detected.

Data Auditing: Site physicians 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 will be subjected to auditing throughout the duration of the trial. A Regulatory Binder Review by OHR will include the following essential documents: IRB Protocol, Consent Form and Amendment Approvals, IRB Closure Letter, List of Authorized Signatures, Laboratory Certifications, Protocol and Amendment Signature Pages, FDA Form 1572 (updates, if any), Curriculum Vitae corresponding to the FDA Form 1572, Financial Disclosure Questionnaires, and Monitoring Log. Additional monitoring by OHR may include: source documentation verification; drug accountability; adverse event documentation; and facility assessment.

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: The protocol will be reviewed by the PENN and NU IRBs and will only be implemented after successful approval from the IRBs. Annual reporting and auditing will be conducted by the IRBs. All procedures will be approved by the IRBs. A protocol-specific Data Safety Monitoring Board will be used for this trial as well (see below). The PENN and NU IRBs will ensure participant safety and data integrity in collaboration with the DSMB.

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

The DSM Board

The DSMB will consist of a statistician, a physician, and a behavioral scientist. The primary concern of the DSM Board, however, will be the monitoring of side effects between the placebo and the varenicline groups. The DSMB will meet every 6 months to review accrual, retention, and side effect and adverse event reports. The study statistician will present unblinded data to the DSMB to determine if unacceptable side effects are occurring. The DSMB can request additional data or recommend the trial be suspended. We are currently using a DSMB and the proposed DSM plan for ongoing PENN varenicline clinical trials (U01 DA020830). Details of the DSMB meetings are as follows:

During the course of the study, data and safety monitoring will be performed on an ongoing basis by the DSM Board led by a PENN biostatistician unaffiliated with the trial and by project staff and the respective site IRBs. The Chair of the DSMB and the DSMB committee will review the trial data as described below. The DSMB will consist of 3 members: a biostatistician, who will serve as DSMB Chair, a physician, and a member of the PENN Office of Regulatory Affairs (IRB). The DSMB will meet twice per year to review study 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 DSM meeting and included in the report which will be compiled following DSM Board meetings and then updated at the trial's conclusion.

- brief description of the trial
- baseline socio-demographic characteristics
- accrual, retention and disposition of study participants (recruitment vs. goal, withdrawal rate)
- quality control issues (assessment of randomization procedures, including stratification)
- regulatory issues (review of protocol changes)
- Side effects by treatment arm (overall and by site)
- Serious Adverse events by treatment arm (overall and by site)
- Efficacy

Structure of DSMB meeting:

a. Each meeting will consist of 3 parts. First, an open session will occur in which the PI and the DSMB will review the conduct of the trial (e.g., accrual, protocol compliance, general toxicity). Next, to maintain the blind of the study, a closed session involving only the DSMB and the study biostatistician will be held wherein Dr. Wileyto will present unblinded side effect results to the DSMB as requested. This will focus on the presentation of the rate of increase in any side effect from baseline to a follow-up across treatment arms. Lastly, 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.

b. The DSMB written recommendations will be provided to the PIs and to the IRBs. The DSMB will summarize adverse event reports for the study PI and the IRB Chair, and the PI must implement any DSMB recommendations expeditiously. All DSMB recommendations will also be forwarded to the NIH and the FDA (where necessary).

5. Management of Information for Multi-center Research where a Penn Investigator is the Lead Investigator of a multi- center study, or Penn is the lead site in a multi-site study.

Ms. Ware, who directs the PENN DMS in use with NU, will oversee the DMS for this trial. MS ACCESS permits real-time data entry, storage, and QA by server-based remote access and scannable forms which increases standardization across personnel. We have >10 years of experience with this DMS for smoking cessation trials. The DMS generates database tables, constructs semantic constraints on fields, and is used for data entry, storage, retrieval, and security. The DMS uses visit dates (e.g., week -1, 0, 1, 3, etc.) to describe procedures and measures to be ascertained. The DMS mimics the appearance of CRFs completed at visits. Each visit date is "milestoned" (e.g., completed, scheduled, missed). During data entry, validation occurs via: 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 subject privacy is accomplished by: minimizing use of identifying information, use of ID numbers rather than names, keeping all data in locked files, and, maintaining of the dataset linking names with ID numbers accessible only by the statistician.

