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PROTOCOL TITLE

1. Full Title

An Effectiveness Trial of Maintenance Therapy for Nicotine Dependence

2. Brief Title

A study to evaluate the benefits of long-term treatment with nicotine patches for nicotine dependence

STUDY SPONSORSHIP

1. Funding Sponsor

National Institute on Drug Abuse, R01 DA025078

2. Primary Sponsor

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PROTOCOL ABSTRACT

The transdermal nicotine patch is the most widely used form of tobacco dependence treatment. Yet, abstinence rates following patch treatment are only ~20% at 6-months and ~9% at 12-months. There is a growing recognition that nicotine dependence is a chronic disease which requires maintenance therapy. While current guidelines established by the USDHHS's Public Health Service (PHS) recommend 8-week duration for transdermal nicotine therapy, support for this recommendation is limited. In a randomized placebo-controlled efficacy trial comparing standard (8-week) vs. extended (24-weeks) treatment with nicotine patches, we found that, at 24 weeks, quit rates were 30% in the 24-week arm vs. 20% in the standard therapy arm; however, by week 52, the quit rates were equivalent across the arms. This suggested that the benefits of extended treatment with transdermal nicotine are largely dependent on the continuation of active treatment. However, as an efficacy trial, this study was conducted under controlled conditions with strict inclusion/exclusion criteria to enhance internal validity. If recommendations for the duration of nicotine patch therapy are to be formally revised to encourage maintenance therapy, these findings must be replicated and extended under "real-world circumstances". In addition, as done in clinical trials to support the use of methadone maintenance for opiate dependence, replication must include a treatment arm that receives therapy for 52 weeks. We will conduct a randomized effectiveness trial to evaluate the benefits of maintenance therapy with transdermal nicotine patches for smoking cessation. 540 smokers will receive brief counseling and will be randomized to: standard (8-weeks), extended (24-weeks), or maintenance (52 weeks) transdermal nicotine therapy. The primary outcome will be biochemically verified 7-day point prevalence abstinence at week 52. Additional study aims include assessing: 1) treatment side effects across study arms; 2) longitudinal patterns of relapse and recovery across treatment arms; 3) mediators and moderators of treatment effects; and 4) cost-effectiveness.

OBJECTIVES

1. Overall Objectives

This randomized effectiveness trial will: 1) Assess the effectiveness of maintenance therapy with transdermal nicotine (52-weeks) vs. standard (8-weeks) and extended (24-weeks) therapy for increasing biochemically confirmed 7-day point prevalence quit rates; 2) Assess longitudinal patterns of smoking lapses and recovery to abstinence in standard, extended, and maintenance therapy; 3) Evaluate the cost-effectiveness of maintenance therapy, vs. standard and extended therapy; and 4) Assess the safety of maintenance therapy with transdermal nicotine (52-weeks) vs. standard (8-weeks) and extended (24-weeks) therapy.

We will also address the following aims to supplement our understanding of mechanisms of treatment effect and to develop a more complete model of therapeutic response: 1) Explore mechanisms of treatment effects, including differences across treatment arms in changes in withdrawal symptoms, nicotine craving, and affect; and 2) Explore individual difference factors that influence response to standard vs. extended vs. maintenance therapy to identify those most vs. least likely to benefit from maintenance therapy for nicotine dependence.

2. Primary Outcome Variable(s)

The primary outcome will be biochemically verified 7-day point prevalence abstinence at week 52.

3. Secondary Outcome Variable(s)

Secondary outcomes include: smoking rate, lapse and recovery events, prolonged abstinence, cost-effectiveness, withdrawal symptoms, nicotine craving, affect, adherence, and side-effects.

BACKGROUND

The Public Health Significance of Cigarette Smoking

The health and economic costs of tobacco use are enormous. Each year, cigarette smoking causes over 400,000 premature deaths in the US and 4.2 million deaths worldwide from cancer, cardiovascular and respiratory diseases, and perinatal conditions (McKay & Erickson, 2001; CDC, 2005a). Tobacco use accounts for at least 30% of all cancer deaths in the US and smoking is causally linked to lung, head and neck, esophageal, pancreatic, bladder, kidney, cervical, and gastric cancer, and leukemia (USDHHS, 2004). Indeed, tobacco use is responsible for more deaths than alcohol, AIDS, car accidents, illegal drugs, murders, and suicides combined (USDHHS, 2004). The US spends \$76 billion annually in health care costs due to tobacco-related diseases, while indirect costs due to tobacco use (i.e., lost productivity, absenteeism, recruitment and retention of replacement workers) cost the US economy \$82 billion/year (CDC, 2002). Despite prevention efforts, changes in social policy, and the development of new treatments for nicotine dependence, 18.5% of women and 23.4% of men in the US are current smokers (CDC, 2005b). Indeed, even with a range of nicotine replacement therapies, bupropion, and the newly FDA-approved varenicline, only 1 in 3 smokers utilizing these agents will achieve long-term abstinence (Cahill et al., 2007; Hughes et al., 2007; Stead et al., 2008). Barring a dramatic turn of events in the next few years, the Healthy People 2010 objective of reducing US adult smoking to 12% will not be attained and the economic and health consequences of nicotine dependence will continue.

The Efficacy of Transdermal Nicotine for the Treatment of Tobacco Dependence

Nicotine replacement therapy (NRT) increases smoking cessation rates significantly vs. placebo or counseling (Fiore et al., 2008; Schnoll & Lerman, 2006). Nicotine gum is often used improperly and is not effective across all settings (Cepeda-Benita et al., 1993). Nicotine nasal spray and inhaler can be aversive, lowering compliance rates vs. other NRTs (Kaufmann et al., 2004; West

et al., 2001). While there are data to support the use of the nicotine lozenge, the 2008 PHS treatment guideline concluded that the scientific support for this NRT is limited (Fiore et al., 2008). Relative to these NRTs, transdermal nicotine has the fewest side effects and yields the highest compliance rates. As a consequence, the transdermal nicotine patch is the most widely used form of tobacco dependence treatment in the US (Jonk et al., 2005; Pierce & Gilpin, 2002) and Europe (Tilson et al., 2004; West et al., 2005). The transdermal nicotine patch is also available over-the-counter (OTC), allowing for new recommendations concerning its use to be easily disseminated and adopted.

A meta-analysis of 40 placebo-controlled clinical trials of transdermal nicotine (Stead et al., 2008) and the recent PHS guideline (Fiore et al., 2008) conclude that transdermal nicotine increases the odds of cessation vs. placebo by ~70%. However, only ~20% of smokers are able to maintain abstinence for 6 months following patch treatment (Fiore et al., 2008; Stead et al., 2008) even when patches are accessed OTC (Pierce & Gilpin, 2002). At 12-months, only ~9% of individuals who use transdermal nicotine are abstinent (Russell et al., 1993; Imperial Cancer Research Fund General Practice Group, 1993). At 6-months, the efficacy of standard therapy with transdermal nicotine is comparable to bupropion (Hughes et al., 2007), but lower than the new nicotinic receptor partial agonist medication, varenicline, which produces 6-month quit rates of ~35% (Cahill et al., 2007; Gonzalez et al., 2006; Jorenby et al., 2006). Bupropion and varenicline, however, can yield side effects and have numerous medical contraindications that limit who can use these treatments (Schnoll & Lerman, 2006). For instance, the Federal Aviation Administration and the Federal Motor Carrier Safety Administration have recently added varenicline to their list of drugs that should not be used by pilots or truck drivers.

Duration of Transdermal Nicotine Treatment: Standard vs. Maintenance Therapy

Current guidelines established by the US Department of Health and Human Service PHS (released May 7, 2008) recommend 8 weeks of transdermal nicotine therapy (Fiore et al., 2008). Several studies across various countries show that smokers largely adhere to the guidelines to use NRT for the recommended duration even with OTC access (Shiffman et al., 2003; Paul et al., 2003; Hasford et al., 2003; Shaw et al., 1998). Indeed, Shiffman et al. (2003) reported that <2% of nicotine patch users used patches beyond the recommended duration. Nevertheless, the 2008 PHS guideline recognizes that nicotine dependence is a chronic disease, with smokers cycling through repeated periods of relapse and remission, and underscores the need for research on long-term therapy for nicotine dependence (Fiore et al., 2008). Indeed, nicotine dependence shares many of the characteristics of chronic diseases such as asthma and diabetes and other drug dependencies that are treated with a maintenance approach but, unlike these conditions, nicotine dependence is treated acutely (see Steinberg et al., 2008). Long-term NRT use is safe, especially vs. continued smoking, and has a low abuse liability (Steinberg et al., 2008). One central reason for the continual recommendation of 8 weeks of transdermal nicotine is the lack of adequate clinical trial data of maintenance therapy to include in formal meta-analyses as part of PHS guideline presentation (Fiore et al., 2008; Medioni et al., 2005).

The Current Evidence Base for Maintenance Therapy with Transdermal Nicotine. A recent Cochrane review compared the odds ratios for transdermal nicotine trials with ≤ 8 weeks of treatment to the odds ratios from trials with > 8 weeks of treatment and found no effect for treatment duration (Stead et al., 2008). However, almost all of the trials that represented > 8 weeks of treatment provided only 10-12 weeks of treatment. Further, this comparison included studies which varied in sample size, population studied, treatment duration, patch dose, presence of adjunctive behavioral counseling, and outcome measures used. In this review, only 4 trials compared varying duration of patch therapy. A close look at the 4 studies underscores the lack of complete data to assess the benefits of maintenance therapy with transdermal nicotine. Three of the 4 trials (Bolin et al., 1999; Glavas & Rumboldt, 2003; Hilleman, 1994) included < 140 subjects and, thus, had limited statistical power. Further, these studies compared quit rates following 3- or 6- weeks of treatment vs. 6 weeks (Glavas & Rumboldt, 2003) or 12 weeks (Bolin et al., 1999; Hilleman, 1994) of treatment. These studies, therefore, did not include the standard therapy arm (i.e., 8-weeks) or include a treatment arm that received NRT for a meaningfully longer duration.

The third study, the CEASE trial, represents the only large, adequately powered, placebo-controlled randomized study of standard (8-week) versus extended (22-week) transdermal nicotine therapy (Tonnesen et al., 1999). The CEASE trial found no significant difference in cessation rates at the end of treatment between the two treatment arms. However, since the CEASE trial was designed to evaluate the effects of varying doses of transdermal nicotine on cessation rates, in addition to treatment duration, several aspects of the study design and data analysis limit the study findings for assessing the effect of maintenance treatment. The doses selected (i.e., 15mg and 25mg) are incongruent with the doses considered in the PHS guidelines (i.e., 7mg, 14mg, 21mg) and a 16 hour-a-day dosing schedule was used rather than continuous 24-hour dosing. Moreover, the only measure of cessation rate examined in this trial was continuous abstinence (not even a puff) from the quit day to the end of treatment (week 22). This was the conventional, gold-standard measure of abstinence at the time. Over the past several years, however, new guidelines for evaluating smoking cessation clinical trials have been established (Hughes et al., 2003). And, a critical change reflected in these guidelines is the movement away from using the very conservative measure of treatment outcome represented by continuous abstinence in smoking cessation clinical trials, to a more appropriate outcome measure of point prevalence. There were several reasons for this change (see below).

Point Prevalence vs. Continuous Abstinence. First, there has been a growing recognition that many smokers who lapse early in treatment subsequently recover and maintain long-term abstinence (Hughes et al., 1992). These “sleeper effects” in smoking cessation trials are common; Hughes et al. (1992) reported that 23% of smokers who were confirmed abstinent between 3 and 6 months post-target quit date had smoked a few cigarettes during the initial weeks of the study. Jarvis et al. (1984) reported that 43% of smokers regained prolonged abstinence after an early lapse. A strict use of continuous abstinence would have considered these individuals to be smokers. Second, use of point-prevalence abstinence (vs. continuous abstinence) may be preferable for assessment of “rescue therapies”, like transdermal nicotine, that may have “delayed effects” by increasing the likelihood of recovery from smoking lapses (Shiffman et al., 2006). For example, Jamerson et al. (2001) showed that 7% of subjects who failed to quit smoking within the first 3 weeks of transdermal nicotine treatment were abstinent between weeks 4 and 9. The complete pharmacological effect of NRT is likely to require repeated dosing over several days or weeks for many individuals (Hughes et al., 2003). Third, point prevalence abstinence may represent a psychometrically stronger variable vs. other abstinence measures. Velicer and Prochaska (2004) examined the reliability and validity of point prevalence, continuous, and prolonged abstinence, and concluded that point prevalence had the highest concurrent validity. Lastly, given current technologies, point prevalence abstinence is the only outcome measure that can be biochemically verified to ensure the validity of self-reported abstinence. As such, current guidelines for the evaluation of smoking cessation clinical trials recommend the use of point prevalence abstinence as an outcome (Hughes et al., 2003). Point prevalence abstinence can detect “sleeper” and “delayed” treatment effects, has greater validity, and can be biochemically verified (Velicer et al., 1992). In contrast, continuous abstinence incorrectly assumes a linear change in abstinence and cannot be biochemically verified (Velicer et al., 1992). These are potential explanations for the lack of treatment effect for increased treatment duration in the CEASE trial.

