Protocol 2014-0213

Varenicline and Combined NRT for Initial Smoking Cessation and Rescue Treatment in Smokers: A Randomized Pilot Trial

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Short Title: Varenicline and Combined NRT for Smoking Cessation

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1.0 BACKGROUND

Introduction. Smoking is a significant public health problem and is responsible for nearly 5 million premature deaths each year worldwide [1] including 443,000 in the US [2]. Although significant advances have occurred in smoking cessation therapy, an estimated 19% (43.8 million) of Americans continue to smoke [3]. Over 40% of smokers make a serious cessation attempt each year, but annually less than 3% of all smokers successfully quit [4], attesting to the addictiveness of nicotine and the chronic relapsing nature of nicotine dependence. Several approved smoking cessation medications exist, including varenicline, bupropion, and several types of nicotine replacement therapy products (NRT), each with demonstrated efficacy against placebo [5-8]. However, there is considerable heterogeneity in the treatment response both within and across treatments. In a recent treatment meta-analysis, varenicline and combination NRT (specifically the nicotine patch combined with the nicotine lozenge) showed superior abstinence rates compared to all other treatments [9]. Individual variation in response to medication suggests that “one size does not fit all” and improving our understanding of individual level predictors of treatment outcome is critical to advancement of the field.

The challenge we face in our society as a whole, is how to widely implement and disseminate effective smoking cessation and prevention strategies across the spectrum of the population. In the area of cessation, we currently have several cessation interventions that range in intensity, cost, reach and level of efficacy. These include, for example, physician advice and counseling, quit-lines, pharmacotherapies, various combinations of these elements, and novel behavioral treatments. In addition, recent research in smoking cessation has highlighted the potential for applying pharmacogenetics and novel biomarkers to personalize interventions and maximize treatment success. Our major challenge lies in knowing how to optimize cessation success for a given smoker, through selection of a treatment best suited for their particular constellation of pre-cessation characteristics. Treating everyone with a one-size fits all approach fails to capitalize on the potential to match smokers to a specific treatment based on factors observable prior to quitting, (baseline) which previous research has shown to influence treatment success. These factors may include level of dependence or motivation; presence of a psychiatric disorder (mood and/or anxiety) or alcohol/substance abuse, individual differences in reward sensitivity, and genetic profiles associated with response to pharmacotherapy. A second challenge is posed by the nature of tobacco dependence disorders - a chronic disease characterized by alternating periods of relapse and remission. Failure to appreciate the chronic nature of tobacco dependence impedes the treatment of tobacco use and clinicians’ understanding that effective treatment may require repeated quit attempts and changes in treatment strategy when cessation is not achieved.

Treatment of chronic, frequently relapsing illnesses often requires sequential decision-making to maximize the probability of subsequent treatment success, conditional upon what is known about patients and their responses to previous treatments. Interventions targeting smoking cessation and abstinence face two types of decisions: 1) choice of treatment initiation, 2) choice of subsequent treatments if initial attempts at cessation do not succeed. The majority of clinical trials, parallel-group, randomized, double-blind designs attempt to inform the first decision. They fall short in two ways: 1) Such trials identify average effects of treatment without addressing potential heterogeneity in patient response, and 2) These trials fail to address questions regarding the most efficacious treatment strategies when patients fail to benefit from their initial treatments.

In this study, we will conduct a Sequential Multiple Assignment Randomized Trial (SMART) clinical trial in which 500 smokers will be recruited from Harris County and surrounding

communities through advertisements and ongoing collaborations with Harris Health and other community systems. Identified smokers will be offered an opportunity to participate in a randomized clinical trial offering free smoking cessation counseling and medication. Unlike many smoking cessation clinical trials, we will attempt to recruit smokers who are ready to quit as well as those who are not sure or might not be quite ready to make a quit attempt, but are willing to take part in a study and participate in treatment that might change their smoking behavior. These "unmotivated" smokers, who are sometimes excluded from pharmacotherapy clinical trials, will be offered the same medication and behavioral treatment options as the smokers who are ready to quit, and will be told that they can participate in the study to learn about smoking reduction and cessation, and change their smoking behavior. This strategy will allow us to evaluate important treatment questions on a much larger, more representative group of smokers, thus increasing potential impact on the total smoking population. A handful of previous treatment studies with these smokers have reported increases in quit attempts as well as increased abstinence rates [10,11], including one study with varenicline [12]. Each participant in this study will work towards his/her own personal cessation/reduction goals with their assigned therapist during their brief counseling sessions.

SMART's constitute a class of designs that address the sequential decision-making problems that are salient for treatment-recalcitrant, chronically relapsing disorders [13]. Randomization/re-randomization of patients at pre-specified decision-points permits estimates of the posterior probability that a treatment option will result in cessation/abstinence conditional on the patient's previous response/non-response. These posterior probabilities will inform clinical treatment decisions. Randomization of participants to one of two initial, treatment conditions (Phase 1), 21 mg nicotine patch + 2 mg nicotine lozenges to be used as needed to adequately manage and prevent cravings in high risk situations (combined nicotine replacement therapy; **CNRT**), and varenicline 2 mg (2 milligram total daily dose; **VAR**) will provide estimates of abstinence at six weeks from the quit-date. Participants achieving abstinence at this point will remain on the initial treatment. Patients failing to achieve abstinence, who were initially allocated to CNRT or VAR will undergo re-randomization (Phase 2) to a) continuation of the same treatment; b) switching to the untried intervention (i.e. CNRT or VAR), or; c) augmentation of the CNRT treatment with an additional 21 mg nicotine patch (high dose nicotine patch + 2 mg nicotine lozenges to be used as needed to adequately manage and prevent cravings in high risk situations; **CNRT+**) or augmentation of the VAR treatment with an increase in dose from 2 mg (total daily dose) to 3 mg (total daily dose) (high dose varenicline; **VAR+**). This permits estimates of the probability of benefit of switching versus augmentation versus a longer trial of the patient's current treatment, after they have failed at initially achieving abstinence. This design permits assessment of the differential effects of strategies available to participants who initially fail to achieve abstinence. Simultaneously, randomization of participants permits assessment of differential responding as a function of baseline covariates. To the degree that reliable subgroup identification is possible subsequent clinical trials will attempt to enrich randomization such that participants likely to differentially benefit from a treatment at either of the two decision-points will be randomized to the more favorable treatment at rates proportional to their probability of benefit. It is likely that sample sizes in some of the resulting treatment pathways will be relatively small. This is not a reason to avoid such groups: clinically these decisions are already being made. To the degree that trial data can inform these clinical decisions they should receive attention [14]. As such Bayesian analyses will evaluate both the effect of a given treatment or treatment strategy, as well as the probability that subgroup effects exist.[15] We will use end-of-treatment (12 weeks) abstinence as the main criterion variable but will also consider symptoms of withdrawal, craving and negative affect as part of a multivariate outcome analysis, which will allow us to further distinguish potentially important outcomes (e.g., withdrawal) where *abstinence* rates are comparable across treatments. Probability of side effects and cost of treatment will also be

considered in the model where treatments confer relatively equal benefit for any given subgroup.

Two prior open label studies have shown promising results in the augmentation of varenicline treatment for smoking cessation. In both studies the dose was increased from 2 mg to 3 mg if patients **tolerated varenicline well but continued smoking.** In one study that included 73 patients who continued to smoke after 8 weeks of varenicline 2 mg (total daily dose) treatment, 4 additional weeks of varenicline 3 mg (total daily dose) treatment resulted in 40% abstinence rates. The increase in dosage was associated with adverse events in 22 patients (30%) [16], though they were mostly mild. Only 2 patients discontinued treatment due to adverse events (nausea, in both cases). More specifically, the reported events are as follows: nausea (22), abnormal dreams (17), vomiting (13), insomnia (12), and headache (7). No neuropsychiatric events were reported. A naturalistic study with an open label design conducted here at MD Anderson Cancer Center involved 88 cancer patients that received varenicline for 12 weeks. Of those, 44 patients received 2 mg/day for the whole 12 weeks and 44 got an increase to 3 mg per day (2 mg q.a.m. and 1 mg q.p.m.) between weeks 6 and 8. At the end of treatment, 4 out of the 44 patients (9%) in the 2 mg control group and 11 out of the 44 patients (25%) in the experimental group (3 mg) achieved abstinence. Patients whose medication was increased to a higher dosage (3 mg) were significantly more likely than those who continued to received 2 mg varenicline to report 7-day abstinence at week 12 ($\chi 2 = 3.94$, $p = .05$, OR = 3.33, 95% CI: 1.12 – 11.45) [17]. No increase in neuropsychiatric side effects was noted. In both cases, the results suggest that the increase in dosage was not only incrementally and statistically beneficial in achieving abstinence, but was also **well-tolerated by the participants**.

All of the commercially available forms of nicotine replacement therapy (NRT), i.e. gum, transdermal patch, nasal spray, inhaler, lozenge and sublingual tablet, are effective as part of a strategy to promote smoking cessation, enhancing long-term abstinence rates as much as 50 to 70% [18]. The 2008 US clinical practice guidelines[5] state that the long-term use of nicotine patch with another form of ad lib NRT is more effective than nicotine patch alone and recommend that physicians consider this option. Recent reports indicate that recommended changes to NRT product labeling by the FDA include a removal of the warning that consumers should not use an NRT product if they are still smoking, chewing tobacco, using snuff or any other product that contains nicotine—including another NRT. The FDA suggests to consumers, “There are no significant safety concerns associated with using more than one over-the-counter (OTC) NRT at the same time, or using an OTC NRT at the same time as another nicotine-containing product—including a cigarette” (http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm345087.htm). Studies have also found that higher doses of the nicotine patch relieves withdrawal and craving and might improve concentration [19,20]. In a recent review, the authors concluded that increasing nicotine dose in NRT products either through combination or high-dose patches should not be restricted to highly dependent smokers and that increased nicotine delivery resulted in few clinically significant adverse events [21]. Though not entirely understood, it is thought that the increased efficacy of combination NRT may be partially related to the low, but continuous level of nicotine replacement offered by the patch supplemented with episodic use of the lozenge (or gum) to deal with breakthrough withdrawal symptoms [22]. Though the high-dose patch offers a higher level of continuous nicotine replacement, it may not be sufficient to deal with episodic increases in withdrawal symptoms that might be ameliorated with lozenge use.

Innovation. The novelty of this design is that it will allow us to dynamically evaluate “rescue” pharmacotherapy interventions for smokers who are initially unsuccessful in their attempt to quit. Moreover, we are evaluating the two active treatment combinations that are known to be the most effective for cessation, potentially maximizing success rates; and increasing our

understanding of whether switch or augmentation medication approaches lead to better abstinence outcomes for those who fail in their cessation efforts during the acute phase of treatment. *It is important to emphasize that the effectiveness of medication switching or augmentation as a rescue intervention has never been evaluated for smoking cessation.* While participants will be told that their medication "may be changed" during the study, all medication assignments as well as re-assignments will be double-blinded. Findings from this SMART design study could inform the design of an adaptive trial that might include additional augmentation strategies, matched assignment to treatment conditions and dropping of treatment arms found ineffective in the SMART study.

2.0. OBJECTIVES

Specific Aims.

Aim 1: To estimate (a) the effects at 12 weeks of either continuing on their current medication, switching to the other medication, or increasing the dose of their current medication among smokers initially treated with either varenicline 2 mg (VAR) or nicotine patch + ad lib lozenge (combined nicotine replacement therapy; CNRT) but who relapsed to smoking by week 6 of treatment, and (b) the effects of 12 weeks of continued treatment on either VAR or CNRT among individuals who are abstinent from smoking at 6 weeks. Among participants failing to respond to CNRT at Week 6, we hypothesize that switching to VAR will be superior to CNRT augmentation or continuation, and that CNRT augmentation will be superior to continuation at Week 12. Among participants failing to respond to VAR at Week 6, we hypothesize that augmentation (VAR+) will yield higher rates of abstinence than switching to CNRT or remaining on VAR at Week 12. Among participants who are abstinent at Week 6, we hypothesize that those on VAR will be more likely to be abstinent at week 12 than those on CNRT. The primary outcome measure for Aim 1 will be biochemically verified (expired CO<6 ppm) 7-day point prevalence smoking abstinence at the end of treatment (Week 12) analyzed using logistic regression.