6. Risk/Benefit Assessment

There is minimal risk for serious adverse events. The treatments and procedures used in this study have been shown to be relatively safe. Varenicline has also studied in several clinical trials and shown to be safe and efficacious. Nevertheless, there are risks in participating in this trial, which are described above.

However, the risks of participating in this trial are offset by the potential benefits for participants and society. Participants will have behavioral counseling and the opportunity to receive 12 weeks or 24 weeks of varenicline, a medication with proven efficacy for smoking cessation in the general population of smokers. Consequently, participants will have the opportunity to quit 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 furthering scientific knowledge concerning ways to improve cessation treatment for smokers.

SUBJECT COMPENSATION

Subjects will be compensated for their time up to a maximum of $110 (Table 3.). Subjects will also be reimbursed for transportation expenses related to their participation in the study with $10 for each in-person visit. Participants will receive compensation for achieved phone sessions at the subsequent in-person visit.

Table 3. Subject Compensation

Study Session	Session Compensation	Travel Compensation
Intake Session (Week -1)	**$10**	**$10**
Pre-Quit (Week 0)	**$10**	**$10**
Target Quit Day (Week 1)	**$10**	**$10**
Week 4	**$10**	**$10**
Week 8	**$10**	**-**
Week 12	**$10**	**$10**
Week 14	**$10**	**-**
Week 18	**$10**	**-**
Week 24	**$10**	**$10**
Week 26	**$10**	**-**
Week 52	**$10**	**$10**
	$110	**$70**
	Total: $180	

INFORMED CONSENT

1. Consent Process

A fully trained study staff member will obtain informed consent using the combined consent and HIPAA form approved by the PENN and NU IRBs. The process will take place before study data are collected and prior to any treatment. The consenting process will occur in person during the Intake Session and will involve a one-on-one discussion of the study requirements and procedures and an opportunity for subjects to ask questions and express concerns. The subjects will receive a copy of the combined consent and HIPAA form for their records. In addition, the subjects 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 subjects will be considered competent to provide informed consent (i.e., they will be asked if they understand what they are consenting for).

2. Waiver of Authorization

No waiver of informed consent is requested.

RESOURCES NECESSARY FOR HUMAN RESEARCH PROTECTION

Qualifications of Investigators. Brief highlights are presented below for principal investigators.

Robert Schnoll, Ph.D. (Principal Investigator): Dr. Schnoll's research focuses on the evaluation of cessation interventions with clinical populations including cancer patients (Schnoll et al., 2005; Martinez et al., 2009), the identification of empirical methods to tailor smoking cessation interventions to improve treatment efficacy (Patterson, Schnoll et al., 2008; Lerman, Schnoll et al., 2007), and the integration of smoking cessation interventions into medical practice (Schnoll et al., 2006a; 2006b; Schnoll & Engstrom, 2004; Schnoll et al., 2003b). Dr. Schnoll's smoking cessation clinical trials with cancer patients (Schnoll et al., 2005; 2010a) demonstrates the ability to complete smoking cessation clinical trials with smokers with medical and psychiatric comorbidities. Dr. Schnoll has also conducted smoking cessation clinical trials using varenicline (Schnoll et al., 2011) and serves as PI and site-PI, respectively, for two ongoing varenicline clinical trials (R21 DA026404; U01 DA020830). These trials have afforded Dr. Schnoll the opportunity to develop the skills needed to coordinate a varenicline randomized clinical trial for nicotine dependence.