An Efficacy Trial of Extended Transdermal Nicotine Patch Therapy. We recently completed recruitment for a placebo-controlled randomized efficacy trial of extended transdermal nicotine therapy. We randomized 571 smokers to: 1) standard therapy (8 weeks 21mg nicotine patch and 16 weeks of placebo patch), or 2) extended therapy (24 weeks of 21mg nicotine patch), plus brief counseling. Follow-up evaluations continue. The primary outcome is biochemically verified 7-day point prevalence abstinence at week 24; point prevalence abstinence was also verified at week 52 to assess if the benefit of extended therapy disappeared once treatment ended. At week 24, point-prevalence cessation was significantly higher in the extended therapy vs. the standard arm (30% vs. 20%; OR = 2.93 [1.23-6.98], $p = .008$). However, at week 52, the quit rates were equivalent across the treatment arms (16% vs. 15%; OR = 0.85 [0.31-2.30], $p = .75$), suggesting that the benefits of transdermal nicotine may be sustainable only when

treatment is maintained. Importantly, the point prevalence quit rate at week 24 for those on extended therapy exceed those for bupropion (Hughes et al., 2007) and are comparable to those for varenicline (Gonzalez et al., 2006). While this efficacy trial provided exciting new evidence that extending transdermal nicotine therapy to 24 weeks significantly improves quit rates, this trial did not include a treatment arm that received maintenance therapy for the 52-week trial. Thus, to extend our efficacy data, we will conduct a trial of maintenance therapy with transdermal nicotine that will include a treatment arm that receives continuous therapy throughout the 52 week trial, a study design used to demonstrate the effectiveness of methadone maintenance for opiate addiction. Additionally, the design conforms to criteria for an effectiveness trial, whereas the prior trial was an efficacy trial.

Lapse and Recovery: Mechanism for Maintenance Therapy Effects

The concept of maintenance therapy for nicotine dependence is based on the notion that nicotine dependence is a chronic disorder with numerous attempts to quit and relapse. Studies show that many smokers (23-43%) lapse early in treatment, but recover and maintain abstinence (Hughes et al., 1992; Jarvis et al., 1984; Swan & Denk, 1987). This process of recovery from early lapses to abstinence can explain why maintenance therapy is more effective than standard (acute) therapy with transdermal nicotine. Many smokers provided with transdermal nicotine will have a lapse to smoking, but whether this lapse leads to a relapse may be affected by the continual presence of treatment. Smokers who lapse but are provided with maintenance treatment will have the opportunity to “re-start” or “recover” given continual access to treatment, whereas smokers who lapse but are not provided with continual access to treatment will see their lapse transition into a relapse. While limited data are available to illustrate this, our team has conducted three studies to support this hypothesis, using a novel statistical methodology: recurrent events analysis. This dynamic modeling analysis can capture medication effects on a series of lapses and recoveries to abstinence, unlike models of single outcome criteria. Initially, we showed in a placebo-controlled clinical trial that bupropion, vs. placebo, could promote recovery after a smoking lapse (Wileyto et al., 2005). Bupropion reduced the risk of relapse, vs. placebo, and increased the likelihood of recovery to abstinence among those who lapsed. In a separate study, we found that nicotine patches promoted recovery from a lapse more often than bupropion (Wileyto, 2006). More recently, we examined lapse-recovery models for those who received 8- vs. 24-weeks of transdermal nicotine (Schnoll et al., 2008); participants given 8 weeks of treatment were more likely to lapse during weeks 9-24, vs. those who stayed on treatment. And, between weeks 9 and 24, those who received 24 weeks of treatment were ~50% more likely to recover to abstinence after a lapse, vs. those who received 8 weeks of treatment (HR = 1.42 [1.08-1.90], $p = .014$). This study will continue this research to show that maintenance transdermal nicotine therapy increases abstinence rates by assisting smokers with recovering from lapses.

Cost-effectiveness of Nicotine Replacement Therapies

The resources available to treat medical conditions in the US, including nicotine dependence, are limited. Whether it is the individual smoker, an employer, a government agency, or an insurance company, decisions about using or supporting a particular medical treatment consider the clinical effectiveness and relative financial costs. Assessment of the economics of treatments for nicotine dependence can involve cost-utility analysis (quality adjusted life years), cost-benefit analysis (cost savings), and cost-effectiveness analysis (CEA; life years gained). These assessments have their strengths and weaknesses, but cost-effectiveness may be more useful given the inclusion of measures of treatment effectiveness, financial costs, and health outcomes. Cost-effectiveness has been used widely in the nicotine dependence treatment field (Ronckers et al., 2005; Song et al., 2002) and continued use in clinical trials permits comparisons to existing data.

Published studies of cost-effectiveness of counseling, NRT, and bupropion have varied in terms of the analytic methods used and assumptions for computing clinical outcomes and costs (in part because these studies are conducted in different countries.) However, the results of these analyses generally converge, showing that NRT is cost-effective in terms of life-years saved (Woolacott et al., 2002) and costs per life year saved (Ronckers et al., 2005). Smoking cessation interventions can yield 1-3 life years saved, with NRT costing \$1,441-\$3,455 per life-year saved

(Song et al., 2002). Relative to just counseling for smoking cessation, the incremental cost per life year saved for adding NRT is \$3,455 (Song et al., 2002) to \$8,794 (Ronkers et al., 2005). These values compare quite favorably to the well accepted threshold ratio used in the economic literature of \$50,000 per life year (Hirth, 2000) and to the median cost per life year saved of \$19,000 for various medical interventions (Tengs et al., 1995). The nicotine patch was second only to bupropion in incremental cost per life-year saved in a recent analysis involving smokers across 6 countries and was more cost-effective than other preventative medical procedures such as cholesterol- and blood-pressure lowering medications (Cornuz et al., 2006). The cost-effectiveness of transdermal nicotine is also supported in sensitivity analyses which change model parameters to worsen or improve the analytic scenario (Cornuz et al., 2006).

While the use of pharmacotherapies for nicotine dependence, including NRT, is generally cost-effective (Heitjan et al., 2007; Song et al., 2002), the cost-effectiveness of maintenance therapy for nicotine dependence is unknown. Since the primary implication of our results would be to advise maintenance therapy with the nicotine patch, this represents a greater financial cost to smokers, employers, or insurance providers. If we expect insurance providers, for instance, to support maintenance therapy for nicotine dependence as a covered benefit, data are needed to help assess the cost-effectiveness of this approach, vs. the standard 8-week regimen. Demonstrating that increased quit rates from maintenance therapy are achievable at a reasonable financial cost is critical to support new recommendations for third-party coverage of maintenance therapy for nicotine dependence. Dr. Daniel Polsky will oversee the evaluation of the cost-effectiveness of maintenance therapy for this trial. This will provide novel critical data.

Efficacy Trials vs. Effectiveness Trials: Translation to Practice

An important question in science concerns the strengths and limitations of efficacy vs. effectiveness trials (Fuhrer, 2003; Gartlehner et al., 2006; Nathan, 2004). Efficacy trials typically evaluate the benefits and safety of a treatment using a randomized double-blind design. The study may involve the comparison between two medications or between a novel treatment approach (e.g., long-term maintenance transdermal nicotine) and standard therapy (e.g., standard transdermal nicotine). The trial is conducted under highly controlled conditions with strict inclusion/exclusion criteria. A primary goal is preserving internal validity. In contrast, effectiveness trials assess the benefits and safety of a treatment in the context of routine use or “real-world” conditions. The study can be conducted in clinical settings, but inclusion and exclusion criteria are relaxed to reflect typical users of the treatment (e.g., in this study we will not exclude those with diabetes or depression, which were excluded in our efficacy trial). Safety and cost-effectiveness are outcomes in effectiveness trials. As such, effectiveness trials emphasize the external validity of treatments vs. internal validity. Issuing recommendations for the use of transdermal nicotine as a maintenance therapy requires both efficacy and effectiveness data given the history of medications which have been shown to be safe in efficacy trials, but not safe or efficacious in effectiveness trials (Lexchin, 2005) and in light of recent removal of medications tested only in efficacy trials, but subsequently linked to an increased risk of adverse events during broad use (e.g., Avandia). An effectiveness trial of maintenance therapy with transdermal nicotine patches may be especially critical given its OTC status. Confidence in translating to clinical practice the recommendation that smokers utilize transdermal nicotine patches as maintenance therapy for nicotine dependence, therefore, should be determined by the accumulation of data across both efficacy and effectiveness trials. These data are also critical for organizations such as the PHS to make evidence-based recommendations through publication of treatment guidelines.

CHARACTERISTICS OF THE STUDY POPULATION

1. Target Population

This randomized effectiveness trial is designed to determine the clinical and cost-effectiveness of maintenance therapy vs. standard and extended therapy with transdermal nicotine among 540 community smokers from Philadelphia (UPENN) and Chicago (Northwestern University). Since

this is an effectiveness trial, participants will not be blinded to treatment condition, a placebo patch will not be used for those randomized to standard or extended arms, and inclusion/exclusion criteria will be limited. Participants will be: 1) males and females over age 18 who smoke at least 10 cigarettes/day; 2) able to communicate in English; 3) able to use NRT safely (e.g., no allergy to latex, no serious abnormal ECG reading); 4) able to provide written informed consent for study procedures; and 5) residing in the geographic area for at least 12 months. Participants will be ineligible for the trial if they: 1) are unable to communicate in English; 2) Have a current diagnosis of psychosis and/or manic depression, 3) have a current medical condition that would make using transdermal nicotine patch unsafe (e.g., allergy to latex, serious, abnormal ECG reading); participants with asthma, diabetes, hypertension, or heart disease (e.g., coronary artery disease, abnormal heart rhythm, an arrhythmia) will be permitted to enroll in the study with medical clearance from the participant's physician or the study physician; 5) have had a heart attack within the past 6 months, 5) are pregnant or planning to become pregnant or lactating, or 6) are currently enrolled or plan to enroll in another research or smoking cessation program within the next 12 months.

There will be no exclusion based on gender or race/ethnicity for recruitment into this trial. At UPENN, the efficacy trial recruited a sample comprised of 45% women and 16% racial/ethnic minorities (Schnoll et al., 2008); a separate smoking cessation trial at UPENN, which used targeted efforts to recruit minority smokers, yielded a sample comprised of 55% women and 52% racial/ethnic minorities (Schnoll et al., in press). At Northwestern University, a recent smoking cessation clinical trial with fluoxetine recruited a sample comprised of 54% women and 38% ethnic/racial minorities (Spring et al., 2007). Thus, the research team has shown the ability to recruit a diverse sample in terms of women and ethnic/racial minorities.

2. Accrual

A sample of 540 smokers will be included in this clinical effectiveness trial to assess the benefits of maintenance treatment with nicotine patch on quit rates. The trial will be conducted through two large city university sites with extensive experience conducting smoking cessation clinical trials. As done for our previous smoking cessation clinical trials (Schnoll et al., in press; 2008; Spring et al., 2007), we will use media ads (newspaper, radio) as the main form for recruitment. We will use media sources with large African American and Hispanic-American readership or listenership as well as media sources with young adult audiences. This method of recruitment, though expensive, has allowed our research groups to ascertain large (i.e., >500) and diverse (i.e., >30% racial/ethnic minority) study samples in our clinical trials. As a secondary form of recruitment, we will distribute posters and flyers advertising the study to medical clinics across the UPENN and Northwestern-affiliated hospitals. The ads and flyers will include instructions for enrollment and a toll-free phone number for participants to call to enroll in the study. A Research Assistant at the sites will screen incoming calls from prospective participants for basic eligibility (e.g., number of cigarettes/day) and study interest. Participants who are eligible and interested in the study will be scheduled for a formal intake session, which will involve providing informed consent and a complete eligibility evaluation. Those eligible after the intake session, will complete a baseline assessment, and be randomized to treatment arm. To assess external validity, eligible persons who refuse entry will be asked for a reason and probed for whether or not the decision was linked to the NRT to be used in this study and the requirement of randomization to the treatment arms.

In addition to these recruitment strategies, this trial will accrue, from other ongoing smoking cessation protocols, participants who were deemed ineligible before enrollment. These participants will have successfully completed a more stringent eligibility process using the same measures, and their eligibility status for this protocol will thus be known. We will allow these participants to enroll to this trial using an expedited process as long as they enroll within a 60 day window. Their eligibility for this trial will be based on the measures from the previous study. These participants will be asked to sign the study consent form; however, they will not be asked to undergo another physical and psychiatric evaluation. Their medical history, medications, diagnoses, and blood pressure will be checked prior to enrollment.

Statistical power for the trial was based on the primary aim of the comparison in week 52 point prevalence quit rates between those maintained on nicotine patch for 52 weeks vs. those on 8- and 24-weeks of nicotine patch. Based on our efficacy trial, we expect the week 52 quit rates (biochemically-confirmed 7-day point prevalence) to be 16% for standard and extended treatment participants. We know of no data, however, to determine the week 52 quit rates for those maintained on transdermal nicotine for 52 weeks. In our efficacy trial, we found that at week 24 those maintained on treatment reported a quit rate of 30% (Section C.1.), 10 percentage points higher than those provided with 8-weeks of treatment. Thus, it is reasonable to assume that the quit rate for those maintained on treatment at week 52 would be 26%, a 10 percentage point increase. Thus, we powered this study to detect a difference between the ST and ET conditions vs. the MT condition of 10% (16% vs. 26%).

3. Key Inclusion Criteria

Participants will be: 1) males and females over age 18 who smoke at least 10 cigarettes/day; 2) able to communicate in English; 3) able to use NRT safely (e.g., no allergy to latex, no serious, abnormal ECG reading); 4) able to provide written informed consent for study procedures; 5) residing in the geographic area for at least 12 months, and 6) if required, have medical clearance to proceed with the study. Medical clearance can be provided by the participant's primary physician or by the study physician (Dr. Frank Leone). Participants with asthma, diabetes, hypertension, or heart disease (e.g., coronary artery disease, abnormal heart rhythm, an arrhythmia) will need medical clearance to enroll.