Exploratory Aim 2: To estimate the effects of six weeks of varenicline 2 mg (VAR) and nicotine patch + ad lib lozenge (CNRT) on abstinence. We hypothesize that the probability of abstinence at week 6 will not differ as a function of Phase I treatment.

Exploratory Aim 3: To estimate the moderating effects of initial treatment assignment (VAR or CNRT) on the effects of treatment continuation, switching, or augmentation at Week 12 among those who relapse to smoking at Week 6. *We hypothesize that augmentation will demonstrate superiority for participants originally receiving VAR compared to those who received CNRT for abstinence at week 12. We hypothesize that switching will demonstrate superiority for participants originally receiving CNRT compared to those who received VAR for abstinence at week 12*.

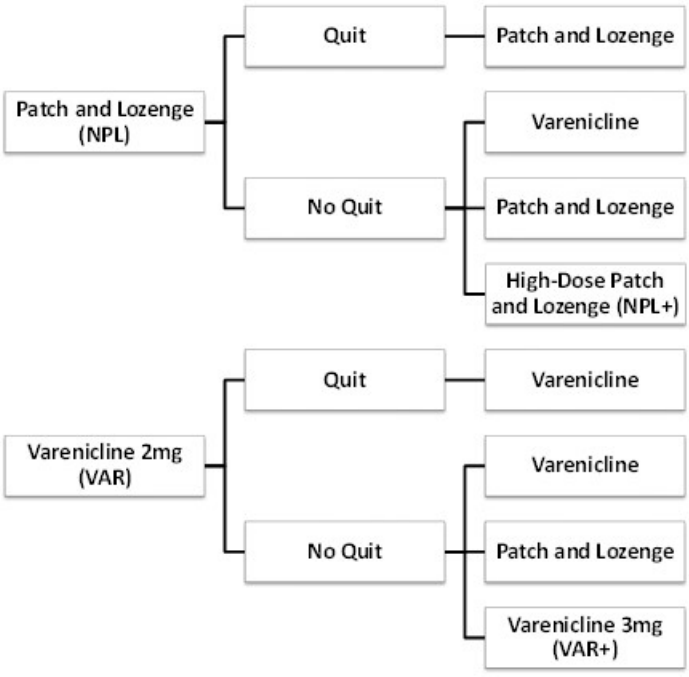
Exploratory Aim 4 : To estimate the probability that abstinence at the end of week 6 (Phase 1) among those initially randomized to VAR or CNRT conditions, will be moderated by salient baseline covariates. The covariates of interest include: 1) motivation, 2) dependence level, 3) nicotine metabolic ratio (normal vs. slow). In each case logistic regression will evaluate the point-prevalence of smoking at Week 6 as a function of the specified baseline covariate, treatment assignment, and the interaction of the specified covariate with treatment.

Exploratory Aim 5: Per smoking cessation clinical trial guidelines [23], additional secondary outcomes will also include prolonged and continuous abstinence at 3 and 6 months. *Effects of Treatment on Affect, Other Withdrawal Symptoms, and Craving:* Evaluation of affect, withdrawal, craving and nicotine reinforcement (PANAS, CES-D, WSWS, mCEQ) will use

generalized linear modeling to determine the degree to which treatments/treatment strategies affect these variables at Weeks 6 and 12 [24,25]. *Adverse Events:* We will use Beta-Binomial models to examine differences in probability of adverse events by treatment.

3.0 PATIENT ACCRUAL AND ELIGIBILITY

Figure 1. Study Design



Participants. The present study will use a double-blind 2-group parallel design, randomizing up to 510 smokers (up to 10 pilot participants and 500 study participants) to one of two initial treatment conditions (Phase 1), nicotine patch 21 mg + ad lib 2 mg lozenge (**CNRT**), and varenicline 2 mg (**VAR**). This will provide estimates of abstinence at six weeks from the quit-date. Patients failing to achieve abstinence, who were initially allocated to CNRT or VAR will undergo re-randomization (Phase 2) to a) continuation of the same treatment; b) switching to the untried intervention (i.e. CNRT or VAR), or; c) augmentation of the CNRT treatment with an additional 21 mg patch (high dose nicotine patch + ad lib lozenge; **CNRT+**) or augmentation of the VAR treatment with an increase in dose from 2 mg (total daily dose) to 3 mg (total daily dose) (high dose varenicline; **VAR+**). This permits estimates of the probability of benefit of switching versus augmentation versus a longer trial of the patient's current treatment, after they have failed at initially achieving abstinence (see **Figure 1**). While we only plan to enroll 510 eligible smokers on the current protocol, our past experiences recruiting from the Houston community has shown that we will need to screen and register in CORe at least three times the needed number of subjects. Thus, we estimate that we may need to screen at least 1000 people in order to attain the number of eligible people needed for data analytic purposes. Adaptive randomization (minimization) [26] will be used to stratify the sample by motivation, gender, and race. The procedures described for recruitment, screening and assessments will closely follow those which we have used in numerous other medication trials [27-30]. Given our experience and established RCT infrastructure, we expect to have no trouble recruiting for this study (over the past 10 years the PI has recruited over 2500 smokers into clinical trials). Briefly, volunteers who want to quit smoking or change their smoking behavior will be recruited from the Houston area using radio and TV advertisements and prescreened by telephone for basic eligibility requirements (age, location, tobacco use, contraindicated medical conditions, etc.). Phone eligible subjects will be scheduled for in-person medical screening for a more thorough review of their medical and psychiatric suitability for the study.

Key Inclusion Criteria.

- Age: 18-75 years old
- Smoking 5 or more cigarettes, little cigars and/ or cigarillos per day, on average, within the 2 months preceding the screening visit and expired CO ≥ 6 ppm (if ≤ 5, then positive cotinine test)
- Interested in treatment that might change smoking behavior
- Able to follow verbal and written instructions in English and complete all aspects of the study
- Provide informed consent and agree to all assessments and study procedures
- Have an address and telephone number where they may be reached
- Be the only participant in their household

Key Exclusion Criteria

Standard criteria for transdermal nicotine and varenicline smoking cessation trials will be used. Exclusion criteria will include the following:

- Within the month immediately preceding the screening visit, use of any form of tobacco products other than cigarettes, little cigars and/or cigarillos on 3 or more days within a week if the individual refuses to refrain from such tobacco use during the course of the study.
- Current enrollment or plans to enroll in another smoking cessation program in the next 12 months
- Plan to use other nicotine substitutes (i.e., OTC or prescription medication for smoking cessation) or smoking cessation treatments in the next 12 months
- Uncontrolled hypertension (SBP greater than 180 or DBP greater than 110)
- History of severe kidney disease (e.g. chronic or acute kidney failure) with creatinine clearance below 30 and/or severe liver disease with liver tests over 4 times the upper normal level.
- Laboratory evaluations (kidney and liver) outside normal limits and of potential clinical significance in the opinion of the investigator
- Serious or unstable disease within the past 3 months
- History (last 3 months) of abnormal heart rhythms, cardiovascular disease (stroke, angina, heart attack) may result in ineligibility. These conditions will be evaluated on a case by case basis by the Study Physician.
- Current use of certain medications:
    - Smoking cessation meds (last 7 days), i.e., Wellbutrin, Bupropion, Zyban, NRT, Chantix
    - Certain medications to treat depression (last 14 days), i.e. MAOIs and Elavil (Amitriptyline)
    - A case by case determination will be made by study physician for medication on precautionary list, i.e. nitroglycerin
    - Daily use of opioids for 30 days or more on phone screen or at screening is exclusionary however PRN use is allowed (i.e., 3:7 days per week or less or if more frequent, use less than a month's duration.
- Meet criteria for the following psychiatric and/or substance use disorders as assessed by the MINI: items C (current manic or hypomanic episode only), I (alcohol abuse - Alcohol Addendum-past 6 months only; current alcohol dependence), J (substance abuse - Substance Abuse Addendum – past 6 months only; current substance dependence), K (current/lifetime psychotic disorder or current/lifetime mood disorder with psychotic features).

  - Individuals who meet criteria for *non-exclusionary* psychiatric disorders that are considered clinically unstable and/or unsuitable to participate as determined by the Principal Investigator and/or Study Physician.
- Individuals rated as moderate (9-16) to high (17 or greater) on suicidality as assessed by Module B of the MINI.
- Psychiatric hospitalization within 1 year of screening date.
- A positive urine pregnancy test during the screening period. Women who are two years post-menopausal, or who have had a tubal ligation or a partial or full hysterectomy will not be subject to a urine pregnancy test.
- Pregnant, breast-feeding or of childbearing potential and is not protected by a medically acceptable, effective method of birth control while enrolled in the study. Medically acceptable contraceptives include: (1) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (2) barrier methods (such as a condom or diaphragm) used with a spermicide, or (3) an intrauterine device (IUD). Contraceptive measures sold for emergency use after unprotected sex are not acceptable methods for routine use.
- History of hypersensitivity or allergic reaction to Varenicline, NRT, or any component of these formulations.
- Any medical or psychiatric condition, illness, disorder, or concomitant medication that could compromise participant safety or treatment, as determined by the Principal Investigator and/or Study Physician.
- Subject considered by the investigator as unsuitable candidate for receipt of an investigational drug or unstable to be followed up throughout the entire duration of the study.
- Positive toxicology screen for any of the following drugs: cocaine, opiates, methadone, benzodiazepines, barbiturates, amphetamines, methamphetamines, PCP, or THC. a. Participants with valid prescriptions for opiates, benzodiazepines, barbiturates, amphetamines or methadone will not be excluded b. Participants failing the toxicology screen will be allowed to re-screen once. If they test positive again, they will not be allowed to return. Study physician may clear participant to continue on if there is a reasonable possibility the positive drug screen is the result of cross-reactivity with the participant's concomitant medications resulting in a false positive.

Note: For the purpose of eligibility requirements and ongoing smoking status, "cigarettes" will also include the tobacco products that are commonly known as "little cigars" and "cigarillos". Little cigars are commercially manufactured and sold in packs similar to cigarettes. Cigarillos are commercially manufactured and sold in packs of varying quantities.

4.0. STUDY DESIGN AND PROCEDURES

Subject Recruitment and Procedures

Participants who want to participate in a treatment to quit smoking or change smoking behavior will be recruited from Houston metropolitan area using newspaper, radio and TV public service announcements, feature articles in the MD Anderson newsletter, and posted flyers. The Tobacco Research and Treatment Program's web screener database for tobacco users, outlined in IRB-approved PA18-0423, also may be used as a recruitment source for this study. This database houses data collected from an internet-based screening questionnaire to recruit tobacco users from the Houston area, as well as across Texas more broadly, who may be interested in participating in tobacco use and cessation studies at MD Anderson Cancer Center. PA18-0423 allows the sharing of data with IRB approved MD Anderson protocols.

Interested participants will be offered modest monetary compensation for their time. We expect to have no difficulty recruiting the needed number of smokers. The MDACC Tobacco Treatment Program (TTP) is directed by the PI and has a high degree of community visibility. We have had considerable success recruiting participants for our clinical trials research.

Population Description. The population of the Houston community from which the sample will be drawn (includes Harris county) is estimated at 3,596,086 people. The ethnic distribution has been reported as 59% Caucasian (42% of which are not of Hispanic origin); 19% African-American; 5% Asian; and .4% Native American, with 33% Hispanic or Latino (of any race). We expect to recruit English speaking minority smokers in proportion to the population demographics, and smoking prevalence.

Pre-Screening Telephone Assessment. All smokers will be prescreened by telephone for basic eligibility requirements. An initial description of the study design will be provided and data will be obtained on age, smoking history, other tobacco use, medical and psychiatric history, medication use, and pregnancy/lactation status. All subjects who remain eligible after pre-screening will either be sent an email with the currently approved informed consent documents and information session slides for their review or be scheduled for a subsequent informational session where the study requirements will be explained in more detail and the informed consent reviewed.