Brian Hitsman, Ph.D. (Clinical Site Principal Investigator): Dr. Hitsman's research focuses on nicotine dependence treatment, especially among those with co-occurring psychiatric disorders. He has been involved in tobacco treatment research since 1993, including NIH-funded trials of fluoxetine and bupropion combined with behavioral therapy (e.g., Hitsman et al., 2001). Dr. Hitsman is well known for his evaluation of depression and depressive symptoms as predictors of tobacco treatment outcome (Hitsman et al., 1999; 2002; 2003) and showed that adherence to fluoxetine, measured using a plasma assay, predicted cessation outcome (Hitsman et al., 2001). He also served as co-investigator/site coordinator on phase 3 trials of rimonabant and varenicline (Niaura et al., 2008; Hitsman et al., 2011). Dr. Hitsman was a member of the NIMH workgroup on tobacco use and cessation in psychiatric disorders (Ziedonis, Hitsman et al., 2008) and a contributing author of the 2010 Surgeon General's Report on the biology and behavioral basis for smoking attributable disease.

Research Staff

The following research staff will be directly involved with the implementation and execution of the current study.

UPenn Staff:

Frank Leone, M.D., Co-Investigator & UPENN Study Physician
Corey Langer, M.D., Co-Investigator
Caryn Lerman, Ph.D., Co-Investigator
E. Paul Wileyto, Ph.D., Co-Investigator
Susan Ware, B.S., Database Manager
Rebecca Ashare, Ph.D., Cognitive Testing Coordinator
Jessica Weisbrot, M.S.W., Research Staff
Alex Flitter, M.A., Research Staff
Dominique Spence (Vaughn), Research Staff
Paul Sanborn, M.S., Research Staff
Anita (Annie) Hole, Ph.D., Site Psychologist

Andrew Miele, B.A., Research Staff
Joseph Bastian, B.A., Research Staff
Morgan Thompson, B.A., Research Staff
Su Fen Lubitz, B.A., Research Staff
Grace Crawford, B.A., Research Staff
Nathaniel Stevens, Research Staff
Katrina Serrano, B.A., Research Staff
Cheyenne Allenby, B.A., Research Staff
Chan To, B.A., Research Staff
Victoria McLaughlin, B.A., Research Staff

Northwestern Staff:

Nisha Mohindra, M.D., Co-Investigator & NU Study Physician
Ravi Kalhan, M.D., Co-Investigator & NU Study Physician
Bonnie Spring, Ph.D., Co-Investigator
Anna Veluz-Wilkins, MA, Project Manager
Allison Carroll, MS, Research StaffNancy Jao, MS, Research Staff

Training and Quality Assurance

Drs. Schnoll and Hitsman currently collaborate on an ongoing effectiveness trial of long-term nicotine patch therapy (R01 DA025078). Dr. Schnoll also currently is PI or site PI on 2 varenicline trials (R21 DA026404; U01 DA020830) and Dr. Hitsman served as co-I and coordinator of a past varenicline trial (Niaura et al., 2008). The PIs have >10 years of experience coordinating multi-site smoking cessation trials involving extensive data collection, counseling, and pharmaco-therapy (e.g., Schnoll et al., 2010b; Hitsman et al., 2001). 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, counseling) 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 binder, with sections for every visit/week. Every visit is "milestoned" (e.g., attended, missed, scheduled) to ensure subject tracking through the trial. Drs. Schnoll, Hitsman, and Gariti have developed a counseling manual for training. Lastly, a manual for data collection and entry is developed. We will use a server-based DMS, already in use at NU, which allows for real-time, remote data entry using scanable forms. All training will involve didactic instruction, mock sessions, and feedback in the MOP, assessment of eligibility and side effects, counseling, and the DMS by Drs. Schnoll, Hitsman, Hole, Kalhan, Patel, and Leone. QA focuses on protocol adherence and data validity. We will conduct 100% QA by comparing all hard copy and computer data. In addition, we may audio-tape all counseling sessions and assess protocol adherence by selecting a random 15% of sessions for review.

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