4. Key Exclusion Criteria

Participants will be ineligible for the trial if they: 1) are unable to communicate in English; 2) Have a current diagnosis of psychosis, suicidality, and/or manic depression, 3) have a current medical condition that would make using transdermal nicotine patch unsafe (e.g., allergy to latex, serious, abnormal ECG reading); 4) have had a heart attack in the past 6 months and 5) are pregnant or planning to become pregnant or lactating.

5. Vulnerable Populations

Vulnerable populations will not be recruited to this trial.

6. Populations vulnerable to undue influence or coercion

Children, prisoners, pregnant women, or mentally disabled persons will not be eligible for this trial. Individuals who are economically disadvantaged and employees or students of the institutions responsible for this trial will be eligible. Personnel responsible for eligibility screening and participant registration will be trained to avoid any coercion to enroll in this trial. Given our extensive experience with conducting smoking cessation clinical trials, we do not anticipate that participants will be coerced to enroll into this trial.

7. Subject Recruitment

This trial will be conducted through two large city university sites with extensive experience conducting smoking cessation clinical trials.

University of Pennsylvania Tobacco Use Research Center (TURC). The PENN TURC, which began in 1999, is an NCI/NIDA-funded center devoted to the evaluation of treatments for nicotine dependence (PI: Dr. Caryn Lerman). The TURC is part of the Department of Psychiatry at the PENN School of Medicine but it is located off-campus, in a community office building within the downtown city of Philadelphia. The TURC has been the treatment facility used to support several large clinical trials, small pilot projects, post-doctoral fellows, and core trial facilities (e.g., Lerman et al., 2004, 2006; Schnoll et al.,

2008, in press). The clinical research conducted at the PENN TURC in the past 5 years alone has produced >130 peer-reviewed publications. The UPENN TURC provides the necessary infrastructure for this trial. The TURC is housed in an office building located within the community in downtown Philadelphia. The TURC encompasses 6,500 square feet, including space for faculty and staff offices, conference rooms, clinic rooms for treatment and assessment, several small laboratory rooms for biological assessments and storage, and data storage facilities (paper and computer). The efficacy trial of extended transdermal nicotine treatment was conducted through the UPENN TURC.

Northwestern University Behavioral Medicine Program. The Northwestern University Department of Preventative Medicine is part of the university's School of Medicine and is comprised of faculty and staff devoted to teaching and research. In addition to preparing students to address disease prevention and control, improve access to and quality of health care, and better organize and finance health care services, the Department of Preventative Medicine supports leading-edge research into numerous medical conditions, including behavioral science and addictions research. The Department of Preventive Medicine is home to several nationally and internationally renowned landmark collaborative studies, including the Women's Health Initiative (WHI) and the CARDIA study. Within this Department, the Behavioral Medicine Program is a clinical and research unit that uses a multidisciplinary approach to understanding, preventing, and treating disease. Researchers with backgrounds in clinical psychology, kinesiology, nutrition, public health, nursing and medicine conduct grant-funded projects to understand the influences of psychological, socio-cultural, and biological factors on health. Behavioral Medicine faculty specialize in the development and implementation of behavioral interventions to promote health, including the evaluation of treatments for nicotine dependence. The Behavioral Medicine Program is located in downtown Chicago with convenient access to city residents. The Behavioral Medicine Program is comprised of 25,243 sq. feet of office space, including suites for faculty and administrative personnel, consulting rooms and meeting rooms for participant assessment and data collection, laboratory suites for the collection and storage of biological data, and data management and storage facilities.

As done for our previous smoking cessation clinical trials (Schnoll et al., in press; 2008; Spring et al., 2007), we will use media ads (newspaper, radio) as the main form for recruitment. We will use media sources with large African American and Hispanic-American readership or listenership as well as media sources with young adult audiences. This method of recruitment, though expensive, has allowed our research groups to ascertain large (i.e., >500) and diverse (i.e., >30% racial/ethnic minority) study samples in our clinical trials. As a secondary form of recruitment, we will distribute posters and flyers advertising the study to medical clinics across the UPENN and Northwestern-affiliated hospitals. The ads and flyers will include instructions for enrollment and a toll-free phone number for participants to call to enroll in the study. A Research Assistant at the sites will screen incoming calls from prospective participants for basic eligibility (e.g., number of cigarettes/day) and study interest. Participants who are eligible and interested in the study, will be scheduled for a formal intake session, which will involve a complete eligibility evaluation. Those eligible after the intake session, will complete informed consent and HIPAA forms, complete a baseline assessment, and be randomized to treatment arm. To assess external validity, eligible persons who refuse entry will be asked for a reason and probed for whether or not the decision was linked to the NRT to be used in this study and the requirement of randomization to the treatment arms.

The UPENN TURC and the Northwestern Behavioral Medicine Program have an established record of conducting large smoking cessation clinical trials (Schnoll et al., 2008; in press; Spring et al., 2007). To demonstrate, more specifically, our ability to ascertain the proposed sample, the following data are from our efficacy trial of extended transdermal nicotine treatment (P50 CA/DA84718; PI: C. Lerman, Ph.D.). In ~55 months of recruitment for our efficacy trial, we screened 3,276 individuals; 1,970 individuals were ineligible and 617 were not interested in the trial; 689 (21%) of those screened attended the intake session. At the intake session, 9 individuals decided to withdraw from the study and 110 were determined to be ineligible for the trial. Thus, 570 individuals were randomized and considered for intent-to-treat analysis over ~55

months of recruitment (~10/month). At Northwestern University, Dr. Spring's fluoxetine study recruited smokers for ~42 months and screened 2,050 potential participants; 662 individuals did not meet eligibility criteria and 1,141 were either not interested or did not proceed to the intake session and randomization. Thus, 247 (12%) of those screened were randomized to treatment arms in ~42 months (~6/month). Taken together, these data demonstrate that the two recruitment and treatment sites are able to recruit and randomize ~16 participants per month. Given the need for staff training and study implementation (3-6 months), the follow-up for the final study participants (12 months), and the projected sample size (n = 540; see Power Calculations below), we will require ~42 months to recruit the sample. Two sites were selected for this effectiveness trial since one site alone could not accrue the large sample needed for this trial in ~42 months.

STUDY DESIGN

1. Phase

This is a Phase IV clinical trial.

2. Design

The study design is a randomized clinical trial. Since this is an effectiveness trial, no placebo will be used.

3. Study Duration

Funding for this trial will last 5 years. We expect participants to be involved in this trial for about 54 weeks. We expect to complete accrual in ~42 months, completing the trial in March 2014.

DRUGS OR DEVICES

Participants will be randomized to receive standard treatment (ST) with the transdermal nicotine patch (21mg* x 8 weeks), extended treatment (ET) with the transdermal nicotine patch (21mg* x 24 weeks) or maintenance treatment (MT) with the transdermal nicotine patch (21mg* x 52 weeks). All subjects will receive 12 sessions of a manual-based behavioral intervention from a trained smoking cessation counselor modeled on the PHS guideline for smoking cessation treatment (Fiore et al., 2008) from Week -2 to Week 48. The transdermal patch will be used to treat nicotine dependence, as indicated.

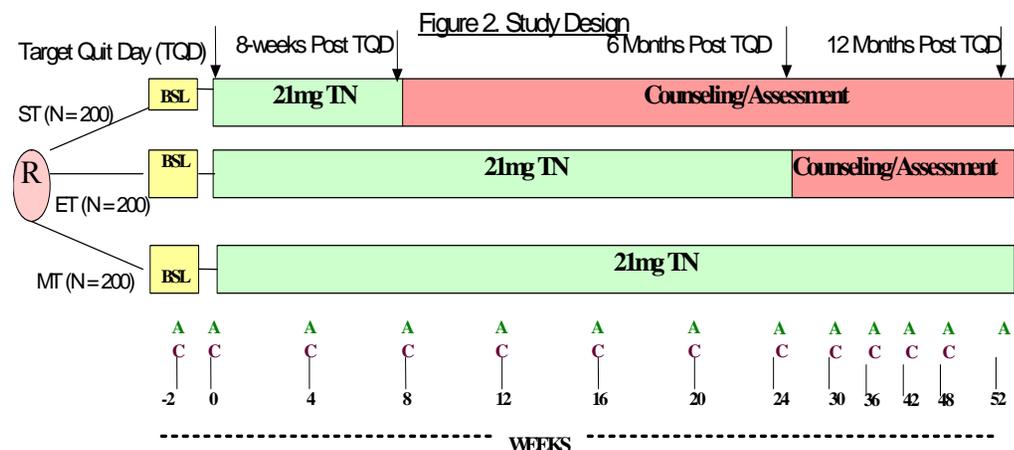
* 14mg and 7mg nicotine patches will be provided to participants for whom the 21mg patch is too strong and who exhibit signs of nicotine overdose. All other study procedures will remain standard.

STUDY PROCEDURES

1. Procedures

Overview of Research Design

We will conduct a randomized effectiveness trial to determine the clinical and cost-effectiveness of maintenance therapy vs. standard and extended therapy with transdermal nicotine among 540 community smokers from Philadelphia (UPENN) and Chicago (Northwestern University). Since this is an effectiveness trial, participants will not be blinded to treatment condition, a placebo patch will not be used for those randomized to standard or extended arms, and inclusion/exclusion criteria will be limited. Subjects will be randomized to receive standard treatment (ST) with the nicotine patch (21mg x 8 weeks), extended treatment (ET) with nicotine patch (21mg x 24 weeks) or maintenance treatment (MT) with the nicotine patch (21mg x 52 weeks; Figure 2). As done in our ongoing trials, media ads with a toll-free phone number will be placed. Recruitment, screening, randomization, treatment, and assessment will be standardized across sites. Individuals contacting the recruitment line will be initially screened for eligibility by phone. Those eligible will be scheduled for an intake session, where eligibility will be confirmed. Those eligible and interested in the trial will complete informed consent and HIPAA documents, will be randomized to study arm, will complete baseline measures, and will provide a saliva sample for nicotine/cotinine analysis and a saliva sample for genetic analyses (Week -2). Participants will also receive a pre-quit counseling session (small group), receive their patches (in 8 week increments), and set a target quit date (TQD) for 2 weeks later (Week 0). At Week 0, all participants will receive a second counseling session by phone and will begin NRT. During the subsequent 52 weeks, participants will receive 10 counseling sessions by phone (10-15 minutes each), and will complete measures (weeks 4, 8, 12, 16, 20, 24, 30, 36, 42, 48). Additional NRT will be mailed to the course of the trial. Outcome completed in-person at weeks 8, 24, 36, participants will be asked to attend the site sample for biochemical verification at primary outcome is 7-day point abstinence at week 52 (self-reported days prior to the assessment and carbon ≤ 10 ppm). Point prevalence abstinence assessed at week 8 and 24 as well. As per (Hughes et al., 2003), secondary outcomes abstinence to week 24 and 52 (relapse consecutive days of self-reported week grace period), time to 7-day relapse lapse and recovery events, and craving, and mood.



ST = Standard Treatment; ET = Extended Treatment; MT = Maintenance Treatment; R = Randomization; BSL = Baseline; A = Assessment; C = Counseling

participants through assessments will be and 52. All to provide a breath these weeks. The prevalence abstinence for 7 monoxide [CO] of and CO will be recommendations include: prolonged defined as 7 smoking, after a 2- (no grace period), withdrawal,

Overview of Study Procedures (See Table 4)

The Intake Session (Week -2): Eligibility Confirmation & Consent. After an initial eligibility assessment and evaluation of study interest by phone, participants are scheduled for an intake session at the respective site. The initial telephone eligibility assessment allows us to reduce the likelihood that participants attend clinic only to learn that they are ineligible. In addition, the telephone eligibility assessment allows for the ascertainment of physician's clearance should the participant have a medical condition that affects safety with using transdermal nicotine (e.g., hypertension). At this intake session, the participant will complete an informed consent and HIPAA document before completing a medical history and a physical exam of vital signs (ECG, blood pressure, pulse, and respiratory rate, and a pregnancy test for women) that will be conducted by study medical personnel to determine study eligibility. Participants who previously underwent a recent (within 60 days) physical and medical history with another smoking cessation protocol will only have to complete an informed consent. If eligible and willing to proceed, the participant will be officially registered on the trial. Hard copies of eligibility screening data and consent/HIPAA forms will be stored in a subject's study binder.

The Intake Session (Week -2): Baseline Evaluation and Randomization. Once registered on the trial, the Study Coordinator will complete a baseline assessment. All participants will complete these assessments regardless of how their eligibility status was determined. This assessment will collect data on: 1) background variables that may serve as covariates and will allow for the assessment of the study's external validity (e.g., smoking history, demographics, depression, nicotine metabolism rate); 2) mediator variables (e.g., withdrawal), and 3) baseline smoking rate/behavior (including CO). In addition, the Study Coordinator will collect two 5ml saliva samples for the computation of rate of nicotine metabolism (i.e., 3-HC/cotinine). One set of saliva samples will be sent to the laboratory of Dr. Neal Benowitz at the University of California San Francisco for cotinine and nicotine assays. The second set of samples will be retained at PENN for storage and analysis as done for numerous previous smoking cessation trials conducted at the TTURC. All baseline data will be collected on Case Report Forms (CRFs) devised for this study and will be stored in the participant's study binder. Once the baseline data collection is complete, the participant will initiate treatment and the Study Coordinator will randomize participants to a treatment arm. Dr. Wileyto, the study biostatistician, will provide a randomization procedure and table for each site, accessible on a web-based DMS. Randomization will be stratified by site and will use permuted blocks of random sizes.