Informational Session and Informed Consent. If an information session is scheduled, ideally, will occur within 14 days of the telephone screen but it may occur anytime between the phone assessment and the Baseline Screening visit. This visit can also be combined with the baseline screening visit. During this session, the study purpose, other study requirements, side effects and contraindications of the medications will be reviewed. The information presented may come in the form of a slideshow (either paper or electronic) which will be developed in collaboration with the Medical Doctor Co-chair of the study (Dr. Maher Karam-Hage) and will be based on current studies using these drugs, as well as manufacturer and PDR information (see Appendix WW) and/or directly from the informed consent document itself. Participants will be given the opportunity to ask questions about the informed consent document or any aspect of the study. Any medical questions that arise during the process, if not addressed in the documentation or discussion provided, will be referred to the medical staff and the information will be provided to the potential participant prior to consenting.

Two Consent forms are used in this study: One to cover the screening process and one to cover actual randomization and treatment. Participants who received the ICDs and Info Session slides electronically will have the opportunity to ask questions about the ICD or other study-related procedures at the first in-person clinic visit (Baseline screening visit) prior to signing the informed consent. The screening consent will be signed at the baseline screening visit and covers procedures that take place prior to any treatment administration. This includes items such as questionnaires, vitals, CO reading, drug screen, UPT if applicable, psychological evaluation, and blood draw, etc.). All of these procedures are required in order to proceed to randomization and are not optional. During the screening process however, the participant will also be presented with an optional procedure regarding their electronic communication preference (i.e. receiving communication via an unsecured method such as text, unencrypted email, etc. or via secured method such as in person consultation, encrypted email, telephone calls, etc.). The consent will be reviewed with the study participant and signed by a senior level study staff member. Subjects will be told that prior to actual study participation, a second consent form covering medical treatment will be required. Participants will be encouraged to

ask questions for understanding and if in agreement will sign the screening consent document with the trained senior staff member.

Baseline Screening.
At the baseline screening (Visit 0), which will occur within 30 days of the telephone screen, study participants will be asked to provide medical/surgical history, smoking history and to complete other assessments as shown in Table 1. A urine drug screen will be conducted to detect the presence of any of the following illicit drugs: cocaine, opiates, methadone, benzodiazepines, barbiturates, amphetamines, methamphetamines, PCP and THC. Participants failing the drug screen will be allowed to reschedule and repeat the visit one time. If they test positive again, they will not be allowed to return. If found ineligible at the screening visit, participants will receive compensation for the visit only if they meet the CO criteria and have a clean drug screen. In some situations, if a participant tests positive on the drug screen and is taking a medication that is believed to be possibly causing a false positive, the medical team may be contacted to discuss the case. The medical team may choose to clear the participant on to the Visit 1 screening/randomization visit with or without the requirement that the participant pass the urine drug screen at that time prior to being enrolled in the project. A cotinine test will be administered to assess cotinine levels only if the expired CO at screening is less than 11 ppm. The use of the cotinine test in subjects between 6 – 10 is not for inclusion/exclusion purposes. Since Visit 1 is considered part of the screening process as well, the same standard will apply at Visit 1. If a NicAlert is used, the value must be greater than 2 for the participant to be eligible. If a NicAlert equivalent is used, it must indicate positive for cotinine. Participants will undergo a neuropsychiatric interview called the MINI. Those patients who in the judgment of the Mental Health Practitioner (MHP) are clinically stable over the last 3 months will be cleared to proceed. The decision to exclude at this point may be based in part on changes in psychiatric symptoms and or medication that suggest a clinically meaningful worsening of their condition. They will also be asked to provide blood samples at this visit. One sample will be used to perform blood chemistry tests to test the following: Bilirubin, Creatinine, GGT, AST, and ALT. These tests are conducted so that liver and kidney function can be assessed. The second blood sample will be used to measure the Nicotine Metabolite Ratio (NMR). The NMR blood sample will be processed at MD Anderson, and may be banked for future testing and use in future studies. Participants unable to complete the Baseline screening visit within 30 days of the initial telephone assessment will be allowed to undergo a second telephone assessment and given an additional 30 days to complete the Baseline screening visit. If they do not complete the Baseline by this time point, they will no longer be considered eligible for study participation and must undergo a 90-day waiting period to re-enroll. Participants will not be randomized into the study at baseline screening given that they must complete the medical screening and the results of the lab work must be received before final eligibility can be determined. Participants who remain eligible after the baseline screening visit will be scheduled to return for the second in- clinic (medical) screening visit (Visit 1) within 30 days. If initial lab values are abnormal, blood work may be repeated before V1. Study physicians will use the results of the second blood draw to determine the accuracy of the initial values and to make a more informed decision regarding study eligibility. If a participant is eligible for another one of our research studies but is not enrolled in that study, the MINI, laboratory tests, and blood pressure collected for that study will be considered valid for 30-60 days and may be used in consideration of determining initial eligibility on this study. Participants will be registered in the institutional database (CORe) within 2 business days of signing consent.

Medical Screening. The Medical Screening will occur at either the Baseline Screening Visit or within 30 days of the Baseline Screening visit (at Visit 1) to determine final eligibility. During the

Baseline Screening Visit or Visit 1, a member of the medical team (MD, PA, APN or Clinical Nurse) will review with the participant medical information collected at the baseline screening visit, e.g., medical/surgical history, results of blood work (if applicable), vital signs and concomitant medications to ensure the accuracy of the information reported and to make sure there is nothing new to add. A qualified medical professional (MD, PA or APN) will be conducting a full physical examination on all participants. Those patients who are medically stable in the last 3 months as evidenced by no acute exacerbation in their symptoms would be cleared to randomization. Following screening, a second consenting process will take place that covers consent to participate in the actual treatment. The treatment informed consent will be obtained and signed by a licensed physician, following the required review of systems and brief physical exam, conducted by mid-level staff. A licensed physician will meet each study subject, review any questions they may have, and confirm that the patient understands the nature of the research being performed. The licensed physician may conduct this consenting process either in person or via an institutionally approved platform (e.g., Microsoft Lync and/or Polycom). If the consenting is performed via videoconferencing, the same procedures as described above will be followed. After completing the treatment consent procedure a prescription will be completed as per protocol to be filled by the pharmacy at MD Anderson Cancer Center. The medical staff (RN, PA, APN, or study physician) will also provide written documentation (dictated to medical chart) that the PA, APN, or study physician medically cleared the potential subject to participate on the protocol and the subject will be randomized into treatment. If a person is deemed ineligible for medical reasons, s/he will notified either in person, via phone or by letter and referred to his/her physician for follow-up, if applicable. Medical personnel may also delay clearance until any screening issues, which are not exclusionary, have been addressed by the potential subject's personal physician.

On occasion, V1 randomization may be delayed beyond 30 days from the Baseline visit due to various reasons including, but not limited to, the following: a) medical findings that may be significant but not exclusionary (in this case, a patient letter noting the area of concern and the required follow-up, if any, may be provided) (see Appendices RR, TT, UU, VV and V), b) participant-related events (e.g., travel, work schedules), or c) study related factors (e.g., full clinic schedule). In these cases, participants' pregnancy status, blood pressure, concomitant medications, mental health history, medical/surgical history, and smoking history will be reviewed before completing the randomization. If there are no significant changes, participants will be allowed to continue to the V1 randomization visit as described above. If there are significant changes, the baseline screening process will be conducted again as deemed appropriate by the medical team.

<u>Re-Visit Schedule and the Visit Window</u>
Every effort will be made to have return visits (both phone and in-person) on the same day of the week for study visits, however, a window will be permissible for all return visits as follows. Visit 2 will only have a +3 day window, Visit 6 will have a +6 day window, V5 will have a -3/+10 day window, Visit 7 will have a -3/+6 day window and Visit 8 will have a +25 day window. Visit 8 window starts after participant has been off study medication for at least 24 hours. If the end of the visit window falls on a weekend, holiday, or other day on which the clinic is officially closed, subjects will be allowed to complete the visit during the next business day except for V2, V5 and V8 which will not be scheduled beyond +3 days for V2, +10 days for V5 and +25 days for V8. In special circumstances, the Visit 5 window can be extended beyond +10 days at the discretion of the study physician. Follow-up visits will have expanded visit windows such that the 3-mo Follow-Up Visit has a window of +1 month or -3 days and the 6-mo Follow-Up Visit has a window of -1 month with an ending period of whenever final abstinence data is

collected or the trial ends, whichever is sooner. For those that miss a follow up visit, staff will call them to invite them to come in as originally planned so that at minimum abstinence data such as the time-line follow back assessment and CO and saliva cotinine, if applicable, can be collected. For those in follow up that report current abstinence and that they cannot come in to complete the visit, we will send them an abstinence questionnaire and if applicable cotinine saliva collection kit which they complete and mail back to us. In exchange for their completed abstinence packet (See Appendix C and D), the subject will receive $20 or a comparable gift card. Missed visits will be recorded in the study database but will not be logged as protocol deviations because they are expected in smoking cessation trials. See Appendix OO. Our subjects on average complete 75% of their visits but 100% compliance is not expected. In addition to a 1-day pre-quit support call, there will also be one 3-day post-quit, a 3-day post re-randomization and a 14-day post re-randomization support call during the course of the study. Note that the two post re-randomization calls will not be conducted in the event the subject is abstinent or off study medication. Because of the +2 day window for Visit 2, V2 and T2 support call may fall on the same day. If they fall on the same day, V2 will be completed and T2 will be cancelled as it is only a support call and no assessments are collected. Because of the +6 day window for Visit 6, V6 and the T4 support call may fall around the same time. If they are within two days of each other, the V6 will be completed and the T4 call will be cancelled as it is only a support call and no assessments are collected. All support calls have a 0-day window because another phone visit or in-person visit is planned no more than 7 days later. At least two call attempts will be made during the course of the day however before the call will be considered missed. Missed support calls will be recorded in the study database but will not be logged as protocol deviations because they are expected in smoking cessation trials.

Start of Medication and Medication Tracking

Subjects will begin self-administration of medication 1 day after Visit 1 and will track their medication dosing and cigarette consumption throughout the study using smoking diaries that will be provided to them by the study counselor (See Appendix E).The diary is considered to be a memory prompt for the participant **and will not constitute a protocol deviation if the subject does not utilize this tool.** Only the timeline follow-back information will be used for validating smoking behavior. A physical pill count will be used for validation of medication intake. In the event that a discrepancy arises between the study diary, participant's verbal report and the physical pill count, study staff will use the physical pill count to determine medication compliance. Ideally, overall medication compliance is done at Visit 8 (week 12), once the participant has completed the active treatment phase. If study medication has not been turned in at Visit 8, compliance will be completed once it has been. In the instance that a participant has become lost to follow up before turning study medication in, compliance will be assumed up to the first missed visit after the last contact. To further aid in the determination of medication compliance, staff will also use the patient's verbal report and medication counts from previous visits, if applicable. Deviations will not be logged for medications unreturned or unaccounted for. Ideally, subjects will take medications for a full seven days before the target quit date (TQD), which occurs on day eight of treatment.

Varenicline Level

A blood draw will be conducted at Visit 5 and Visit 7 to ascertain the level of varenicline in the blood. The purpose of assessing the varenicline is to determine if there is a correlation between abstinence and varenicline levels. If a participant reports they have not taken their varenicline/placebo tablets within the 3 days prior to Visit 5 or 7, no draw will be conducted as

varenicline levels will not be detectable. If a participant is classified as an abstainer at V5 (and therefore stayed on the current medication assignment), a Varenicline draw will not be conducted at V7. The additional blood draw for this sample of patients will not yield answers to research question of dose effect on abstinence since the dose remained constant.

Early Termination of Study Drug

If early termination of study drug is necessary and occurs before the end of the 12-week treatment period (Visit 8), staff will attempt to complete an early termination visit (ET 8) in order to collect any end-of-treatment evaluations, regardless of whether the subject continues in the study. If a subject prematurely and permanently discontinues study drug, they will be encouraged to continue to be followed in accordance with the study protocol through the end of the study and will be offered continued smoking cessation counseling as per protocol. The blood draw (unless redraw requested by study physician) and the end of medication assessment will not be conducted at Visit 8 if an early termination visit already took place.