Behavioral Counseling (Week -2 to Week 48). All subjects will receive a manual-based intervention from a trained smoking cessation counselor modeled on the PHS guideline for smoking cessation treatment (Fiore et al., 2008) from Week -2 to Week 48. Behavioral counseling was included given its' demonstrated efficacy at helping smokers quit (Fiore et al., 2008) and to increase compliance with procedures and retention. Counseling is maintained across the study duration for all treatment arms 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 efficacy trial. Phone counseling was selected for all sessions (except the initial session) since it has demonstrated clinical and cost-effectiveness and can increase compliance and external validity (Fiore et al., 2008; Hollis et al., 2007; Stead et al., 2007). Since all study participants can access telephone counseling through the Pennsylvania and Illinois quit-lines, use of telephone counseling in this trial is consistent with community-based practice and an effectiveness trial. The counseling program begins with a 1-hour in-person small group counseling session (3-6 people in each group) to prepare for the target quit day (Week -2); at Week 0, participants will receive a 30-minute "quit-day" session by phone to prepare for quitting. Lastly, participants will receive ten 15-minute booster sessions by phone at Weeks 4, 8, 12, 16, 20, 24, 30, 36, 42, and 48. The counseling program is designed to enhance awareness for the harmful effects of smoking, assist the person in developing skills to quit and avoid relapse, and instruct the smoker on NRT use. Compliance with patch use recommendations will be emphasized. A random 25% of sessions will be audio-taped and assessed for protocol adherence. An experienced and trained counselor at each site will conduct all sessions and will not conduct any assessments.

Pre-Quit Session (Week -2; 1-hour). At the in-person, small group pre-quit visit, subjects will receive introductory materials (e.g., program overview and logistics) and materials to help them prepare for

their quit date. A quit day for Week 0 will be selected. Support and encouragement will be provided. The counselor will review the personal risks of continuing to smoke (e.g., cancer) and provide a quit plan. Specific strategies will be described: 1) gradual reduction before quit day (i.e., scheduled smoking); 2) self-talk of reasons for quitting; 3) enlisting support of friends and family; 4) awareness of tempting situations and the need to avoid them or create a plan for using alternatives (e.g., distraction); and 5) removing smoking cues. A tip sheet of strategies will be given.

Quit Day Session (Week 0; 30 Minutes). This session will focus on NRT use and strategies to manage withdrawal and avoid relapse. Subjects will be urged to maintain awareness of tempting situations (e.g., being around smokers) and to develop a repertoire of alternatives to cope with danger situations. Other skills for avoiding relapse to be discussed and encouraged are: developing an exercise regimen, relying on the support of friends and family, reminding oneself of the reasons for quitting, and use of self-distraction and reinforcement. These techniques help avoid relapse (Anderson & Wetter, 1997; Fiore et al., 1997). The counselor will review NRT use and clarify concerns that subjects may have.

Relapse Prevention Sessions (Weeks 4, 8, 12, 16, 20, 24, 30, 36, 42, 48; 15 Minutes). These “booster” sessions focus on relapse prevention. Past session material is reviewed and successes or failures are assessed. The Session 1 quit plan will either be revised or reinforced depending on progress. Problem-solving will be a central component to these sessions; the counselor will have participants identify tempting situations (i.e., when slips occurred or cravings high). New concerns about sustained abstinence will be probed (e.g., fear of stress reactions or weight gain) and strategies for managing these issues will be discussed.

Transdermal Nicotine Treatment. During the Pre-Quit counseling session, the counselor will review the purpose of using the nicotine patch (e.g., to help manage withdrawal symptoms; not a substitute for behavioral quitting strategies), provide directions on how to use the patch (e.g., abstinence from smoking, patch location, time, activity, and potential skin reactions), and answer any questions. The supply of transdermal patches will be distributed in 8 week increments; participants in the extended and the maintenance treatment conditions will have additional supplies of nicotine patches mailed to them over the course of the trial in 8 week increments. Participants will be instructed to promptly discontinue the patch and contact the respective study coordinator if they experience severe or persistent local skin reactions (e.g., severe redness, itching, or swelling) at the site of patch application or a generalized skin reaction (e.g., raised patches, hives, or generalized rash). Any serious adverse reactions or significant side effects of transdermal nicotine will be medically evaluated by a physician at the respective site. Patch use by such individuals will be monitored and adjusted as needed. Based on our previous and ongoing experience with NRT studies and extended transdermal nicotine (e.g., Lerman et al., 2004; Schnoll et al., 2008), we expect few serious adverse events. Data from any subject experiencing adverse effects (even if requiring discontinuation of medication) will be analyzed based on an intent-to-treat model. Consistent with the lack of evidence for a difference in effect with tapering (e.g. 4 weeks 21mg, 2 weeks 14mg, 2 weeks 7mg) versus no tapering, all participants receive the 21mg dose throughout the designated treatment phase (i.e., either 8 or 24 weeks; Stead et al., 2008). However, if the 21mg patch proves too strong for some participants, and they begin to experience signs of nicotine overdose, the 14mg and/or the 7mg patch will be provided.

Standard Treatment (ST). The ST condition will receive standard 8-week treatment with transdermal nicotine at 21mg*. Since this is an effectiveness clinical trial, placebo patches will not be provided to ST participants for the remaining 44 weeks. This condition represents current standard of care (Fiore et al., 2008).

Extended Treatment (ET). The ET condition will be transdermal nicotine (21mg*) for 24 weeks as done in our ongoing efficacy trial (Schnoll et al., 2008). Since this is an effectiveness clinical trial, placebo patches will not be provided to ET participants for the remaining 28 weeks.

Maintenance Treatment (MT). The MT condition will be transdermal nicotine (21mg*) for 52 weeks. This treatment arm will represent participants maintained on active treatment for the duration of the

study, like maintenance treatment is defined in clinical trials of methadone maintenance (Ward et al., 1999).

* 14mg and/or 7mg nicotine patches will be provided to participants for whom the 21mg patch is too strong and who exhibit signs of nicotine overdose. All other study procedures will remain standard.

Mid-treatment Assessments. After the baseline assessment at Week -2, assessments will be conducted during the clinical trial at Weeks 0, 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, and 52. All assessments will be conducted over the telephone prior to the counseling session (At weeks 8, 24, 36, and 52 all participants will return in-person for medical screening. A urine pregnancy test will be repeated at weeks 8, 24, 36, and 52.) These assessments will require only about 15 minutes to complete. Assessments include measures of mediating variables (e.g., withdrawal, affect), treatment side-effects, adherence to patch use, and costs and smoking behavior. Conducting repeated assessments over the course of the trial will allow for the systematic evaluation of mechanisms of treatment effect and study outcomes (including costs and smoking behavior), and permit close monitoring of participant safety.

Outcome Assessments. The primary outcome variable is 7-day point prevalence abstinence at Week 52, biochemically-confirmed with CO. Other outcomes include: cost and lapse and recovery data (collected throughout the trial), and 7-day point-prevalence abstinence (biochemically-confirmed) at Week 8 (after the end of standard treatment) and Week 24 (after the end of extended treatment). All data will be collected by telephone by a trained and experienced Research Assistant. Participants reporting abstinence for the 7-days prior to Week 8, Week 24, and Week 52 will be asked to attend the respective clinic to provide a CO sample. Costs for transportation and financial incentives will be covered to increase compliance with this requested visit.

Table 4. Measures/Events

Week	-2	0	4	8	12	16	20	24	30	36	42	48	52
Session Name	Pre-Quit	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12
TREATMENT													
Standard Transdermal Nicotine		X	X	X									
Extended Transdermal Nicotine		X	X	X	X	X	X	X					
Maintenance Transdermal Nicotine		X	X	X	X	X	X	X	X	X	X	X	X
Counseling	X	X	X	X	X	X	X	X	X	X	X	X	
SCREENING/COVARIATES													
Demographics	X												
Smoking history/FTND/Stage of Change/WI-PREPARE/SIMS	X												
Spiritual Well-Being Scale	X												
MINI Psychiatric Interview	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
Reasons for Smoking	X												
Medical history (Physical, ECG, Urine Pregnancy)	X			X				X		X			X
Depression (IDS)	X	X*	X**	X**									
		*	*	*	*	*	*	*	*	*	*		
Nicotine/Cotinine (saliva)	X												
Genes related to nicotine dependence (saliva)	X												
MEDIATING VARIABLES													
Withdrawal (MNWS)	X	X	X	X	X	X	X	X	X	X	X	X	X
Positive and negative affect (PANAS)	X	X	X	X	X	X	X	X	X	X	X	X	X
Smoking urges/craving (QSU-Brief)	X	X	X	X	X	X	X	X	X	X	X	X	X
Anxiety (BAI)	X	X*	X**	X**									
		*	*	*	*	*	*	*	*	*	*		
Alternative Reinforcers (PES)	X	X	X	X	X	X	X	X	X	X	X	X	X
Hedonic Capacity (SHAPS)	X												
Reproductive Cycle (women only)	X							X					
TREATMENT VARIABLES													

Adherence/Usage			X	X	X	X	X	X	X	X	X	X	X
Side effects	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X	X	X
OUTCOMES													
Cessation/smoking rate (CO@ wk 8, 24, 36, 52)	X	X	X	X	X	X	X	X	X	X	X	X	X
Costs		X	X	X	X	X	X	X	X	X	X	X	X

*The MINI modules for substance abuse, alcohol abuse, depressive, suicidality, mania, anxiety, and psychotic disorders will be administered at Week -2. For subsequent weeks, the MINI modules for substance and alcohol abuse, depressive and anxiety disorders will be administered.

** The MINI for anxiety and depression will be administered at all sessions regardless of BAI and IDS scores. Participants meeting diagnostic criteria for anxiety and/or depression related disorders (as defined by MINI criteria) will be provided with a referral for medical help.

Weeks 8, 24, 36, and 52 will be in-person visits to assess safety (vitals, ECG, etc.). Participants who become pregnant during the trial will be followed until birth to determine if any adverse events occur.

Measures (See Table 4)

Screening/Covariates.

Demographics and Smoking History Assessment. Standard surveys will collect: demographics (e.g., age, gender, ethnicity, sexual orientation) and smoking history (e.g., age at initiation, prior abstinence periods, past use of nicotine treatments, current rate). The Fagerstrom Test for Nicotine Dependence (FTND) will be administered; this is a 6-item measure of nicotine dependence (Heatherton et al., 1991) which has good internal consistency (Cronbach's alpha = .64) and high test-retest reliability ($r=.88$; Heatherton et al., 1991). The participant's stage of change regarding smoking cessation will be assessed by Prochaska et al.'s (1992) stage of change scheme: precontemplation (i.e., not considering quitting in the next 6 months), contemplation (i.e., considering quitting in the next 6 months), preparation (i.e., considering quitting in the next 30 days), action (i.e., quit smoking for < 6 months), or maintenance (i.e., quit smoking for > 6 months). Participants will not be required to be at a particular stage; we expect most will be in contemplation or preparation and some will be in precontemplation. Selected questions from the Wisconsin Predicting Patient's Relapse (WI-PREPARE) measure will be administered to test for participant's relapse risk. This new scale may be effective for predicting both short and long term relapse among smokers who want to quit (Bolt et al., 2009). The Subjective Importance of Smoking (SIMS) is a new 17-item measure designed to assess the centrality of cigarettes and smoking to the smoker's identity, the role of cigarettes and smoking as a soother in potentially stressful situations, and the smoker's discomfort when surrounded by non-smokers.

Spiritual Well-Being. This 20-item scale (Paloutzian & Ellison, 1982) is a general indicator of perceived well-being which includes a person's relationship with what they understand to be their spiritual being and their sense of satisfaction with life or purpose in life. This measure will be used to explore spiritual well-being as a predictor of smoking cessation.

Medical History. All medical conditions related to risk for reactions to nicotine patch will be assessed. An ECG will be conducted. A urine pregnancy test will be done. Vital signs (blood pressure, pulse and respiratory rate) will be collected. Additionally current and lifetime prevalence of Axis I psychiatric diagnoses will be determined using the MINI (MINI International Neuropsychiatric Interview) (Sheehan, Lecrubier et al. 1998). This psychiatric evaluation tool will be administered by trained research technicians, and subjects who meet criteria for psychosis, mania, and/or suicidality will be excluded. Furthermore, for the duration of the trial, subjects will complete an assessment of depression symptoms (Inventory of Depression Symptoms) and anxiety (Beck Anxiety Inventory) as well as the corresponding MINI module at each study session. If subjects meet criteria for a clinical diagnosis of depression and/or anxiety during the trial, they will be referred for medical help. Substance abuse and alcohol abuse will also be measured using the MINI at Weeks -2 through Week 52.

Blood Pressure: Participants will receive regular blood pressure monitoring at the Eligibility Visit, and at the Week 8, 24, 36, and 52 CO visits. Participants who present at the Eligibility Visit with a blood pressure reading greater than 160/100 will be excluded. Participants who present at the Week 8, 24, 36, and 52 visits with a blood pressure reading greater than 160/100 will only be able to continue in the study after clearance from the study physician.

Depression Symptoms. The 30-item Inventory of Depression Symptomatology (IDS) will be used to assess participant's self-reported depressive symptomatology at all study visits (Rush et al. 1986, 1996). This scale has demonstrated validity in non-clinical populations. The IDS assesses all the criterion symptom domains designated by the American Psychiatry Association Diagnostic and Statistical Manual of Mental Disorders - 4th edition (DSM-IV) (APA 1994) to diagnose a major depressive episode.