Disposition of Study Drug

Occasionally, research subjects may fail to take a scheduled dose of medication. In such cases, subjects will be instructed to mark the missed dose(s) in their smoking diaries and return the missed dose(s) of medication to the study team. Returned medications will be logged, stored in a locked file cabinet maintained by the study team, and will be destroyed per institutional guidelines. Missed doses will not be logged as protocol deviations because they are expected in smoking cessation trials (see Appendix OO). In our previous trials about 75% of all participants take at least 80% of their intended dose of medication. We will, however, account for medication exposure in our analyses. Unused medications (i.e., those that were never dispensed by Investigational Pharmacy Services) will be maintained by the pharmacy team and will be destroyed per institutional guidelines.

Subject Withdrawal

A withdrawal occurs when an enrolled subject actively withdraws consent for further participation in the study, prior to completion of the protocol. Subjects may withdraw consent from the trial at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator for safety reasons. All attempts will be made to collect medications, and to conduct all evaluations required by the protocol.

Table 1. Study Time Line and Procedures

STUDY TIME FRAME	**SCREENING**			**TREATMENT**													**FOLLOW-UP (30 Day Post EOT & 6 mos Post-Quit)**	
Visit # (See 'note' below)		-1	**0**	**1**[a]	T1	TQD	2[m]	T2[m]	3	4	**5**	T3	6[n]	T4[n]	**7**	**8**[bc]	**9**[d]	**10**[e]
Study Day	-28	-14	1[f]	8	15	16	17	19	24	38	50	53	59	64	73	94	124	197
Days from Quit	-42	-28	-14	-7	-1	0	1	3	8	20	34	39	43	50	57	78	108	181
Days on Medication				0	7	8	9	11	16	28	42	45	49	56	63	84	-30	-104
Days on Medication Phase II												3	7	14	21	42	-30	-104
ASSESSMENTS																		
Phone Screen (Basic Eligibility)	X																	
Orientation		X																
Medical & Other Screening																		
Informed consent signed [k]			X	X														
FTND[o]			X															
CERQ[o]			X															
Smoking Health			X															
Medical History			X															
PHQ				X			X		X	X	X		X		X	X		
Blood Chemistry			X													X		
NMR Blood Sample			X															
Varenicline Level Blood Sample [l]											X				X			
Motivation (TSAMS)[o]			X								X							
Motivation Questions (for stratification)*				X							X							
Pregnancy Test*			X	X							X				X	X		
Urine Drug Screen			X															
Cotinine Test* (if applicable)			X	X							X				X	X	X	X
Height			X															
Weight			X	X							X				X	X	X	X
Blood Pressure/Heart Rt*			X	X							X				X	X	X	X
ROS/Physical Exam [j]			X	X														
MINI			X															
Abstinence Questionnaire/TLFB*			X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
E-Cigarette Questionnaire[g,o]			X															
SLIPS[o]				X							X				X	X	X	X
RPI[o]				X														
WSWS[o]				X			X		X	X	X		X		X	X	X	X
PANAS[o]				X			X		X	X	X		X		X	X	X	X
CES-D[o]				X			X		X	X	X		X		X	X	X	X
SECT[o]				X							X				X	X	X	X
SUPPS-P[o]				X							X				X	X	X	X
Sleep Problems Scale[o]			X															
EMA Assessments[i]				X	X		X	X	X		X	X	X	X				
EMA Daily Diary[i]				X	X		X	X	X	X	X	X	X	X	X			
End of Medication Assessment											X					X		
Smoking diary				X							X				X	X		
Expired CO*			X	X							X				X	X	X	X
Med Count											X				X	X		
Adverse Events				X			X		X	X	X		X		X	X	X	
Concomitant Meds*		X	X	X			X		X	X	X		X		X	X	X	
Support					X			X				X		X				
TREATMENT																		
Counseling				X			X		X	X	X		X		X	X		
Dispense Medication**				X							X							

Table 1. Study Time Line and Procedures

STUDY TIME FRAME	SCREENING			TREATMENT													FOLLOW-UP (30 Day Post EOT & 6 mos Post-Quit)	
Visit # (See 'note' below)		-1	**0**	**1**[a]	T1	TQD	2[m]	T2[m]	3	4	**5**	T3	6[n]	T4[n]	**7**	**8**[bc]	**9**[d]	**10**[e]
Study Day	-28	-14	1[f]	8	15	16	17	19	24	38	50	53	59	64	73	94	124	197
Days from Quit	-42	-28	-14	-7	-1	0	1	3	8	20	34	39	43	50	57	78	108	181
Days on Medication				0	7	8	9	11	16	28	42	45	49	56	63	84	-30	-104
Days on Medication Phase II												3	7	14	21	42	-30	-104

Note: bold visits occur in-person; a-Randomization visit; start medication the next day; bc- End of Treatment visit (Visit 8); d-3mos post quit follow-up (Visit 9); e-6 mos post quit follow-up (Visit 10); f-within 30 days of initial phone assessment but eligible for rescreen and an additional 30 days if needed; g- will be asked at V0 for all subjects. This will be asked again at any point the first time someone reports using e-cigs during study (but not for those who don't); h- Urine cotinine samples will be collected at V9 and V10 if subject comes in-person as scheduled. Subject will have the option to mail in saliva sample at those visits if unable to present to the clinic. For all applicable in-clinic visits, if subject unable to produce a urine sample during the visit in an adequate amount of time, a saliva sample will be collected instead. i- EMA daily diary will be completed every day for 84 days (duration of treatment phase), starting the day after randomization. EMA assessments will done daily for 2 weeks in Phase I, starting the day after randomization and 2 weeks in Phase II, starting the day after V5; *Asked as part of screening procedures at V1 prior to consent and may be asked at follow-up sessions. **Medication dispensing will occur in bulk quantities at V1 (Phase 1) and then again at V5 (Phase 2). In rare instances such as stock, pharmacy or scheduling issues, a pt may be dispensed meds ahead or behind schedule to compensate for issue. If pt cannot come at V5, the decision whether the participant may continue on study drug will be left to the discretion of the study physician. Note: Subjects will be given a window in which to complete a visit before the visit is considered missed (see protocol for additional details& exceptions). j-ROS/Physical may take place at baseline screening or Visit 1. k-screening consent signed at V0 & treatment consent signed at V1. l – If pt reports they have not taken their varenicline/placebo tablets within the 3 days prior to Visit 5 or 7, no draw will be conducted as varenicline levels will not be detectable. If abstainer at V5, no VAR draw will be conducted at V7. ; m – if T2 and V2 fall on same day, T2 cancelled; n – if V6 and T4 within 2 days of each other, T4 will be cancelled.; o – if opted for, ppts may receive study questionnaires up to 5 days prior to the clinic visit so that they can complete them in advance to reduce clinic time

Assessments and Questionnaires

Participants that have agreed to electronically receive questionnaires in advance of the visits may automatically be sent an email containing a participant specific link up to 5 days before the scheduled appointment. Participants will have up to 5 days prior to their appointment to access the link and complete the questionnaires for a $10 bonus.

MINI International Neuropsychiatric Interview. Current psychiatric disorders will be assessed using version 6.0 of the MINI [31]. The MINI screens for several DSM-IV Axis 1 diagnoses including depression, anxiety, bipolar and eating disorders, as well as substance and alcohol abuse. The MINI also provides a graded assessment of suicidality (low-high risk). The MINI is shorter and takes less time to administer than the Structured Clinical Interview for DSM-IV disorders (SCID) [32] but has been validated against that instrument [31,33].

The Demographic, Health and Smoking Health Questionnaires. These instruments expand on the data obtained during the pre-screening, providing more detailed information on demographics, health/medication history, alcohol, caffeine, and other drug use, for use in the medical screening. Information on smoking history (e.g., year's smoked, previous quit attempts, relapse, current smoking rate, and other nicotine/tobacco use) is also obtained. These questionnaires have been used in our previous and current cessation studies to provide descriptive data for the study population (e.g., [27,28]).

The Fagerström Test for Nicotine Dependence (FTND). The FTND is a 6 item questionnaire that measures nicotine dependence by assessing various components of smoking behavior such as daily intake, difficulty in refraining from smoking, and time to first cigarette [34,35]. In some studies, the scale has been found to correlate with cotinine level [36,37] and to predict smoking treatment outcome [38]. It was modified from the most commonly used nicotine dependence measure, the

Fagerstrom Tolerance Questionnaire [39]. Time to first cigarette (within 30 minutes) has been noted to be the item accounting for the majority of the variance in this scale and the one most highly correlated with multidimensional scales of nicotine dependence [40].

The Wisconsin Smoking Withdrawal Scale (WSWS). The WSWS [41] will be used to assess withdrawal symptoms. We will use the Anger, Anxiety, Concentration, and Sadness subscales of WSWS, and the Craving subscale to ascertain the effects of quitting on mood and urges to smoke, respectively. The WSWS has scale coefficient alphas between 0.75 and 0.93 and the mood and craving scales demonstrate increases as a function of nicotine abstinence as well as prediction of treatment outcome. Items from the Minnesota Withdrawal [42] are included in the scale for comparability to earlier studies using that measure.

The Positive and Negative Affect Scale (PANAS). The PANAS [43] is comprised of two 10-item mood scales: Positive Affect (PA) and Negative Affect (NA). Participants rate different feelings and emotions on a scale of 1-5. Various time instructions (e.g., today, past few days, past week, general, etc.) have been used with acceptably high alpha reliability ranging from .86 to .90 for PA and .84 to .87 for NA. Post-cessation PANAS negative affect is a robust predictor of relapse [44,45].

The Center for Epidemiologic Studies Depression Scale (CES-D). The CES-D is a 20-item self-report measure developed to assess depressive symptoms in community (nonclinical) populations [46] and in recent studies of smoking cessation [47]. This scale consists of four factors: depressed affect, enervation, lack of positive affect and interpersonal problems.

The Patient Health Questionnaire – Mood Module (PHQ)

The Patient Health Questionnaire Mood Module (PHQ) is a 9-item self-report measure that was developed to assess the participant's mood over the last two weeks [48] and is used in conjunction with the Mental Health Safety Plan (see Appendix H).

The Texas Smoking Abstinence Motivation Scale (TSAMS). This is a 10-item assessment created specifically for smoking cessation research to measure a participant's motivation to quit smoking [49].

Motivation Question. This item, based on the Stages of Change model of behavioral change [50], will be used to determines high or low level of motivation to quit smoking for stratification purposes.

CERQ-short. The CERQ-short is an 18 item validated questionnaire that assesses an array of cognitive emotional regulation strategies and consists of 9 subscales: self-blame, acceptance, rumination, positive refocus, refocus on planning, positive reappraisal, putting into perspective, catastrophizing, and other-blame [51]. These regulation strategies have been related to a variety of affective outcomes and may be related to cessation rates in this study.

Sleep Problems Scale. This 4-item scale, designed to assess symptoms of sleep disturbance as a function of treatment and nicotine withdrawal [52], will be administered at baseline.

The Self-Efficacy Temptation and Confidence Scales (SETC). The SETC Scales assess Bandura's construct of self-efficacy and evaluate an individual's efficacy (i.e. confidence) to abstain from smoking in 20 situations that represent typical smoking cues [53]. These situations form four subscales, comprising five items each, examining cues related to negative affect,

social/positive, physical concerns, withdrawal symptoms, and urges. The same items are used to evaluate an individual's temptation to smoke, providing a measure of cue strength to relate to the efficacy evaluation. Both efficacy and temptation are rated on 5-point Likert scales ranging from not at all to extremely

Specific Loss of Interest and Pleasure Scale (SLIPS). The SLIPS is the first validated measure that allows for the assessment of recent changes in anhedonia in non-clinical and clinical samples. Anhedonia, or loss of pleasure and/or interest in people or things, is a key component of many forms of psychopathology. Extant anhedonia measures only assess current state or longstanding trait anhedonia, which risks discounting recent changes. Thus, the Specific Loss of Interest and Pleasure Scale (SLIPS), was created to assess recent changes in anhedonia. Each of the 23 items are ranged from 0 to 3 to indicate the degree of change in interest in or pleasure from a specific experience, relative to the past.