Nicotine Metabolic Rate (3-HC/cotinine ratio) and Genes related to Nicotine Dependence. A baseline saliva sample will be analyzed for cotinine (and metabolites) to determine rate of nicotine metabolism. Nicotine is metabolized to cotinine and then to 3-HC by the P450 (CYP) 2A6 enzyme

(Nakajima et al., 1996). The 3-HC/cotinine ratio is a stable measure of the rate of nicotine metabolism, which influences response to nicotine dependence treatments (Lerman et al., 2006; Patterson, Schnoll et al., 2008). In addition, all participants will provide about 5ml of saliva for exploratory genetic analysis. Genetic polymorphisms in nicotine metabolizing enzymes (CYP2A6) and in drug targets (CHRNA4, CHRNB2, etc.) will be explored for associations with therapeutic response to treatment. These analyses will be exploratory.

Mediating Variables.

Withdrawal Symptoms. The Minnesota Nicotine Withdrawal Scale will measure withdrawal symptoms associated with quitting smoking (Hughes et al., 1984). The scale assesses 7 DSM-IV items of nicotine withdrawal (e.g., restlessness, irritability). Participants will rate the intensity of their symptoms on the following scale: 0 = not present, 1 = mild, 2 = moderate, 3 = severe, and a summary score will be calculated.

Positive and Negative Affect. The Positive and Negative Affect Schedule (PANAS; Watson et al., 1988), a 20-item Likert-format self-report measure, will assess Positive Affect (PA; 10 items, e.g., enthusiastic) and Negative Affect (NA; 10 items, e.g., distressed), two orthogonal dimensions of affect. The strength of the PANAS for this study is the inclusion of a dimension of PA, which may be related to the neurobiological reward system of smoking. The PA and NA subscales are internally consistent in both college and psychiatric samples (coefficient alphas = .84 to .91), and they exhibit good convergent and discriminant validity (Watson et al., 1988). PA and NA (with a one-week frame of reference) will be assessed at pre-treatment and during the trial.

Smoking Urges/Craving. The 10-item brief Questionnaire of Smoking Urges (QSU; Cox et al., 2001) will assess craving for cigarettes. The QSU contains 2 subscales (anticipation of reward, relief from negative affect). Craving has been related to long-term cessation in many, but not all, trials (Killen et al., 1997).

Alternative Reinforcers. The 320-item Pleasant Events Schedule (PES) [270, 271] was adapted to measure alternative reinforcers. To reduce response burden, items were collapsed into content classes. Items such as art work and photography were collapsed into arts and hobbies. This resulted in 45 items, which were similar to reinforcers generated by responses from young adults [238]. The cross product score of frequency (0=none to 3=often) and enjoyability (0=none to 3=very) for each item provides a measure of reinforcement from the activity. Individuals will not provide ratings for activities that have not engaged in over the past 30 days. This measure has been used to assess rewarding events in substance abusers and substance use has been shown to predict a low frequency of pleasant events [87, 88]. Lower PES scores have been associated with depression [270-272].

Anxiety. The 21-item Beck Anxiety Inventory asks respondents to rate how much he or she has been bothered by each symptom over the past week on a 4-point scale ranging from 0 to 3. Items are summed to obtain a total score that can range from 0 to 63.

Hedonic capacity. We will assess hedonic capacity with the 14-item Snaith-Hamilton Pleasure Scale (SHAPS). The SHAPS has excellent psychometric properties in clinical and non-clinical samples (1-3).

Reproductive Cycle. We will assess how mood mediates smoking relapse by collecting data on reproductive cycle and mood. Two measures, the Reproductive Status Questionnaire and the Daily Record Severity of Problems, will be administered to women at eligibility/pre-quit and at Week 24.

Treatment Covariates.

Compliance/Usage. Self-reported use of the nicotine patch will be assessed prior to each session as the proportion of recommended patches used (Lerman et al., 2004). In addition, we will provide

participants with stamped, self-addressed envelopes to return unused patches. Level of compliance will be compared across treatment arms. Also, within treatment arms, we can correlate nicotine patch use with smoking outcomes. Lastly, we will ask participants at each time-point about use of medications that may affect smoking behavior (e.g., varenicline).

Side Effects. A measure of side effects created and used in our past and ongoing NRT studies (Lerman, Wileyto et al., 2004) combines items from measures used in trials of transdermal nicotine (Hurt et al., 1993). It assesses the frequency of side effects (e.g., nausea, rash). As in past studies, symptom severity (past 7 days) will be rated by subjects from 0 (none) to 4 (severe). Side effects can be considered as a covariate in analyses as the overall frequency and/or presence of side effects as well as an outcome variable for Aim 1.

Concomitant Medication Review. Participants will be asked at study visits 1-12 to report if they have taken any new medications (prescription or non-prescription). They will also be asked to report if they have used or are currently using any other forms of smoking cessation treatment.

Outcomes Variables.

Abstinence (primary outcome). Smoking status will be assessed and biochemically verified. A standard timeline follow-back method (Brown et al., 1998) will be used, as we have done previously (Lerman, Kaufmann et al., 2004). Participants who report complete abstinence (not even a puff of a cigarette) for at least the 7 days prior to the assessment at weeks 8, 24, and 52 will be asked to complete an in-person visit for biochemical verification of abstinence (see below). The primary outcome will be biochemically verified 7-day point prevalence at 52 weeks. As per convention, participants are assumed to be smoking if they self-report to be smoking at week 52, cannot be reached to provide data at week 52, fail to provide a CO sample at week 52, or provide a CO sample at week 52 that is > 10ppm (SRNT Subcommittee on Biochemical Verification, 2002). Additional outcomes include biochemically confirmed 7-day point prevalence abstinence at weeks 8 and 24, continuous abstinence (from target quit day to weeks 8, 24, and 52), and prolonged abstinence with relapse defined as 7 consecutive days of smoking, also biochemically verified, allowing for a grace period (Hughes et al., 2003). We provide financial incentives to complete assessments, including in-person assessments. In our ongoing efficacy trial, our current rates of completion for week 24 and week 52 are 88% and 86%, respectively. Thus, only a small fraction of participants are expected to fail to provide biochemical verification of smoking status. To prevent a reduction in compliance from an effectiveness trial, we will increase incentives to the participant. Lastly, as described below, we will evaluate the study data using intent-to-treat (missing outcome data = smokers), completers-only, and other missing data modeling approaches.

Biochemical Verification. Self-reports of smoking cessation during treatment and at the end of the treatment phase will be verified using carbon monoxide (CO) with a cutoff of 10ppm. Subjects reporting abstinence, but exhibiting CO levels above threshold, will be treated as smokers in the analysis (SRNT, 2002).

Smoking Behaviors. As in our published research (Lerman, Kaufmann et al., 2004), timeline follow-back data will 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 be used to address study aims pertaining to lapse and recovery events (e.g., Wileyto et al., 2005) and to compute secondary measures of smoking cessation (e.g., prolonged abstinence).

Costs. Costs will be estimated by multiplying the counts of medical resources used by the unit costs of those resources. This is called the resource costing method which is one of the most useful means for estimating patient-level costs (Brown, 1998; Gold, 1996; Glick, 1995; Drummond, 1991). The objective of the cost variable is to summarize the health care services used from the perspective of society. It is not simply to summarize the costs of the protocol. The direct costs of treatment involve the use of the patch and counseling. When these services are used within the treatment protocol they are logged. An

assessment of non-study medical services will provide the detailed accounting of non-study service use necessary to estimate patch and counseling use (and other costs) outside of the study. We will also assess the use of any pharmacotherapy for smoking cessation used outside the study. The unit costs of the nicotine patch and other pharmacotherapies will be collected from wholesale prices and the unit cost of counseling will be derived from the study budget and from a DATCAP assessment (www.datcap.com/program.htm). A complete cost assessment also includes medical costs potentially indirectly associated with treatment and smoking (French et al., 1996). Medical resources that are not part of the treatment are recorded on the Non-Study Medical Services (NSMS) form. The form captures non-treatment visits, and physician and hospital visits through self-report. Validity of self-reported health care use has been shown (Wallihan et al., 1999; Roberts et al., 1996; Jay et al., 1994; Harlow & Linet, 1989). This form was designed by Dr. Polsky for his ongoing study of opioid dependence treatments. Unit costs for these resources will come from reimbursement rates provided by the Center for Medicare and Medicaid Services. Lastly, we will also assess the indirect cost of productivity loss through lost wages due to time devoted to treatment and lost days of work from illness. These costs will be captured by the outpatient client DATCAP developed by Dr. French (<http://www.datcap.com/client.htm>).

Retention and Compliance. Both sites have extensive experience with retaining study participants in clinical trials and maintaining compliance with study protocols. First, in terms of retention of study participants, in our efficacy trial of extended transdermal nicotine, less than 10% of participants withdrew from the study. Further, our rates of assessment completion were: week 8 = 74%; week 24 = 88%; and week 52 = 86%. Week 8 completion rate was lower since all participants were required to attend in person. For the Northwestern University fluoxetine trial, 31% of participants withdrew from the trial; this rate is higher than we expect in the proposed study, since this trial included intensive in-person group therapy and 10% of withdrawals were due to drug side-effects. The assessment completion rate approached 67%, which compares favorably to large smoking cessation randomized trials (e.g., Jorenby et al., 1999; Gonzales et al., 2006). Second, in terms of compliance with nicotine patches in the efficacy trial, the rates of patch adherence (i.e., wearing the patch at least 6 out of 7 days every week) among abstainers at weeks 8, 16, and 20 were 85%, 58%, and 61% for the 8-week treatment arm, and 91%, 86%, and 75% for the 24-week treatment arm. These rates are based on a conservative definition of adherence and exceed previous reports (Alterman et al., 1999). In the fluoxetine trial, 81% of placebo subjects and 78% of fluoxetine subjects were adherent to treatment (Spring et al., 2007).

To ensure a high level of retention and compliance in this trial we will: 1) educate subjects about the benefits of complying with the protocol; 2) use phone counseling and assessments and require only abstinent subjects at weeks 8, 24, and 52 to attend clinic; 3) schedule in-person sessions at times convenient for the subject, including evening and weekends; 4) maintain close contact to meet subjects' needs; and 5) as is standard practice in smoking cessation trials (Hall et al., 2004; Niaura et al., 2005), provide financial incentives for completion of sessions. Incentives will be increased to prevent lower compliance and retention that may occur in effectiveness vs. efficacy trials. In our ongoing NRT effectiveness trial (ACS RSGPB-05-240-01-CPPB), use of incentives for participation (distributed by mail) has yielded an 85% retention rate. Given the favorable side effect profile for transdermal nicotine and the completion of follow-ups for smokers by phone, we project that <20% of participants will withdraw from the trial and >80% of participants will complete follow-up evaluations, which will exceed rates in varenicline trials (Jorenby et al., 2006; Gonzales et al., 2006). As is advised in smoking cessation clinical trials (Hughes et al., 2003), we use intent-to-treat for primary analyses, which assumes that missing outcome data are coded as smokers; other analytic methods will be used also to address missing data (see below).

2. Statistical Analysis

Data Analysis. Dr. Wileyto will oversee all data analysis except for cost-effectiveness analysis, which will be conducted by Dr. Polsky. Preliminary analyses of demographics and potential covariates using chi-square or individual logistic regression analyses will be carried out to determine whether individual variables are related to quit rates (e.g., gender, dependence, depression). On a preliminary basis, variables demonstrating significant relationships to quit rates will be included in regression models. In this way, it will be possible to test for the effect of treatment and interactions after accounting for the contributions of

covariates. We will also assess differences in attrition across treatment arms and compare individuals who enroll in the trial, vs. those who decline; factors associated with attrition will be treated as covariates in analyses. Further, compliance measures will be evaluated across treatment arms, and controlled for in primary analyses (including rate of nicotine patch use per week and use of nicotine patch beyond treatment period).

Aim 1: Assess the effectiveness of maintenance therapy with transdermal nicotine (52-weeks) vs. standard (8-weeks) and extended (24-weeks) therapy for increasing biochemically confirmed 7-day point prevalence quit rates. The hypothesized effect of treatment arm (i.e., the difference in quit rates between subjects receiving standard or enhanced vs. maintenance treatment) will be tested by a treatment arm term in a logistic regression model that includes terms for possible covariates (e.g., age, gender, nicotine dependence, compliance). 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 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 8 and 24). In addition, as many participants will fail to become completely abstinent, multiple regression analyses and multivariate repeated measure analyses will be used to examine the main effects of treatment arm on changes in smoking rate. Models will be assessed for various measures of abstinence including point prevalence, continuous, and prolonged abstinence as well.