SUPPS-P Impulsive Behavior Scale. The SUPPS-P is a 20-item questionnaire composed of 4 scales that capture different aspects of impulsive behavior, including Premeditation (lack of), Urgency, Sensation Seeking, and Perseverance (lack of) [54]. Impulsivity has been linked to substance abuse, including smoking. As part of exploratory analyses, we will examine whether impulsive symptoms moderate treatment effects on cessation outcome, and whether treatment reduces impulsive symptoms.

Reward Probability Index (RPI). The 20-item RPI is a reliable and valid questionnaire measure of access to reward in the real-world environment [55]. RPI scores measure two factors that relate to one's ability to extract reward from the environment: reward probability (i.e., the number of potential reinforcers and the individual's abilcotity to obtain these rewards) and environmental suppressors (i.e., the presence of aversive stimuli in the environment that prevent access to rewards). In the proposed study, we expect that IRS- smokers will have lower scores on reward probability and higher scores on environmental suppressors than IRS+ smokers.

Electronic Cigarette Questionnaire: This questionnaire will be used as a baseline measure of electronic cigarette use, both past and current. Participants will be asked initially at the baseline screening visit (V0), and then again only if they report use again throughout the study

Ecological Momentary Assessments (EMA). Our EMA methodology is modeled after several of our previous studies in which we enrolled very diverse smoking populations[56-58]. Two categories of EMA assessments will be implemented on the smartphone. One is a daily diary assessment which occurs only once per day. The other category is comprised of EMA assessments that can occur multiple times a day, prompted by a random prompt following a specified sampling algorithm (see appendix DDD). The daily diary assessments will occur every day throughout the treatment phase of the study. To reduce assessment burden, the random and more frequent EMA assessments will occur only two weeks in Phase 1 and 2 weeks in Phase 2. While our sampling algorithms are designed to limit subject burden, the random EMA assessments cover more domains and take more time than the daily diary assessments so we have limited them to this time period consistent with previous studies by Shiffman and colleagues[59-63].

The daily diary EMA assessments will occur 30 minutes after waking each morning and will assess events from the previous day such as cigarettes per day (CPD), alcohol consumption, affect, sleep, motivation, and medication compliance. For the random EMA assessments, participants will be prompted to complete additional random assessments 3 times per day. The smartphone will provide immediate feedback of compensation provided for the completion of each assessment as noted below. For random EMA sampling, each day will be divided into 3 blocks so that assessments are not completed within close proximity of one another. During

each block, 1 EMA assessment will be triggered at random to assess affect, craving, and other momentary contextual factors (i.e., expectancies, motivation, smoking availability, self-efficacy, and perceived stressors). The software prevents assessments from occurring within close proximity of other assessments. Because prompts may occur at inconvenient times, participants can delay prompts for up to 20 minutes by touching an icon on their smartphone when it is impossible or inconvenient to respond (e.g., driving). This improves compliance and does not bias the data [64].

EMA trainings will be provided to participants as needed. The smartphone also displays feedback reports (e.g., amount of compensation earned). Total time devoted to EMA is fairly reasonable (between 17-30 minutes/day on average), with compliance rates of >75%, even among low-SES populations [56-58]. Our previous research has shown that >90% of completed assessments include no delays [57] and EMA reactivity is nonexistent or small [65]. Other smart phone features will include automatic real-time download of data to our server, appointment reminders, as well as the option to call and/or text participants if the expected data are not forthcoming (e.g., no diary input on a given day). Missed EMA assessments will not be logged as protocol deviations because they are expected in smoking cessation trials.

The EMA application has gone through a risk assessment process and has been approved by Governance, Risk, and Compliance (GRC) at MD Anderson (See appendix CCC). Application ID APPID-267543.

The EMA component will be initiated by those subjects randomized after the application is complete and ready for use. In the event the application is not ready for use, those randomized subjects will not participate in the EMA, and a deviation will not be logged.

Abstinence. Abstinence data will be collected at all contacts using a timeline follow-back (TLFB) procedure [66,67] as we have done in our previous studies [30]. In addition to cigarette smoking, we will also use the TLFB procedure to measure the use of other forms of tobacco and nicotine, such as cigars and e-cigarettes. Abstinence outcomes conform to the Society of Research on Nicotine and Tobacco (SRNT) [68] guidelines. In this study, end of treatment (EOT) seven-day point prevalence abstinence (no smoking for the past 7 days) will serve as the primary outcome measure.

Secondary outcome measures will include continuous and prolonged abstinence at the 3 and 6 months follow-up. The common starting point for assessing prolonged abstinence is the end of the grace period (i.e., 2 weeks following EOT here). For prolonged abstinence, relapse is defined by smoking 5 or more cigarettes from the end of the grace period to a future time point (e.g., EOT, 3- and 6- months post-quit date) [68]. We will also assess continuous abstinence over the 4 weeks after EOT of treatment (i.e. EOT-plus 30 days). This time frame for validating continuous abstinence is consistent with the FDA requirements for establishing efficacy in all recent pharmacotherapy, including the pivotal studies of varenicline [69,70].

All data will be obtained at EOT, 3 months and 6 months post-quit. In-person reports of abstinence will be verified by expired CO < 6 ppm and/or a positive urine cotinine at follow-up. Participants unavailable for timeline follow-back assessment will be considered non-abstinent.

Cotinine. Cotinine is the first metabolite of nicotine and has a half-life of about 20 hrs. Urine cotinine will be obtained at the time of randomization and at follow-up points shown in Table 1. Cotinine values will provide information regarding the participant's tobacco exposure within the previous 24-36 hours. Baseline cotinine values may be used in the descriptive analyses of smoker characteristics, along with other variables from the smoking history questionnaire. Cotinine values from subsequent assessments may be used as a crosscheck on abstinence requirements during follow-ups for those individuals reporting abstinence but unable to

complete an in person visit (where expired CO would be assessed). Urine samples may also be used to analyze nicotine and Anabasine levels. Anabasine is used as a biological marker to determine if nicotine is present in the blood due to a nicotine replacement therapy or from tobacco use. If a participant is unable to provide a urine sample for cotinine, a saliva sample may be taken instead.

Adverse Event Monitoring & Concomitant Medication.

Participants will be assessed for side effects and concomitant medications using standard FDA guidelines recommended for these two procedures. Adverse event terminology and grades will be determined using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, published by the U.S. Department of Health and Human Services. A response time matrix will be used to guide the medical team on how long they have to respond (immediately to 48 hours) to the notice of an adverse event based on its rating. If someone from the medical team deems it clinically appropriate, the medical team or study staff may provide the subject with patient education materials printed from the MD Anderson database related to the AE they are experiencing. The subject will not be taken off study drug unless the study physician or his/her personal physician recommends that we do so. Liver (LFT's) and renal function renal function (creatinine clearance) will be evaluated at baseline and at the end of treatment. Out of range values at baseline will be logged in the subject's medical history. Blood chemistries will be repeated as needed accordingly when clinically warranted. If the subject does not attend the Visit 8 End of Treatment visit, a blood draw may be conducted at the first follow up visit the subject attends. Participants reporting chest pain or chest pressure will be administered a Chest Pain/Chest Pressure questionnaire (see Appendix G.) and will be triaged accordingly.

Adverse events will be reviewed by our medical personnel and the PI. The study physician may adjust medication doses as consistent with good clinical practice to manage AEs according to his/her clinical judgment. Medication doses may also be adjusted if subjects' reports of side effects cause concern even if there are no specific subject complaints. Adverse event monitoring will continue up to 30 days after medication is completed. If an AE is spontaneously reported after the AE reporting period is over, the AE will be recorded in the patient's progress notes. Those AEs that are probably, possibly or definitely related to treatment will be followed until resolution or end of study, whichever comes first. In the case of reports of suicidal ideation, depression or anxiety which we believe may be related to treatment, if possible, we will engage in our normal psychological assessments (see Appendix H). This may not always be possible if reported by phone. In any case, procedures for Good Clinical Practice will be followed with respect to medical management of the symptoms. A specific plan for monitoring increased depression and suicidality is presented in the appendix (see Appendix H). Details regarding the monitoring/management of treatment-emergent anxiety are also included in Appendix H. The clinical assessment tool we use is the HAD (the Hospital Depression and Anxiety Scale) and the procedures outlined in Appendix H apply to both symptoms of anxiety and depression. Moreover, because aggression and irritability are intimately associated with anxiety, these symptoms are also captured in our monitoring and management procedures. Treatment- emergent psychosis is extremely rare in smoking cessation trials. If it does occur, it will be captured by our assessment of adverse events. These cases will be referred for further evaluation by a Ph.D. licensed Clinical Psychologist and/or the Addiction Psychiatrist, who is a co-investigator on this protocol. The Addiction Psychiatrist will determine the course of clinical management according to methods of good clinical practice. The PI or physician is responsible for determining the attribution of adverse events to study medication.

For this trial, AEs will be recorded according to the Recommended Adverse Event Recording Guidelines for Phase III protocols (see shaded areas of the AE table below).

Serious Adverse Event Reporting (SAE) Reporting MD Anderson IND Office Guidelines
An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

Table 6. Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	PhaseI Phase II	PhaseI PhaseII Phase III	PhaseI PhaseII Phase III
Unlikely	Phase I	Phase I	PhaseI Phase II	PhaseI PhaseII Phase III	PhaseI PhaseII Phase III
Possible	PhaseI Phase II	PhaseI PhaseII Phase III	PhaseI PhaseII Phase III	PhaseI PhaseII Phase III	PhaseI PhaseII Phase III
Probable	PhaseI Phase II	PhaseI PhaseII Phase III	PhaseI PhaseII Phase III	PhaseI PhaseII Phase III	PhaseI PhaseII Phase III
Definitive	PhaseI Phase II	PhaseI PhaseII Phase III	PhaseI PhaseII Phase III	PhaseI PhaseII Phase III	PhaseI PhaseII Phase III

- Death
- A life-threatening
- adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient
- hospitalization or prolongation of existing hospitalization
- A persistent or
- significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Investigator Communications with Pfizer

For all IIR studies using a Pfizer Product and/or Device: Pfizer requires that, within 24 hours of first awareness of the event (or immediately) if the event is fatal or life-threatening), the principal investigator will report to Pfizer by facsimile any Serious Adverse Event (SAE) that occurs during the SAE reporting period in a study subject assigned to receive the Pfizer product. In addition, for studies using a Pfizer device or Pfizer product packaged with a device, reportable events include not only SAEs but also Device Incidents and Device Near-Incidents.

Reporting Forms: The principal investigator will report such SAEs using the Pfizer IIR SAE reporting form or the approved local regulatory form (i.e. FDA MEDWATCH form, CIOMS, etc.) and the Reportable Event Fax Cover Sheet provided by Pfizer. SAEs should be reported as soon as they are determined to meet the definition, even if complete information is not yet available.

Reporting Period: The Reportable Events that are subject to this provision are those that occur from after the first dose of the Pfizer product through 28 days after discontinuation of the Pfizer product.

Follow-up Information: The institution and/or principal investigator will assist Pfizer in investigating any SAE and will provide any follow-up information reasonably requested by Pfizer.

Regulatory Reporting: Reporting an SAE to Pfizer does not relieve the institution and/or principal investigator of the responsibility for reporting it to the FDA or local regulatory authority, as required.

Assessment Protocol and Participant Burden. All abstinence and self-report assessments will be conducted by either counseling or non-counseling research staff (e.g., counseling associates, research coordinators, research assistants, nursing and medical staff, etc), who like other staff are blind to medication assignment. Self-report measures are administered on a computer-based program or by phone. To reduce the potential frequency of missing data, we follow a standardized procedure for contacting the participant with appointment reminders by telephone, text and/or email and sometimes letters and in the event a session is missed every attempt is made to reschedule the visit within the designated window. As a last resort, telephone visits may be conducted for certain in-person visits. In these cases Adverse Events, Concomitant Medications, Abstinence Questionnaire, PHQ and counseling may be assessed/administered. The entire in-person assessment protocol should take no longer than 45 minutes. We have conducted numerous trials using these and many other psychological and cognitive assessments with little problems in participant compliance. Past experience has shown us that the longer a participant is enrolled, the greater the chance that they will fail to complete a visit. So, although we strive to ensure patients complete each visit, we expect that some will not and as such, we will not require every visit be completed in order to participate in the study (nor will we log protocol deviations for missed visits; see Appendix OO). Similarly, we will not log protocol deviations for missing assessments associated with missed visits.

Treatment

Pharmacotherapy.

All of the commercially available forms of nicotine replacement therapy (NRT), i.e. gum, transdermal patch, nasal spray, inhaler, lozenge and sublingual tablet, are effective as part of a strategy to promote smoking cessation, enhancing long-term abstinence rates as much as 50 to 70% [18]. The 2008 US clinical practice guidelines [5] state that the long-term use of nicotine patch with another form of ad lib NRT is more effective than nicotine patch alone and recommend that physicians consider this option. Varenicline is the latest marketed non–nicotine-based smoking cessation medication, approved in 2006 in the US. As a partial agonist (or mixed agonist/antagonist in older terminology), varenicline is thought to enhance smoking abstinence and diminish nicotine withdrawal symptoms while lowering the rewarding effect of smoking. Pooled analyses from several early controlled trials reported that varenicline resulted in cessation rates three times higher than placebo [69-71]. A recent meta-analysis reported that varenicline was more effective than the nicotine patch (OR 1.51; 95% CI 1.22 to 1.87), nicotine gum (OR 1.72; 95% CI 1.38 to 2.13), and 'other' NRT (inhaler, spray, tablets, lozenges; OR 1.42; 95% CI 1.12 to 1.79), but was not more effective than some combination NRT (OR 1.06; 95% CI 0.75 to 1.48) [72]. Combination NRT also outperformed single formulations) [72]. Specifically the NRT combination of patch plus lozenge has been shown to be highly effective against placebo and mono-therapies including bupropion [9]. In another recent treatment meta-analysis evaluating over 15,000 smokers with a random effects model, varenicline was shown to be more effective than all other mono-therapies (NRTs; Bupropion) or combinations (NRT combination and bupropion NRT combinations) at every time point (i.e., end of treatment, 3 month and 6 month follow-up) except at 6 months in comparison to a high dose nicotine patch and combination NRT. Additional safety information regarding these medications is included in the Protection of Human Subjects section of this protocol.

All participants will receive both forms of study medication (varenicline and nicotine patch with ad lib nicotine lozenge, one active and one placebo). Pharmacotherapy (Phase 1) both Varenicline and NRT (patch plus lozenge), will be initiated the day after the randomization visit

(see **Figure 1**), 7 days prior to the quit date. During that first week, CNRT subjects will receive placebo varenicline and varenicline subjects will begin active medication. Varenicline dosing will follow the recommended dosing schedule (i.e., 0.5 mg/day varenicline for days 1-3; 0.5 mg bid; for days 4-7; and 1 mg bid thereafter). CNRT subjects will receive active 21 mg patches and 2 mg ad lib lozenges; varenicline subjects will be given matching placebo patches and matching placebo lozenges.

For those participants that are abstinent at week 6 (Visit 5), medication will continue until the end of treatment (week 12; Visit 8). For those participants who continue to smoke at week 6, a second randomization (Phase 2) will occur as described previously and subjects will receive 6 more weeks of medication, which will be administered as described previously ie, Phase II non-abstainers that are re-randomized to the switching arm will be titrated the same as those on active varenicline in Phase I. Additionally, The VAR+ group will receive 1 extra mg (3 mg total daily dose) to be taken with the PM dose and the CNRT+ group will receive an additional 21 mg nicotine patch (42 mg total daily), applied in the AM as usual. Inactive placebos will be provided to the other treatment groups.

The active nicotine patch (21 mg) and matching placebos will be purchased from NAL Pharmaceuticals. The active nicotine lozenge (as Nicotine Polacrilex) 2 mg and matching placebo will be purchased from NAL Pharmaceuticals. The active clinical image varenicline and placebo will provided by Pfizer. The active and placebo varenicline and the active and placebo nicotine patches and lozenges will be sent to the University of Pennsylvania for blister-packing and blinded kit preparation. Medications will be provided at no cost to the participant.

Subjects' thoughts about their treatment assignment will be assessed by querying participants at Visit 5 and then again at the end of treatment, using a brief questionnaire we developed for our current medication trials (see Appendix I.). If the visit where the assessment would have been given is missed, it will be captured at the next completed visit whether phone or in-clinic. While not a valid measure of blinding success, this assessment provides valuable insight regarding the subjects' perception of their medication assignment and the associated side effects (see Appendix I). Medication dispensation, pill counts and assessment of adverse events will be carried out by medical and other research staff members who have been trained on these procedures.

<u>Dose Modifications for Blood Pressure</u>
In the event that a subject has a manual blood pressure reading that indicates a 15% or greater increase over baseline (systolic or diastolic) *and* blood pressure is > 160/100, the following steps will be taken:

1) Discontinue ad lib nicotine lozenges. Subject will be advised to monitor blood pressure and report results at next staff contact.
2) If the 15 % increase continues at subsequent contact after the discontinuation of the lozenges, the hours of usage of the nicotine patch will be modified or discontinued per physician clinical judgment.

Note: In the event that a subject's blood pressure exceeds 180/110 at any subsequent visit, the nicotine lozenge and the nicotine patch will be discontinued.

The varenicline dose will not be adjusted.

Medication Blinding. The blinding will be handled by the data management team in accordance with the minimization procedure being used for subject stratification and random assignment. A master key mapping group assignment and kit identifiers to the un-blinded drug information will be developed in conjunction with the pharmacy who will maintain the master key. The Tobacco Research and Treatment Program has computer programmers that write the randomization programs and automatically utilize the data (minimization factors) that have been entered into the database to conduct the randomization. That program will be written directly into the study database. The study coordinator conducts the randomization after all eligibility criteria are met and recorded in the database (by design the program will not work otherwise). The group assignment is then transmitted to the pharmacy, by the study coordinator. Pharmacy will dispense the medication accordingly. Blinded reports are available that provide information on the distribution of factors within treatment group as a cross check on the program's accuracy. We have implemented this process in several other protocols.

Breaking the Blind. Un-blinding of single cases by the investigator will only be performed if relevant for the safety of the participant. The PI along with the Program Director (PD) will be responsible for implementing procedures for maintaining the blind and for breaking the blind when necessary. The PI must notify the IND Medical Monitor/Office prior to the un-blinding of a participant. In emergency situations, the Principal Investigator (PI) would consult with the Program Director (PD) and/or the research team's Data Management Supervisor (DMS) to obtain immediate blinding information for the participant. The PD/DMS would then pass this information on to the PI to enable the participant to be treated. In non-emergency situations, the same procedures would apply, however the PI and PD will discuss and evaluate the request, then, the PI after consulting with the study physician would be responsible for making the decision of whether or not to un-blind. When the blinding code is broken, the reason will be fully documented and included on the appropriate data collection forms. Additionally, since unblinding can affect the integrity of the study, any unblinding that occurs will be reported to the MDACC DSMB. The PI will request the DSMB to approve the release of unblinded data after all subjects have completed the follow up period. After the DSMB has approved the release of the unblinded study data, subjects can be provided with their medication assignment(s) if requested.

Behavioral Counseling As shown in Table 1, following randomization all smokers will receive brief individual behavioral smoking cessation counseling as is the recommended standard for use with pharmacotherapy [5]. The counseling protocol is manual driven (see Appendices J and K), has been used in several of our previous studies [30,44,73], and will consist of 4 in-person and 4 phone visits and up to 4 brief supportive phone calls (one day pre-quit,3 days post quit, 3 days post rerandomization and 14 days post rerandomization), lasting 10-15 minutes each, spanning the 12 week active treatment phase. This is similar to previous studies with varenicline [69,70] though we will provide slightly fewer (10 versus 12) treatment sessions. The phase 2 safety calls (the 3 day post rerandomization and the 14 day post rerandomization safety calls) will not be conducted for abstinent participants or participants that have come off study medication. Counseling content will follow our previous study [30] and briefly involves preparation for quitting, identification of high risk situations for smoking, development of coping skills and direct support before and after the quit date, motivational intervention [74] for keeping or resetting a quit date, management of withdrawal symptoms and medication compliance.. We have extensive experience from our previous trials in training and monitoring the integrity of the counseling protocol including recording time and content of each session [30,44,73].

Participant Compensation Following randomization, participants will be remunerated up to $594 plus parking vouchers or metro cards (if available) for completing all visits and assessments

from baseline/screening through the end of the study. This includes up to $84 for completion of all EMA assessments, and $30 (EMA) phone return bonus. See Appendix L for the Compensation Schedule. In an effort to reduce clinic burden, when the Ver 12 revision is approved, we will begin sending questionnaire links to participants in advance of their scheduled clinic visits and offering a $10 bonus if they complete electronically prior to coming in to the clinic visit. The current compensation scheme has been adjusted accordingly and will only effect newly consented participants after the revision is approved. Those that already signed consent (whether screening and/or treatment) under the previous scheme will be compensated according to the previous scheme. Questionnaire links are already sent to participants prior to scheduled **phone** visits but there is no compensation bonus associated with completion prior to the scheduled call.

Open-Label Pilot. Using procedures identical to those previously outlined (with the exception of placebo medications), we will run up to 10 pilot participants in an open label format, should our medication placebos not be available at the time of study start-up; otherwise pilot subjects will receive placebo as per protocol . The purpose of the pilot is to test our procedures and associated SOPs, develop an optimal and efficient study flow, and adjust procedures according to feedback (with appropriate protocol revisions, if necessary). Subjects will receive open label varenicline provided by Pfizer or obtained by MDACC Investigational Pharmacy for use in this study and commercially available over-the-counter nicotine patches and nicotine lozenge. A separate consent form will be used for the open label format.

5.0. DATA ANALYSIS

General Data Analytic Strategy

The primary aim of proposed trial is to estimate (a) the effects at 12 weeks of either continuing on their current medication, switching to the other medication, or increasing the dose of their current medication among smokers initially treated with either varenicline 2 mg (VAR) or nicotine patch + ad lib lozenge (CNRT) but who relapsed to smoking by week 6 of treatment, and (b) the effects of 12 weeks of continued treatment on either VAR or CNRT among individuals who are abstinent from smoking at 6 weeks. Our primary outcome endpoint is end of treatment (EOT; week 12) seven-day point prevalence abstinence biochemically verified using expired CO (<6 ppm). Our primary analytical approach will involve Bayesian statistical methods to assess the probability that such an interaction exists. Our analytical plan is shaped by the limitations of conventional (Frequentist) methods for addressing this question and the advantages of a Bayesian approach for assessing the probability that a given strategy might successfully be expanded into a larger-scale program that addresses smoking as a chronic, relapsing disorder. This data, valuable in its own right, can justify the commitment of resources needed for such an expansion. Further, current uncertainty regarding the probability of abstinence from smoking as a function of treatment strategy is readily incorporated in a Bayesian approach permitting more robust planning and design.

The Bayesian approach addresses the following study questions: 1) ”Among initial responders, what is the probability VAR confers benefit relative to CNRT on abstinence at six and twelve weeks, what is the best estimate of this effect, and what is its precision?” 2) “Among non-responders at six weeks, what are the relative probabilities that augmentation/switching confer benefit at twelve weeks for those initially receiving VAR versus CNRT, what are the best estimates of these effects and what is their precision?” 3) “Among non-responders at six weeks who initially received VAR what is the probability of benefit of augmentation/switching versus continuation for abstinence at twelve weeks, what are the best estimates of these effects and their precision?” 4) “Among non-responders at six weeks who initially received CNRT what is

the probability of benefit of augmentation/switching versus continuation for abstinence at twelve weeks, what are the best estimates of these effects and their precision?" By estimating the probability that such effects exists, we are assessing the probability that the alternative hypothesis is true, a probability that is, by definition, not accessible to Frequentist methods. The FDA has discussed the use of Bayesian statistical methods to make decisions regarding the efficacy of new treatments as an alternative to Frequentist methods in developing clinical applications [75-80]. The current proposal will provide the best, unbiased estimates for the interaction of Phase I and Phase II treatments as well as for the benefit conferred by remaining on the same treatment, switching or augmenting treatments, conditional upon failure to achieve abstinence in Phase I, while also estimating the probability that such effects exist. Posterior distributions can then be used as informative priors for continued monitoring in expansions of treatments and treatment strategies exhibiting initial promise.