Aim 2: Assess longitudinal patterns of smoking lapses and recovery to abstinence in standard, extended, and maintenance therapy. To investigate whether the effect of maintenance treatment on relapse is attributable to promoting recovery from a lapse we will use Cox regression to analyze recurrent-event data (Wileyto et al., 2005). These processes have been shown to be asymmetric, such that factors promoting lapse are not the same as those promoting recovery (Swan et al., 1987; Wileyto et al., 2005). These data will be extracted from our time-line follow-back data on smoking behavior and summed as transitions between runs of abstinent days and runs of days that include smoking. Following our prior work (Schnoll et al., 2008; Wileyto et al., 2005), we will conduct separate analyses; time-to-lapse will be investigated in the cohort of subjects who are currently abstinent and time-to-recovery will be investigated in a cohort constructed from those currently smoking. Effects are reported as a rate-ratio (hazard ratio) and the interpretation is similar to that of the odds-ratio in logistic regression. Data-plans for recurrent models vary widely on details of when subjects initially find themselves at risk for the first, second, or later event, and whether each event in the sequence is treated as a subpopulation for stratification (Hosmer & Lemeshow, 1999). We have found that the representation that most consistently meets the proportional hazard assumption is Hosmer & Lemeshow's (1999) conditional A, which ensures that subjects are never at risk for different events concurrently, and stratifies on event sequence. In our past work (Schnoll et al., 2008; Wileyto et al., 2005), we have extended this data-plan to include gaps, so that a subject who has a first lapse, is not immediately at risk for a second lapse, but instead enters that risk set after the next recovery event. In addition to stratification, we will account for correlations between the lapse and recovery processes using a covariate to represent the relative time spent in each state prior to the event.

We will fit 2 separate models, one for abstinent subjects at risk for lapse events, and one for currently smoking subjects at risk for recovery events. We will use discrete time-varying covariates to estimate responses over the various phases of the protocol. The protocol is partitioned where changes occur over time, including 3 key phases: 1) extended vs. maintenance vs. standard (weeks 1-8), 2) extended and maintenance vs. no therapy (weeks 8-24), and 3) maintenance vs. no therapy (weeks 24-52). Because we will have multiple observations per subject, we will use cluster-correlated robust variance estimate (Williams, 2000; Rogers, 1993) to adjust the standard errors to reflect the correlation of observations from the same subject. Adequacy of model fit will be assessed by examining scaled and unscaled Schoenfeld residuals. Trends in the scaled residuals will determine whether the model meets the proportional hazards assumption. Where violations occur, we will model the effect using a time-dependent hazard-ratio, either discrete or continuous. We will be able to test the significance of comparisons by the appropriate construction of Wald tests after fitting. Though the use of the robust variance approach does not allow for likelihood ratio tests, Wald tests may still be conducted after fitting.

Aim 3: Evaluate the cost-effectiveness of maintenance therapy, vs. standard and extended therapy.

The cost estimates and cost differences between treatment arms will be expressed with the mean because this measure permits a budget assessment of treatment. We will use the parametric t-test. Because of the often skewed distribution of cost data, the normality assumption underlying this test may be violated. As a result, the non-parametric bootstrap will be used as a check on the robustness of the parametric t-tests. This issue is also relevant in the choice of multivariate methods for cost estimation. Regression on the logarithmic transformation of costs were earlier considered ideal. However, since the shortcomings of this approach have become known, the use of the generalized linear model has become more accepted (Manning & Mullahy, 2001; McCulloch & Nelder, 1989; Blough, 1999). Further, we will adjust for attrition using inverse-probability weights (Lin, 2000).

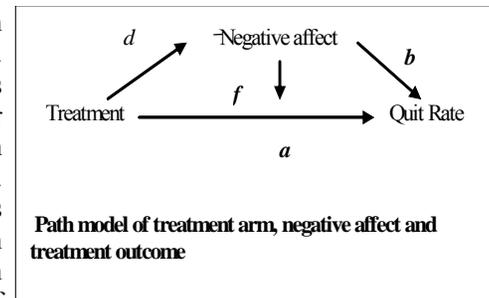
The CEA will compare the cost (i.e., the sum of all measured categories of costs, including treatment, medical and, indirect costs, independent of whether or not the categories differed between treatment arms) and effects of maintenance treatment to standard and extended treatment. If one arm is found to be more costly and more effective, there is a trade-off between the additional effectiveness and the additional costs needed to achieve those outcomes. This trade-off is represented by the incremental cost-effectiveness ratio (ICER), which in our analysis will be calculated as a ratio of the difference between mean costs in each treatment group and the difference between the cessation rates across the treatment arms at week 52. This ratio will represent the additional cost of maintenance therapy vs. standard and extended treatment to produce an additional quitter.

Hypothesis testing for an ICER involves determining whether the ICER is significantly less than the maximum acceptable ICER (ceiling ratio). Unfortunately, definitive data on the maximum willingness to pay for a quit is not known. When considering costs per life-year saved, a ceiling ratio of \$50,000 is often used, but wide bands around this number are common. Because of the poorly behaved statistical properties of the ICER as with any ratio (Glick, Briggs & Polsky, 2001), we will transform the ratio into incremental net monetary benefits (INMB) with the following transformation: $[L * E] - C$ where L =ceiling ratio, E =difference in mean effects, and C =difference in mean costs. The test of the hypothesis that the ICER is less than the ceiling ratio is equivalent to the test of the hypothesis that the INMB is > 0 . The standard error for INMB is estimated using the formula in Willan (2001) and amounts to the typical formula for standard error. The primary hypothesis is that the 12-month ICER will be cost effective if the INMB expression of 12-month ICER is > 0 at an α less than 0.05. Further, we judge the cost-effectiveness ratio as being acceptable if the confidence interval for the INMB excludes 0.

Our primary economic outcome is the cost per quit but, in secondary analysis, we will evaluate dollars per life-year saved. The advantage of the cost per quitter analysis is that all of the data come directly from the clinical trial. No extrapolation or modeling is needed. Further, the result is meaningful when comparing across treatments for nicotine dependence. Because a comparison to other medical treatments will help determine societal cost-effectiveness, we also include an evaluation of cost-effectiveness in terms of dollars per life-year saved. This secondary analysis looks at cost-effectiveness of the intervention over a time horizon of a lifetime. Because this is a relatively brief trial in a generally young and healthy population we will use a simulation-based analysis to project effects of quitting into long-term mortality and costs following the method of Heitjan et al. (2007). This projection is based on parameters that have wide ranges so we will conduct a sensitivity analysis to assess the sensitivity of our estimates of costs and cost-effectiveness to the speculative nature of some of the values that will be used in the analysis. We will consider how cost-effectiveness may change with different: 1) costs of treatment; 2) methods to handle attrition of cost data; and 3) ceiling ratios.

Secondary Aim: Assess the safety of maintenance therapy with transdermal nicotine (52-weeks) vs. standard (8-weeks) and extended (24-weeks) therapy. We will assess differences between treatment arms in adverse events and side effects from patch use. Side effects from patch use (e.g. rash, headaches, sleep problems) assessed using a checklist administered at regular time-points will be summed to form a total side effect score at each time-point and for the duration of the study. To capture the periods when symptom levels peak, analyses of side effects will focus on the first few weeks following the target quit date (weeks 2-4), but we will also have data up to week 52 to assess any long-term side effects. ANOVA will be used to compare mean levels of adverse side effects between the treatment arms. Rate of adverse events not captured by this checklist but reported by participants will also be compared across treatment arms.

Exploratory Aim 1: Explore mechanisms of treatment effects, including differences across treatment arms in terms of changes in withdrawal symptoms, nicotine craving, and negative and positive affect. The effects of treatment on the mediators of positive and negative affect, withdrawal, and craving will be assessed using linear regression analysis, as these outcomes are continuous. The primary models will include main effects for treatment arm and interaction terms. Structural equation modeling will be used to obtain a more comprehensive understanding of these mechanisms. In particular, it is hypothesized that changes in negative affect, for example, will mediate the interaction effects between treatment arm and 52-week quit rates. Our preliminary data suggest that changes in mediators during the first 2 weeks post-quit mediate the effects of treatment on quit rates. Thus, we will focus on measurements for this time-period. However, differences across treatment arms may be evident once treatment ends (i.e., weeks 8 and 24). Our assessments of mediators throughout the trial will allow us to explore treatment arm effects on trends in mediators over time and at time-points based on treatment duration. After first demonstrating that treatment condition 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 will depend on negative affect. Specific hypotheses will be tested by conducting 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 also be compared to guide the interpretation of results and determine the practical significance of any statistically significant differences. Modification indices will be examined to guide model interpretation and modification. These models will be implemented through the Mplus data analysis package, which easily accommodates the combination of binary and continuous variables required. This analytic approach allows us, at least in principle, to test whether treatment effects on quitting are due to other mechanisms (e.g., reduction in negative affect). Tests for mediation by withdrawal and craving may also be conducted in this fashion.



Exploratory Aim 2: Explore individual difference factors that influence response to standard vs. extended vs. maintenance therapy to identify those most vs. least likely to benefit from maintenance therapy for nicotine dependence. We will assess the effects of subject variables as moderators of treatment arm effects. The significance of subject variables can be evaluated by fitting logistic regression models relating quit rates to treatment and relevant covariates. The likelihood ratio test can determine whether including nicotine metabolic rate or other subject variables in the model contributes significantly to model fit. Evaluating the effect of maintenance treatment on outcome by slow vs. fast metabolizers of nicotine, for example, is essentially doing a subgroup analysis of the interaction effect separately by metabolic rate status. To test the significance of a moderating influence of subject variables, two-way interaction terms (e.g., treatment x nicotine metabolic rate) can be added sequentially in successive steps in a hierarchical logistic regression model. The results of analyses of genetic variability will also be used to explore individual differences related to treatment response.

Missing Data. The most valuable way to deal with missing data is to avoid the problem in the first place by keeping subjects connected to the trial and motivated to complete measures. In our efficacy trial, compliance and retention rates were > 86% thanks to our monitoring of participants and use of incentives. We will continue to apply and improve these methods in this effectiveness trial. But, if there is a substantial fraction of missing data, we will deploy the best available statistical methods. Primary analyses will assume that all subjects for whom smoking outcome data are unavailable are current smokers (intent-to-treat). This assumption, which is conventional in smoking cessation research, attenuates the differences between treatment arms in quit rates, making it conservative. Nevertheless, there are scenarios (e.g., the quit rate is higher among the dropouts than the completers on ST and the reverse in MT) where this method might exaggerate a treatment effect. Most dropout with respect to smoking status will occur during treatment, and it will be monotonic because the majority of subjects who miss a visit will not be regained. Hence, other options for dealing with missing data include a “completers-only” analysis, which assumes “missing completely at random” in that the missingness is assumed to be independent of the outcomes and covariates (Little & Rubin, 2002). “Last observation carried forward” assumes that no distant treatment effects or relapses occur in the not-fully-observed subjects. We can analyze our data using these methods as well. However, we will also consider alternative approaches that make less restrictive assumptions, including the “missing at random” (MAR) and the “not missing at random” (NMAR) approaches. MAR assumes that missingness is not affected by the value of the potentially missing outcome variable, conditional on the observed data; NMAR assumes that missingness may be related to the missing variable. A practical MAR-based approach is the multiple imputation method of Little & Yau (1996) that imputes unobserved smoking status based on treatment, observed subject covariates, and observed smoking history. We will also consider selection models, which factor the joint distribution of the data and missingness pattern into the marginal distribution of the data and the distribution of the missingness patterns given the data and pattern-mixture models, which make the alternative factorization into the marginal missingness pattern distribution and the conditional distribution of the data given the missingness. Selection and pattern mixture models are partially NMAR and thus make the least restrictive assumptions about missing data. However, they require assumptions on relations between missing and observed data, as the models are not identifiable from the data, and these assumptions are not testable from the observed data. Consequently, different versions of the models will be implemented, and the approaches will be compared in a sensitivity analysis. The analyses will provide information on the plausibility of the assumptions and on the influence of missing data on parameters for the analyses related to the aims. Another approach to evaluating the quality of inferences from incomplete data is to assess their sensitivity to assumptions of nonignorable (NMAR) dropout. We will apply methods developed by Troxel et al. (2004) and Ma et al. (2005) to evaluate these assumptions.

3. Confidentiality

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*): _____

To protect confidentiality, a numeric coding system will be used to represent participants and information linking the numeric code to the subject's name will be kept in a secured file cabinet and office, accessible only by senior study personnel. In addition, computer data files will be stored on password-protected computers and communication among the staff will use participant code numbers, not names. Electronic transfer of data will not include participant names. No data will be presented that includes participant identifying information. No information concerning biological data will be presented with participant names and all facilities processing biosamples will utilize standard protections for participant confidentiality, including a numeric coding system for sample identification. Both sites have secure data management facilities to protect against breach of confidentiality. Data will be stored for 7 years and de-identified data may be shared with other investigators. Audio and video tapes will be destroyed at the end of the study. Data will not become part of the participant's permanent record.

4. Subject Privacy/Protected Health Information

No data will be collected without the participant's written informed consent. Each participant will have the study objectives and the type of data to be collected in this trial clearly explained to them before the study initiation. Data will only be disclosed to entities which we are required to disclose information to (e.g., PENN and Northwestern IRB, NIH). The following protected health information will be collected as part of this trial:

- Name
- Street address, city, zip code
- All elements of dates (except year) for dates directly related to an individual and all ages over 89
- Telephone numbers
- Electronic mail addresses
- Full face photographic images and any comparable images

All data will be stored in locked file cabinets and password protected electronic databases. A database manager at UPENN will be responsible for database security. The PHI listed above will not be disclosed to anyone other than those listed in Section I of this application.

5. Tissue Specimens

At baseline, a 5ml saliva sample for the computation of rate of nicotine metabolism (i.e., 3-HC/cotinine). All saliva samples will be sent to the laboratory of Dr. Neal Benowitz at UCSF for cotinine and nicotine assays. A second 5ml sample of saliva will be maintained for exploratory analyses (e.g., assessment of additional genetic predictors of treatment response).

Also at baseline and at weeks 8, 24, 36 and 52, women who are able to become pregnant will be required to provide a urine sample to ensure that they are not currently pregnant before enrollment. Samples will not be stored for future use.

6. Genetic Testing

We will assess a phenotypic marker of genetic variability in nicotine metabolism rate. Specifically, a baseline saliva sample will be analyzed for plasma cotinine (and metabolites) using liquid chromatography with tandem mass spectrometry to determine rate of nicotine metabolism. Nicotine is metabolized to cotinine and then to 3-HC by the P450 (CYP) 2A6 enzyme (Nakajima et al., 1996). The 3-HC/cotinine ratio is a stable measure of the rate of nicotine metabolism, which influences response to nicotine dependence treatments (Lerman et al., 2006; Schnoll et al., 2008; Patterson, Schnoll et al., 2008). We will determine the role of this phenotypic marker as a predictor of treatment response. In addition, we will explore variability in treatment response and smoking behavior attributable to variation in genetic polymorphisms in nicotine metabolizing enzymes (CYP2A6) and in drug targets (CHRNA4, CHRNA2, etc.). These analyses are exploratory. Samples will be numerically coded to protect confidentiality. The results of testing will not be reported to participants or unauthorized parties and will not be considered part of the subject's official medical record.

RISK/BENEFIT ASSESSMENT

1. Potential Study Risks

The potential risks to participants, and their likelihood and seriousness, are described below. Participants can choose, as an alternative, to not enroll in this study. Overall, there is minimal risk for serious adverse reactions as a consequence of enrolling in this study. Adverse reactions will be assessed and reported as required by Federal law and the IRBs.

Assessment: Subjects may experience emotional distress during assessments from discussing feelings and attitudes about smoking or from learning about the risks from smoking. These events happen very rarely and in almost all cases are short-lived and of low intensity, lasting for 1-2 weeks. Study personnel will be alerted to expect this from a small number of subjects and will be trained to make referrals for mental health services as needed. Personnel will be trained to query for adverse emotional reactions during assessments and will be trained to deal with such reactions and to provide additional referrals if needed. In addition, if assessments indicate psychiatric concerns, referrals to appropriate psychological services will be provided.

Biological Sample Collection: Patients may experience mild discomfort from providing 5ml saliva samples. All samples will be collected by a trained member of the research team or by a member of the healthcare team at the clinical site.

Nicotine Replacement Therapy: Nausea, vomiting, weakness, diarrhea, dizziness, and rapid heart beat/increased blood pressure occur rarely and are most often caused by continuing to smoke while using the patch. If these reactions occur, and the participant is currently smoking and using the patch (i.e., the participant has lapsed but still is wearing the patch), participants will be counseled to reestablish a target quit day and gradually reduce their smoking rate. Participants will not be instructed to discontinue their patches if they have lapsed unless a serious adverse event has occurred, since several lines of research

indicate that: 1) continuing patch use even when a lapse to smoking has occurred can increase the probability that recovery to abstinence will occur (Schnoll et al., 2010); 2) high doses of nicotine, including 63mg doses, do not lead to serious adverse events even with concurrent smoking (Zevin et al., 1998); and 3) patch use prior to a designated target quit day and with concurrent smoking does not lead to serious adverse events and can increase the chances for successful cessation (Rose et al., 2009). Indeed, such findings have led to a general reconceptualization of the issue of concurrent tobacco and nicotine patch use in which smokers are now advised to continue nicotine patch use even if they have lapsed following a target quit day (see Kozlowski et al., 2007). The risk of adverse response to the patch will be minimized by admitting subjects to the study only if they do not have preexisting conditions that increase the risk for these reactions (i.e., serious heart disease). Some individuals who use the patch experience minor skin irritation, such as redness, rash, or minor swelling, and insomnia and dream abnormalities. Insomnia and dream abnormalities can be resolved by removing the patch during the night while sleeping. All of these reactions cease once the patch is removed.

Reproductive Risks: Because NRT safety for an unborn baby is unknown, participants will be told that they should not become pregnant while on this study. Women on the study should not nurse a baby. If the woman is of childbearing potential, she must use an adequate form of contraception for at least one month prior to the study, while NRT is being taken, and for at least one month after the end of the trial. If the woman is pregnant or breast feeding, she may not participate in this study, and if she becomes pregnant during the study, she will be asked to discontinue use of the study medication. She will have the option to continue with counseling and completion of study questionnaires. She will be followed until pregnancy outcome to collect information regarding adverse events and complications during pregnancy, as well as, birth outcome. If the pregnancy results in live birth, general health outcomes will be collected pertaining to the child for a period of up to two weeks. Women will be asked to submit to a pregnancy test to make sure that she is not pregnant before starting the study.

Withdrawal Syndrome: Many individuals who quit smoking exhibit a pattern of symptoms related to withdrawal from tobacco use. These symptoms include: sadness and anxiety, irritability, anger, difficulty concentrating, appetite change and weight gain, insomnia, and decreased heart rate. Eliminating the risk for these would not be possible, although in most cases these events are short-lived and have low intensity, lasting for 2-4 weeks. The study personnel will be trained to recognize these symptoms and educate the participants about them (e.g., their duration, methods for reducing them). Use of the patch will minimize the severity of withdrawal.

Threats to Privacy/Confidentiality: Since self-report and biological data will be collected and stored as part of this study, it is possible that subject privacy or confidentiality can be threatened. Study sites have sophisticated computer systems to prevent the unauthorized access to study data and 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 web-based data collection procedure will minimize the possibility of loss of privacy or confidentiality.

2. Potential Study Benefits

Participants who enroll in this trial will benefit from the knowledge that they are contributing in an important way to potentially furthering scientific knowledge concerning ways to improve treatment for smokers. All smokers will receive behavioral counseling and transdermal patch to quit smoking. The proposed study aims to provide data critical to establishing the benefits of maintenance therapy with transdermal nicotine. This study may replicate and extend existing efficacy data to an effectiveness trial setting and demonstrate the benefits of maintenance therapy for nicotine dependence in the same way that clinical trials with methadone maintenance demonstrated the efficacy of maintenance treatment for opiate dependence. Together, these studies would provide data critical to the re-evaluation of maintenance therapy for nicotine dependence as part of future PHS guideline preparation. Further, the results of this study, coupled with the efficacy findings, may form the basis to establish transdermal nicotine as a maintenance therapy for nicotine dependence.

3. Alternatives to Participation

Participants can choose to continue smoking or to quit on their own or through other mechanisms such as state quit-lines.

4. Data and Safety Monitoring

For this study, we will use standard UPENN and Northwestern procedures and infrastructure for data and safety monitoring. We will not use a protocol-specific Data Safety Monitoring Board since the NRT to be tested is over-the-counter and there is minimal risk in taking this NRT. The side effects are known and of a mild nature and, thus, the UPENN and Northwestern IRBs are adequate to ensure participant safety. The specific elements of our plan are as follows: 1) All project staff will complete certification in the protection of research participants; and 2) the protocol will be submitted for review to the IRBs of each site. All procedures and policies outlined by the IRBs will be followed for this study. Investigators at each site will supply their designate IRB with ongoing progress reports for the study and a formal review of each study will be conducted at least every 364 days or more frequently as designated by the IRB. The IRB may suspend, terminate or restrict the study as appropriate. Each participating investigator will complete certification in the protection of research participants. Finally, Dr. Schnoll, along with Ms. Ware, will manage the flow of documents to participating sites and external agencies to facilitate ongoing and timely review of the protocol. Ms. Ware will oversee data security. The IRBs will audit the study if needed and will review all data on a regular basis or at a rate dependent on accrual or at least every 12 months. All serious adverse events (SAEs) will be reviewed on a real time basis first by the study site Principal Investigators and then by a study physician, Dr. Frank Leone. An existing protocol for adverse event reporting and forms for adverse event reporting will be used. There are no stopping rules established for this trial and there is no study blind.

As for stopping rules, any report of a severe adverse event related to study medication (e.g., skin redness, rash, or itchiness, palpitations or rapid heart beat, dizziness, weakness, or light headedness, nausea or vomiting, or any additional symptom of nicotine overdose will be reviewed in real-time with the study physician who will determine the course of action. The study physician may advise to stop medication until the symptom abates and re-start. If the symptom reappears, the participant can opt to leave the study or continue with counseling and assessments.

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 (Study Physician)
- Safety monitoring committee
- Data and safety monitoring board

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 Data Management System at the UPENN TURC, will oversee DMS responsibilities for this trial. As done for our ongoing efficacy trial and previous multi-site clinical trials directed by the UPENN TURC (Schnoll et al., in press), ORACLE and MS ACCESS will be used to permit real-time data entry, storage, and quality assurance, via web-based remote access. We have more than 10 years of experience developing and utilizing such DMSs for multi-site smoking cessation clinical trials. This system will be established at the PENN TTURC and distributed to the Northwestern site. A protocol for determining adverse events will be used based on the severity of the event and whether it is expected or not expected. The study physician will review all severe adverse events within 24 hours. The PIs at each site will be responsible for reporting the adverse event to both IRBs. All protocol modifications will be made at both sites. No formal interim analysis is planned.

6. Risk/Benefit Assessment

The risks of participating in this trial are minimal. The transdermal nicotine patch yields known side effects that are mild in nature. Balanced against the possibility that the study participant may quit smoking and the society may learn about the benefits of maintenance therapy for nicotine dependence, this study represent reasonable risks for the potential benefits.

SUBJECT COMPENSATION

As is standard practice in smoking cessation trials (Hall et al., 2004; Niaura et al., 2005), we will provide compensation for completion of sessions. Compensation will be important in this trial to prevent lower compliance and retention that may occur in effectiveness vs. efficacy trials. The compensation is not substantial enough to provide undue inducement to participate in the research. Rather, the compensation is meant to show appreciation for the completion of study measures and/or travel to the treatment site for study-related responsibilities. Below is a schedule of compensation.

There will be 12 time-points for which we will provide reimbursements. We will provide \$15.00 for each time-point for which assessments are complete. Subjects will be paid in cash following week 8 (maximum of \$45), week 24 (maximum of \$60), week 36 (maximum \$30) and week 52 (maximum of \$45). Sample size considers a 20% attrition rate. In addition, all subjects will be asked to return to the Center at weeks 8, 24, 36 and 52. We will provide an additional \$15 reimbursement to participants who complete this visit, as well as \$15 to compensate for travel expenses.

Time Point	Number of Participants (with 20% attrition)	Cost/person
Week 0	540	\$15
Week 4	530	\$15
Week 8	520	\$15
Week 12	510	\$15
Week 16	500	\$15
Week 20	490	\$15
Week 24	481	\$15
Week 30	471	\$15
Week 36	461	\$15
Week 42	451	\$15
Week 48	441	\$15
Week 52	431	\$15

INFORMED CONSENT

1. Consent Process

Following verbal consent, participants will complete an initial eligibility assessment and evaluation of study interest by phone, initially eligible participants are scheduled for an intake session at the respective site (Week -2). The initial telephone eligibility assessment allows us to reduce the likelihood that participants attend clinic only to learn that they are ineligible. In addition, the telephone eligibility assessment allows for the ascertainment of physician's clearance should the participant have a medical condition that affects safety with using transdermal nicotine (e.g., hypertension). At this intake session, participants will provide written study consent and complete study HIPAA documents before having final study eligibility ascertained with a medical history and a physical exam (including a pregnancy test for women). If eligible and willing to proceed, participants will be officially registered in the trial. Hard copies of eligibility screening data and consent/HIPAA forms will be stored in a subject's study binder. The participants will have the opportunity to read over the consent and HIPAA forms and ask questions of the Study Coordinator as needed. All participants will be competent to provide informed consent.

2. Waiver of Authorization

Not applicable.

RESOURCES NECESSARY FOR HUMAN RESEARCH PROTECTION

Experience of Members of the Study Team

Dr. Robert Schnoll (PI) is an Assistant Professor in the Department of Psychiatry and Abramson Cancer Center at UPENN where he directs a collaborative research program to evaluate treatments for tobacco dependence. Dr. Schnoll's research focuses on the study of new treatments for tobacco dependence, the examination of novel ways to use existing treatments for tobacco dependence to improve their efficacy, and the study of issues relevant to smoking cessation clinical trials. Currently, Dr. Schnoll is PI on 2 R01s and an ACS Research Scholar Grant, and is co-PI for a Pennsylvania DoH-funded grant. Dr. Schnoll has almost 10 years of experience conducting smoking cessation clinical trials, including studies with modafinil (Schnoll et al., in press), bupropion (Schnoll et al., 2008), and NRT/behavioral interventions (Schnoll et al., 2003; 2005).

Dr. Caryn Lerman (Co-I) is Mary W. Calkins Professor of Psychology in Psychiatry and the Annenberg Public Policy Center and Deputy Director of the UPENN Abramson Cancer Center. She has more than 250 peer-review publications and, in the past 10 years, has been the PI on 10 R01s, a U01 cancer genetics network, and 2 consecutive P50-supported Tobacco Use Research Centers (TURC). Dr. Lerman received the Society of Behavioral Medicine (SBM) New Investigator Award (1989), the American Psychological Association Award for Outstanding Contributions to Health Psychology (1995), the Cullen Award for Tobacco Research from the American Society of Preventive Oncology (2004), the Alton Ochsner Award for Research Relating Tobacco and Health (2007), and the American Cancer Society Cancer Control Award (2007). She served on the NCI Board of Scientific Advisors (1998-2003), the National Human Genome Research (ELSI) Evaluation and Planning Review Board (1997-2000), and co-chaired the NCI/NIH Tobacco Research Implementation Plan that generated recommendations for a national research agenda. She currently serves as a member of the National Advisory Council for Human Genome Research. Dr. Lerman has conducted numerous large, multi-site smoking cessation clinical trials (e.g., Lerman et al., 2002, 2004, 2006).