Preliminary data analyses will inspect baseline, group differences and compliance variables for correlations with specified outcomes. Variables demonstrating baseline, group differences, for which there is a correlation with outcomes, will be treated as potential confounders [81,82]. Two sets of analyses will determine the degree to which any group differences might confound conclusions regarding treatment: one including, and one excluding the relevant variable as a covariate.

Broadly, the analytic strategy will use generalized linear modeling. Continuous, dichotomous and time-to-event data will utilize linear, logistic, and proportional hazards regression respectively (Proc GENMOD and Proc PHREG; SAS v. 9.3). Longitudinal analyses will employ generalized linear mixed models (Proc MCMC; SAS 9.3). All of these SAS procedures permit Bayesian analyses. Keeping with standard practice for clinical trials in smoking cessation, primary analyses will use intention-to-treat principles, with missing observations imputed as smoking. Secondary analyses will implement joint modeling of observed outcomes and the missing data which is robust to ignorable missingness [83,84]. Sensitivity analyses will evaluate robustness of analytic conclusions to missing data. Non-ignorable missing data patterns will be addressed through pattern-mixture modeling methods [84].

Prior distributions for comparison of proportions will use ~Beta(a = 1, b = 1) priors. Linear, logistic and Cox Proportional Hazards regression coefficient priors will take the form ~N (mean = 0, var = 1 x 10^6) in the linear, log (odds) and log scales respectively. Level one error variances will be specified as ~Inverse Gamma (shape = 0.001, scale = 0.001); level two variances will use ~Uniform(0,1000) distributions. Sensitivity analyses using optimistic and pessimistic, skeptical priors will evaluate prior assumptions [85]. Inverse probability weight will permit unbiased effect size estimates in the context of re-randomization. Finally, coding procedures will permit identification of each salient effect. Specifically, at the initial randomization VAR and CNRT will be coded as 1 and -1 respectively. For the re-randomization: 1) non-responders receiving continuation therapy will be coded 1 while all other participants will be coded 0; 2) non-responders receiving augmentation will be coded 1 versus 0 for all other participants; 3) non-responders re-randomized to switching treatment will be coded -1 versus 0 for all other participants.

Data Analytic Models

Logistic regression will utilize the following model for evaluating abstinence at twelve weeks:

$$logit(y) = \beta_0 + \beta_1 * a_1 + \beta_2 * anr_{21} + \beta_3 * anr_{22} + \beta_4 * anr_{23}$$

$$+ \beta_5 * a_1 * anr_{21} + \beta_6 * a_1 * anr_{22} + \beta_7 * a_1 * anr_{23}$$

Where a_1 is the indicator variable for initial treatment randomization, and anr_{21}, anr_{22}, anr_{23} represent the coded vectors for non-responder continuation, augmentation and switching respectively. Effects for each outcome cell at twelve weeks are as follows:

$$NRT + Loz_{responders} = \beta_0 - \beta_1$$

$$Var\ 2mg\ _{responders} = \beta_0 + \beta_1$$

$$NRT + Loz_{nonresponders} \rightarrow NRT + Loz = \beta_0 - \beta_1 + \beta_2 - \beta_5$$

$$NRT + Loz_{nonresponders} \rightarrow 2 * NRT + Loz = \beta_0 - \beta_1 + \beta_3 - \beta_6$$

$$NRT + Loz_{nonresponders} \rightarrow Var\ 2mg = \beta_0 - \beta_1 - \beta_4 + \beta_7$$

$$Var\ 2mg\ _{nonresponders} \rightarrow Var\ 2mg = \beta_0 + \beta_1 + \beta_2 + \beta_5$$

$$Var\ 2mg\ _{nonresponders} \rightarrow Var\ 3mg = \beta_0 + \beta_1 + \beta_3 + \beta_6$$

$$Var\ 2mg\ _{nonresponders} \rightarrow NRT + Loz = \beta_0 + \beta_1 - \beta_3 + \beta_7$$

Hypothesis Testing Aim 1: *The probability of abstinence at week twelve as a function of Phase I treatment allocation will demonstrate the superiority of VAR to CNRT.* Logistic regression will evaluate the point prevalence of smoking at Week 12 as a function of participants who remain on VAR or CNRT for the full twelve week trial. The salient contrast is:

$$Var\ 2mg\ _{responders} - NRT + Loz_{responders} = (\beta_0 + \beta_1) - (\beta_0 - \beta_1)$$

Hypothesis Testing Aim 1: *Conditional upon having failed to respond to CNRT in Phase I, the probability of abstinence at week twelve will differ as a function of staying on the same CNRT, augmenting CNRT with an additional nicotine patch (CNRT+) or switching to varenicline 2 mg (VAR). We hypothesize that switching to VAR will be superior to augmentation or continuation, and that augmentation will be superior to continuation.* Among participants failing to respond to CNRT at Week 6, logistic regression will evaluate the point prevalence of smoking at Week 12 as a function of continuing, augmenting, or switching treatment. The specific contrasts follow:

$$NRT + Loz_{nonresponders} \rightarrow Var\ 2mg - NRT + Loz_{nonresponders} \rightarrow NRT + Loz$$
$$= (\beta_0 - \beta_1 - \beta_4 + \beta_7) - (\beta_0 - \beta_1 + \beta_2 - \beta_5)$$

$$NRT + Loz_{nonresponders} \rightarrow 2 * NRT + Loz - NRT + Loz_{nonresponders} \rightarrow NRT + Loz$$
$$= (\beta_0 - \beta_1 + \beta_3 - \beta_6) - (\beta_0 - \beta_1 + \beta_2 - \beta_5)$$

$$NRT + Loz_{nonresponders} \rightarrow Var\ 2mg - NRT + Loz_{nonresponders} \rightarrow 2 * NRT + Loz$$
$$= (\beta_0 - \beta_1 - \beta_4 + \beta_7) - (\beta_0 - \beta_1 + \beta_3 - \beta_6)$$

Hypothesis Testing Aim 1: *Conditional upon having failed to respond to VAR in Phase I, the probability of abstinence at week twelve will differ as a function of staying on the same*

treatment, augmentation using varenicline 3 mg (VAR+), or switching to CNRT. We hypothesize that augmentation (VAR+) will yield higher rates of abstinence than switching to CNRT or remaining on VAR. Among participants failing to respond to VAR at Week 6, logistic regression will evaluate the point prevalence of smoking at Week 12 as a function of continuing, augmenting, or switching treatment. The specific contrasts follow:

$$Var\ 2mg\ _{nonresponders} \rightarrow Var\ 3mg - Var\ 2mg\ _{nonresponders} \rightarrow Var\ 2mg$$
$$= (\beta_0 + \beta_1 + \beta_3 + \beta_6) - (\beta_0 + \beta_1 + \beta_2 + \beta_5)$$

$$Var\ 2mg\ _{nonresponders} \rightarrow Var\ 3mg - Var\ 2mg\ _{nonresponders} \rightarrow NRT + Loz$$
$$= (\beta_0 + \beta_1 + \beta_3 + \beta_6) - (\beta_0 + \beta_1 - \beta_3 + \beta_7)$$

Hypothesis Testing Aim 1: *Conditional upon non-response, augmentation will demonstrate superiority for participants originally receiving VAR compared to those who received CNRT for abstinence at week twelve.* Logistic regression will evaluate the point prevalence of smoking at Week 12 as a function of treatment in Phase I, treatment in Phase II and the interaction of treatments in Phase I and II. The specific contrast follows:

$$Var\ 2mg\ _{nonresponders} \rightarrow Var\ 3mg - NRT + Loz_{nonresponders} \rightarrow 2 * NRT + Loz$$
$$= (\beta_0 + \beta_1 + \beta_3 + \beta_6) - (\beta_0 - \beta_1 + \beta_3 - \beta_6)$$

Hypothesis Testing Aim 1: *Conditional upon non-response, switching will demonstrate superiority for participants originally receiving CNRT compared to those who received VAR for abstinence at week twelve.* Logistic regression will evaluate the point prevalence of smoking at Week 12 as a function of Phase I treatment, Phase II treatment and the interaction of Phase I and Phase II treatments. The specific contrast follows:

$$NRT + Loz_{nonresponders} \rightarrow Var\ 2mg - Var\ 2mg\ _{nonresponders} \rightarrow NRT + Loz$$
$$= (\beta_0 - \beta_1 - \beta_4 + \beta_7) - (\beta_0 + \beta_1 - \beta_3 + \beta_7)$$

Exploratory Aims: To estimate the probability that abstinence at the end of week 6 (Phase 1) among those initially randomized to VAR or NRT conditions, will be moderated by salient baseline covariates. The covariates of interest include: 1) motivation, 2) dependence level, 3) nicotine metabolic ratio (normal vs. slow). In each case logistic regression will evaluate the point-prevalence of smoking at Week 6 as a function of the specified baseline covariate, treatment assignment, and the interaction of the specified covariate with treatment effects.[15,86-88] Initial analyses will use vague, neutral priors as specified in the General Data Analytic Strategy section. Evaluation of the sensitivity of conclusions to this choice of priors will use skeptical, informative priors on interaction terms as recommended by Dixon and Simon.[86] As recommended by the newly revised SRNT [23]guidelines additional secondary outcomes will also include prolonged and continuous abstinence at 3 and 6 months. *Effects of Treatment on Affect, Other Withdrawal Symptoms, and Craving:* Evaluation of affect, withdrawal, craving and nicotine reinforcement (PANAS, CES-D, WSWS, mCEQ) will use generalized linear modeling to determine the degree to which treatments/treatment strategies affect these variables at Weeks 6 and 12 [24,25]. *Adverse Events:* We will use Beta-Binomial models to examine differences in probability of adverse events by treatment.

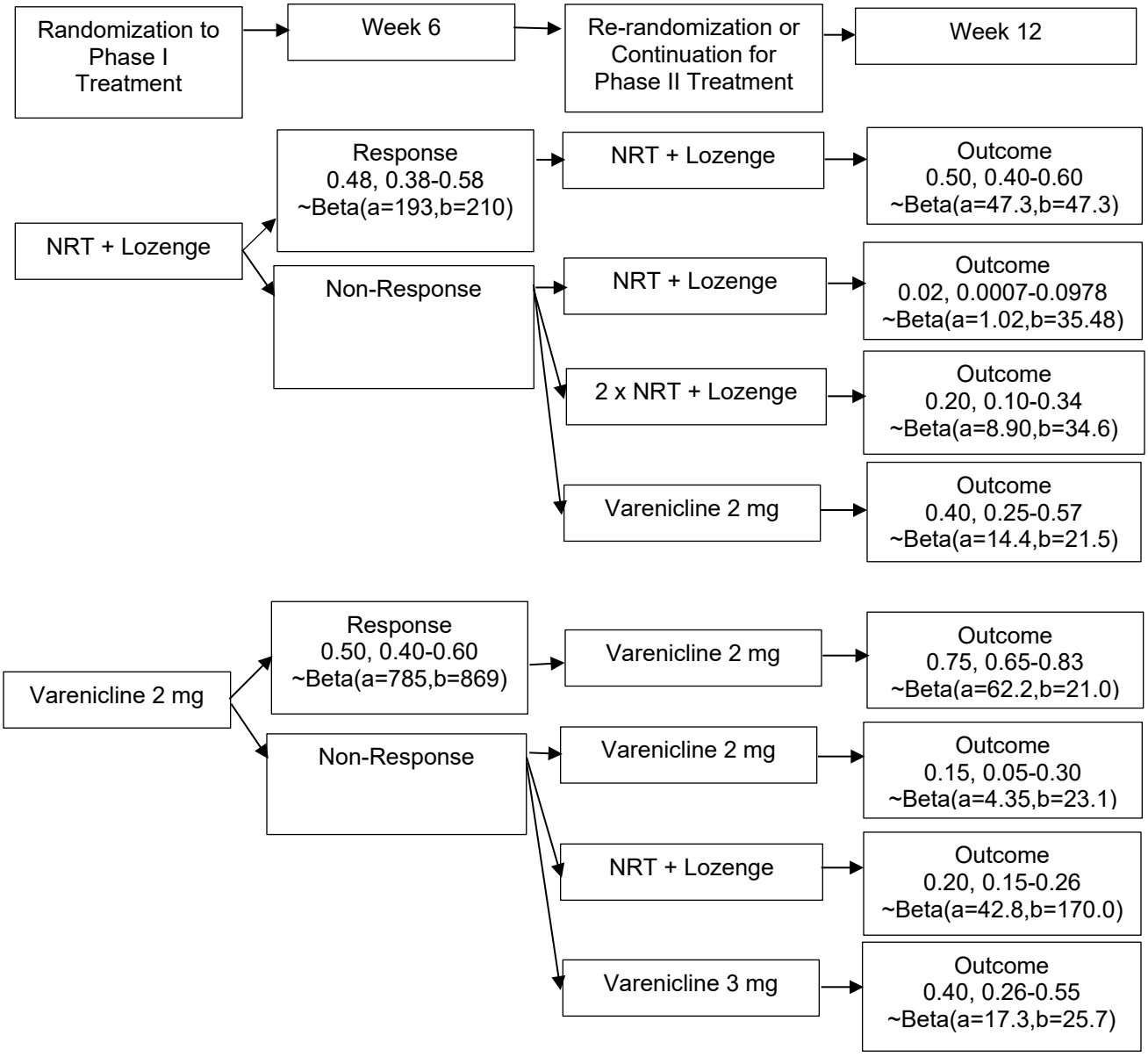
Power. Power estimates for this proposal focus on Hypotheses for Aims 1 through 5, our