Dr. Paul Wileyto (Co-I) is a statistician with the Transdisciplinary Tobacco Use Research Center at UPENN where he collaborates with Drs. Schnoll and Lerman on several smoking cessation clinical trials. A

particular strength of Dr. Wileyto that is relevant to this study is his work concerning the examination of lapse/recovery models in smoking cessation clinical trials (Wileyto et al., 2005; 2006; Schnoll et al., 2008).

Dr. Daniel Polsky (Co-I) is an Associate Professor of Medicine and Health Care Systems at UPENN. He has a Ph.D. in Economics and has served as the Senior Economist on health issues at the President's Council of Economic Advisors. He is an internationally recognized expert in economic evaluation and cost-effectiveness analysis. His research has improved the methods of economic evaluations in clinical trials by contributing to the initiation of hypothesis testing for cost-effectiveness ratios (Polsky et al., 1997) and the estimation of costs (Polsky et al., 2001; Glick, Polsky, 1999), unit costs (Glick, 2001), tests of generalizability (Willke et al., 1998), and patient preferences (Polsky et al., 2002). He has been the PI of several R01s including one from NIAAA to study statistical methods for cost research in alcohol studies and one from NIDA to perform a comprehensive economic analysis of a clinical trial of buprenorphine/naloxone-facilitated rehabilitation for opioid dependent adolescents/young adults. He is a coauthor of the book "Economic Evaluation in Clinical Trials" recently published by Oxford University Press. He serves on the editorial board of *Pharmacoeconomics*.

Dr. Brian Hitsman (PI, Northwestern) is an Assistant Professor of Preventive Medicine at Northwestern University and a member of its Robert H. Lurie Comprehensive Cancer Center. Dr. Hitsman's research focuses on combined psychological and pharmacological treatments for smoking cessation. He has been involved in smoking treatment research since 1993. Dr. Hitsman has been involved in several large NIH-funded clinical trials of fluoxetine and bupropion combined with intensive behavioral therapy (e.g., Hitsman et al., 1999). Dr. Hitsman is well known for his evaluation of the role of depression and depressive symptoms as a predictor of smoking cessation treatment outcome (Hitsman et al., 2003). He most recently served as co-investigator and site coordinator on industry sponsored phase 3 studies of rimonabant and varenicline conducted at Brown University (Raymond Niaura, PI). Dr. Hitsman is the recipient of a NIDA Mentored Clinical Scientist Development Award. He was an invited member of the NIMH workgroup on tobacco use and cessation in psychiatric disorders, and contributor to the forthcoming Surgeon General's Report on the biology and behavioral basis for tobacco attributable disease.

Dr. Bonnie Spring (Co-I, Northwestern) is Professor of Preventive Medicine, Psychology, Psychiatry and Behavioral Sciences at Northwestern University, where she serves as Director of Behavioral Medicine and Co-Program Leader for Cancer Prevention of the Robert H. Lurie Comprehensive Cancer Center. Dr. Spring earned a Ph.D. from Harvard and the American Board of Professional Psychology's Diplomate in clinical health psychology. She is the current President of the Society for Behavioral Medicine, served on the NIH Behavioral Medicine study section, and served on advisory panels to NIH and the National Academy of Sciences. Dr. Spring's research has been funded continuously since 1976, by NIH, American Heart and American Cancer Societies, and the VA. Over the past 20 years, Dr. Spring has served as PI on R01s for multi-site smoking cessation clinical trials, including studies of concurrent vs. sequential treatment for weight and smoking (Spring et al., 2004), fluoxetine for nicotine dependence (Spring et al., 2007), and the use of physician-based smoking cessation treatment (Unrod et al., 2007). Dr. Spring has collaborated on studies of the cost-effectiveness of smoking cessation interventions (Smith et al., 2007). Her DVD on smoking cessation treatment is offered as part of the American Psychological Association's Psychotherapy Video Series, and her treatment manual for smoking cessation with weight control appears in the Oxford University Press series, *Treatments That Work*.

Sue Ware, B.S. (Database Manager) – Ms. Ware is the Database Manager of the TTURC and has coordinated databases for large clinical trials for more than 8 years. For this study, Ms. Ware will work with Dr. Schnoll to develop the data management infrastructure for this study in collaboration with Northwestern. All data will be collected via web-based applications (on a remote server at PENN but via the web from Northwestern University) and stored at the UPENN TTURC. Ms. Ware will devise the database system and handle all data transfer from Northwestern University and facilitate the preparation of datasets for report preparation and data presentation. This system will involve programming, testing, and implementation of a data tracking system as well as data storage, security, integrity, and accuracy systems.

Smoking Cessation Counselors (one for each site) – Counselors, to be selected from current counselors at the PENN TTURC or Northwestern University, will have extensive training in conducting smoking cessation clinical research. Counselors will handle all behavioral counseling sessions for participants and will conduct assessments.

Research Assistants (two for each site) – The Research Assistants (RAs) will have extensive training in conducting smoking cessation clinical research and will be selected from a pool of RAs who currently serve as Research Assistants on clinical smoking cessation trials at the PENN TTURC and Northwestern University. The primary responsibility for the RAs for this project will be to assist with overall study implementation and management (e.g., participant recruitment, eligibility screening, assessments) and to conduct all telephone screening eligibility assessments and all mid-treatment and outcome assessments.

Training

Training and quality assurance (QA) measures will be established to ensure accurate eligibility screening and recruitment, accurate data collection, entry, and management, and optimal delivery of the smoking cessation protocol, including the counseling and NRT. The Key Personnel on this project have more than 10 years of experience coordinating multi-site smoking cessation clinical trials involving extensive data collection and counseling and pharmacotherapy (Lerman et al., 2004; Schnoll et al., in press; Spring et al., 2007). Dr. Patterson, who has served as the Project Coordinator of the efficacy trial of extended transdermal nicotine treatment, will coordinate this study at PENN and lead the training of personnel at Northwestern (with Dr. Schnoll). Dr. Schnoll and Dr. Patterson will travel to Northwestern University at the outset of the study to lead (with Drs. Hitsman and Spring) a week-long training program with Northwestern personnel. Dr. Schnoll and Dr. Patterson will also conduct this training at UPENN. Dr. Schnoll and Dr. Patterson will make annual visits to Northwestern University for monitoring and re-training. Monthly conference calls will review progress, assess adherence, and determine the need for protocol changes or additional training and QA procedures.

As we do for all of our clinical trials, we will develop a manual of operating procedures (MOP) and standard operating procedures (SOP) for this trial to ensure that the trial is conducted in a uniform manner at all sites. This MOP will describe roles and responsibilities for the site coordinator, counselor, and RAs. In addition, the MOP will provide a detailed description of procedures for each point of contact with participants (i.e., for each Week listed in Table 4). For each visit/each week, a checklist of events (e.g., each measure, counseling session) will be created that will be completed by study personnel. Case Report Forms 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 will be “milestoned” (e.g., attended, missed, scheduled) to ensure proper tracking of participants through the trial. A treatment manual for counseling is developed and will be provided to the counselors. Dr. Schnoll and Dr. Patterson will provide individual training to the counselors. The counselor at PENN is already trained in this program and will assist Dr. Schnoll and Dr. Patterson with training the Northwestern counselor. Lastly, a manual for data collection and data entry will be developed for the Research Assistants at each site. As described below, we use a web-based Data Management System (DMS) for our clinical trials, which allows for real-time, remote data entry/storage. Ms. Ware, who oversees this DMS, has already prepared a data entry training manual for Research Assistants and Drs. Schnoll and Patterson will train the Research Assistants.

Training will involve didactic instruction in the MOP, counseling treatment manual, and DMS manual for site coordinators, counselors, and RAs. Dr. Schnoll, Dr. Hitsman, and Dr. Spring will coordinate these training sessions. Week-long training sessions will be conducted at both sites. Annual re-training will be provided at both sites; bi-annual training sessions can be coordinated, as well, if determined to be necessary. The training sessions will involve the review of the study manuals and several mock sessions, including phone screening, in-person eligibility screening, intake sessions, counseling sessions, and all assessments, including behavioral surveys and biological measures. Mock counseling sessions will be video-taped for review and instruction. Mock assessments for all time-points will be completed and entered into the DMS.

QA will focus on protocol adherence. For all our trials, we conduct 100% QA checks on all study data. This involves comparison of all hard copies of Case Report Forms to computer data. In addition, for the first 6 months of the trial, we will video-tape all intake sessions, which include the in-person “pre-quit” counseling session. Dr. Hitsman and Dr. Patterson will review all video-taped sessions for protocol adherence. After 6 months, a randomly-selected 25% sample of intake sessions will be video-taped and evaluated for protocol adherence. In addition, a randomly-selected 25% sample of all subsequent phone counseling sessions will be audio-taped and reviewed for adherence. These video- and audio-taped sessions will be used to determine the need for additional personnel training. Additional QA procedures are described below as part of the DMS.

Access to the Study Population

As done for our previous smoking cessation clinical trials (Schnoll et al., in press; 2008; Spring et al., 2007), we will use media ads (newspaper, radio) as the main form for recruitment. We will use media sources with large African American and Hispanic-American readership or listenership as well as media sources with young adult audiences. This method of recruitment, though expensive, has allowed our research groups to ascertain large (i.e., >500) and diverse (i.e., >30% racial/ethnic minority) study samples in our clinical trials. As a secondary form of recruitment, we will distribute posters and flyers advertising the study to medical clinics across the UPENN and Northwestern-affiliated hospitals. We will also allow participants ineligible for other smoking cessation protocols to enroll into this trial.

The UPENN TURC and the Northwestern Behavioral Medicine Program have an established record of conducting large smoking cessation clinical trials (Schnoll et al., 2008; in press; Spring et al., 2007). To demonstrate, more specifically, our ability to ascertain the proposed sample, the following data are from our efficacy trial of extended transdermal nicotine treatment (P50 CA/DA84718; PI: C. Lerman, Ph.D.). In ~55 months of recruitment for our efficacy trial, we screened 3,276 individuals; 1,970 individuals were ineligible and 617 were not interested in the trial; 689 (21%) of those screened attended the intake session. At the intake session, 9 individuals decided to withdraw from the study and 110 were determined to be ineligible for the trial. Thus, 570 individuals were randomized and considered for intent-to-treat analysis over ~55 months of recruitment (~10/month). At Northwestern University, Dr. Spring's fluoxetine study recruited smokers for ~42 months and screened 2,050 potential participants; 662 individuals did not meet eligibility criteria and 1,141 were either not interested or did not proceed to the intake session and randomization. Thus, 247 (12%) of those screened were randomized to treatment arms in ~42 months (~6/month). Taken together, these data demonstrate that the two recruitment and treatment sites are able to recruit and randomize ~16 participants per month. Given the need for staff training and study implementation (3-6 months), the follow-up for the final study participants (12 months), and the projected sample size (n = 540; see Power Calculations below), we will require ~42 months to recruit the sample. Two sites were selected for this effectiveness trial since one site alone could not accrue the large sample needed for this trial in ~42 months.

Recruitment and Treatment Sites

The proposed trial will be conducted through two large city university sites with extensive experience conducting smoking cessation clinical trials.

University of Pennsylvania Tobacco Use Research Center (TURC). The PENN TURC, which began in 1999, is an NCI/NIDA-funded center devoted to the evaluation of treatments for nicotine dependence (PI: Dr. Caryn Lerman). The TURC is part of the Department of Psychiatry at the PENN School of Medicine but it is located off-campus, in a community office building within the downtown city of Philadelphia. The TURC has been the treatment facility used to support several large clinical trials, small pilot projects, post-doctoral fellows, and core trial facilities (e.g., Lerman et al., 2004, 2006; Schnoll et al., 2008, in press). The clinical research conducted at the PENN TURC in the past 5 years alone has produced

>130 peer-reviewed publications. The UPENN TURC provides the necessary infrastructure for this trial. The TURC is housed in an office building located within the community in downtown Philadelphia. The TURC encompasses 6,500 square feet, including space for faculty and staff offices, conference rooms, clinic rooms for treatment and assessment, several small laboratory rooms for biological assessments and storage, and data storage facilities (paper and computer). The efficacy trial of extended transdermal nicotine treatment was conducted through the UPENN TURC.

Northwestern University Behavioral Medicine Program. The Northwestern University Department of Preventative Medicine is part of the university's School of Medicine and is comprised of faculty and staff devoted to teaching and research. In addition to preparing students to address disease prevention and control, improve access to and quality of health care, and better organize and finance health care services, the Department of Preventative Medicine supports leading-edge research into numerous medical conditions, including behavioral science and addictions research. The Department of Preventive Medicine is home to several nationally and internationally renowned landmark collaborative studies, including the Women's Health Initiative (WHI) and the CARDIA study. Within this Department, the Behavioral Medicine Program is a clinical and research unit that uses a multidisciplinary approach to understanding, preventing, and treating disease. Researchers with backgrounds in clinical psychology, kinesiology, nutrition, public health, nursing and medicine conduct grant-funded projects to understand the influences of psychological, socio-cultural, and biological factors on health. Behavioral Medicine faculty specialize in the development and implementation of behavioral interventions to promote health, including the evaluation of treatments for nicotine dependence. The Behavioral Medicine Program is located in downtown Chicago with convenient access to city residents. The Behavioral Medicine Program is comprised of 25,243 sq. feet of office space, including suites for faculty and administrative personnel, consulting rooms and meeting rooms for participant assessment and data collection, laboratory suites for the collection and storage of biological data, and data management and storage facilities.

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