primary outcome, seven-day point prevalence and treatment or treatment strategy. Estimated rates of seven-day point prevalence for VAR and CNRT at Week 6 derive from meta-analyses[9]. The probability of response at Week 12 conditional on response at Week 6 and continuation or non-response at Week 6 and continuation, augmentation or treatment switching were based on clinical consensus, taking into account the marginal rates of response at twelve weeks reported derived from meta-analysis[9]. We should note that these estimates are based on the more conservative response measure of continuous abstinence and are therefore modest representations of treatment effects. Finally, given the uncertainty inherent in pre-existing empirical evidence and even greater uncertainty for conditional probabilities of response based on clinical consensus and marginal estimates, prudence dictated that robust trial planning rely upon probability distributions of plausible effects rather than simple point-estimates. Such point estimates are unrealistic in failing to countenance the uncertainty in our predictions of effect. Adoption of distributional specification of effect sizes and their associated uncertainty required implementation of a Bayesian statistical approach. Decisions to advance the current study to a confirmatory phase will rely on the posterior probability that an effect exists. Specifically, we stipulate that a posterior probability of $\geq$ 0.90 that the postulated effect exists (i.e. Pr (Pr θ > 0|data) $\geq$ 0.90) constitutes sufficient evidence to warrant further evaluation.

Data Simulation Model

Figure 2 depicts the trial design, and for each outcome ascertainment point provides prior point estimates and 95% credible intervals for the probability of treatment response. These parameters correspond with the beta distributions specified for each outcome ascertainment point. Monte Carlo simulation of the clinical trial that incorporates sampling from these distributions permits estimates of power to detect effects taking into account uncertainty in parameter estimates. Analyses of the data generated from the specified ~Beta distributions for power estimates, used the logistic regression model and coding discussed above with vague, neutral priors for the coefficients in the log form (~N(mean = 0, variance = 1×10^6).

Figure 2.



Monte Carlo simulations (K = 1,000) determined predictive power for the planned analyses. Table 2 displays the probability point-estimates and 95% Credible Limits for each study cell, derived from logistic regression models, averaged across K = 1,000 simulations. The proposed data analysis model extracted the specified parameters.

Table 2.

Effect	Average Point Estimate	Average Interval (95% C.I.) Estimate
Responders		
NRT+Loz	0.504	0.441-0.566
Var 2mg	0.749	0.692-0.801
Non-Responders		
NRT+Loz→NRT+Loz	0.029	0.017-0.047
NRT+Loz→2*NRT+Loz	0.204	0.160-0.255
NRT+Loz→Var 2mg	0.399	0.343-0.458
Var 2mg→Var 2mg	0.159	0.120-0.203
Var 2mg → Var 3mg	0.404	0.347-0.463
Var 2mg → NRT+Loz	0.201	0.157-0.251

Table 3 displays estimates of predictive power to detect any benefit (H_A: $\theta > 0$) conferred by the treatment hypothesized as being superior. Predictive power to detect 0.80, 0.85, 0.90 and 0.95 probabilities of benefit are provided. All superiority hypotheses demonstrate a $\geq$ 80% chance of detecting 0.90 probability of benefit for a sample of N = 500. Table 3 also displays the point-estimates and 95% Credible Intervals of specified effects averaging over the K = 1,000 simulations. These point estimates and credible interval estimates derive from the proposed, data-analytic, logistic regression models. The average 95% Credible Intervals provide an index of the precision with which the current design may render estimates. In terms of clinical meaningfulness, meta-analytic review estimates the absolute risk reduction between two widely accepted first-line treatments (i.e. varenicline and bupropion) is 0.089 which is smaller than the lower-bound 95% Credible Limits for all contrasts in Table 3.

Table 3.

Effect	Posterior Probability Pr(θ>0)	Power to Detect Pr(θ>0)	Average Point Estimate	Average Interval (95% C.I.) Estimate
Effect of Treatment Phase I Responders	0.80	0.948	0.240	0.160-0.327
Hypothesis Test Aim 1	0.85	0.980		
	0.90	0.974		
	0.95	0.963		
Treatment Phase II Following Non-Response to CNRT				
Hypothesis Tests Aim 2				
VAR vs. CNRT	0.80	0.999	0.370	0.309-0.431
	0.85	0.999		
	0.90	0.999		
	0.95	0.998		
CNRT + vs. CNRT	0.80	0.964	0.175	0.125-0.228
	0.85	0.957		
	0.90	0.951		
	0.95	0.939		
VAR vs. CNRT	0.80	0.878	0.195	0.119-0.269
	0.85	0.863		
	0.90	0.842		
	0.95	0.819		
Treatment Phase II Following Non-Response to VAR				
Hypothesis Tests Aim 3				
VAR+ vs. VAR	0.80	0.930	0.245	0.172-0.316
	0.85	0.922		
	0.90	0.915		
	0.95	0.895		
VAR+ vs. CNRT	0.80	0.917	0.202	0.127-0.288
	0.85	0.905		
	0.90	0.890		
	0.95	0.859		
Treatment Phase I * Augmentation	0.80	0.885	0.199	0.123-0.274
Hypothesis Test Exploratory Aim 4	0.85	0.875		
	0.90	0.862		
	0.95	0.837		
Treatment I * Switching	0.80	0.899	0.198	0.123-0.272
Hypothesis Test Exploratory Aim 5	0.85	0.885		
	0.90	0.872		
	0.95	0.846		

6.0. PROTECTION OF HUMAN SUBJECTS

Potential Risks:

Adverse Experiences Associated with Varenicline. As reported in Micromedex (Thompson Healthcare) the frequency of adverse events reported for varenicline are as follows: Abdominal pain (5% to 7%), Constipation (5% to 8%), Flatulence (6% to 9%), Nausea (16% to 40%), Vomiting (1% to 5%); Neurologic: Dream disorder (9% to 13%), Headache (15% to 19%), Insomnia (18% to 19%). The typical side effects are not usually serious in nature and often abate within a few days to weeks after starting medication or once the medication is withdrawn. The most common, nausea, was rated by the majority of patients who experienced it as mild to moderate and resolved after 10-12 days. Less than 3% of smokers in the pivotal trials withdrew due to nausea.

Varenicline, which was first marketed in late 2006 is one of our most effective pharmacotherapies for smoking cessation [89]. However, in the years following its release, reports of serious neuropsychiatric adverse events began to appear, leading the FDA to issue a black box warning of potential increased risk of depression, suicidal ideation, suicide attempt, suicide completion, agitation and hostility associated with its use (http://www.pfizerpro.com/hcp/chantix/safety#bw). These reports were based on post-marketing surveillance tools such as MedWatch, which are voluntary and usually lack the detailed medical history and description of the circumstances required in clinical trials for proper adjudication of the event. Moreover, because patients with current psychiatric disorders and those recently treated for depression were excluded from the original phase 3 trials of varenicline, it was difficult to gauge the level of such risk in this potentially vulnerable group of patients. The uncertainly is also compounded by the fact that changes in negative affect, including depression and agitation are commonly associated with nicotine withdrawal. Nevertheless, this was an appropriate step, given the serious nature of these events and uncertainty of the evidence supporting these claims.

Anthenelli and colleagues conducted a double blind placebo controlled trail assessing the safety and efficacy of varenicline among 525 adult smokers with stably treated current or past major depression and no recent cardiovascular events [90]. The study population included smokers receiving antidepressants (72%) with no dosage changes in the last 2 months or anticipated changes during the study, and/or those successfully treated for depression in the last 2 years. Over a third of the enrollees presented with lifetime suicidal ideation or behavior. The study excluded those with a current or past psychotic, bipolar, or severe personality disorder or current suicidal or homicidal risk. Assessments of depression, anxiety, suicidality and specific neuropsychiatric symptoms of interest, were obtained using standardized instruments/interviews multiple times throughout the study, as were spontaneously reported adverse events.

Continuous abstinence rates were higher for varenicline vs. placebo at the end of treatment and through the 12 month follow-up. Both groups experienced a significant decline from baseline in ratings of depression and anxiety and there were no differences in any psychiatric side effects, including anxiety and mood disorders, hostility/aggression, or suicidal ideation/behavior.

The study by Anthenelli et. al. is the first to provide a direct evaluation of the safety and efficacy of varenicline in a subset of smokers with a current (stable) and past depressive disorder. As expected, the rates of smoking cessation associated with varenicline in this trial are somewhat lower than that observed in the pivotal trials (see for example Jorenby [69]) but the odds ratio is quite favorable (3.35 95% CI 2.16,5.21) and similar to an OR of 3.85 (95% CI 2.69,5.50) seen in

the Jorenby trial. As a prospective RTC, it provides some of the strongest evidence to date that the, smokers with currently stable depression can successfully quit smoking, and that the overall risk of neuropsychiatric side effects during smoking cessation in this population is low and not increased by the use of varenicline.

These results are consistent with other independent studies which failed to show an enhanced risk of neuropsychiatric adverse events with varenicline in both psychiatric [91] and nonpsychiatric patients [30] as well as large observational studies investigating suicidality [92] and psychiatric hospitaizations [93]. Taken as a whole, these results provide a less ominous picture than those emerging from the postmarketing reports, and importantly provide the clinical community with an empirical basis on which to base treatment decisions. A major strength of the study by Anthenelli is the use of repeated standardized psychiatric assessments, which eliminates the potential for selective reporting bias that could emerge from spontaneous, self-reports. These assessments revealed an overall decline in anxiety and depression and no change in other psychiatric symptoms, as opposed to an exacerbation which might otherwise been expected. These results are also consistent with our own findings which show that varenicline pharmaocotherapy can be expected to reduce depressive symptomatology in non-currently depressed smokers, regardless of whether they quit or not [30]. The Anthenelli study did not include patients with untreated or unstable depression or those with other psychiatric disorders. Hence the findings may not generalize to those with more serious psychiatric disturbance. However it is important to note that previous studies schizophrenic patients did produced similar safety findings [91]. Suicidal ideation was low during and after treatment (6.0%-7.5%) and did not differ across the groups [90]. A suicide attempt, which potentially represents one of the most serious adverse events, is extremely rare in this and other studies making it difficult to reach any firm conclusions regarding drug relatedness. However, we do have a context for understanding suicidality in relation to smoking. Nicotine dependence has the third highest population attributable fraction for suicide attempts of any psychiatric diagnosis after major depression and borderline personality [94], and is associated with an increased rate of suicides in patients seeking treatment independent of having a psychiatric disorder [95]. In addition, the large observational studies noted above did not find a signal for suicidal behavior [92,93].

In conclusion, the body of empirical evidence suggests that varenicline is a safe and effective medication for smoking cessation in a variety of patient populations including those with no current psychiatric disorder, and those with stable depression and schizophrenia. While we must always weigh the risk and benefits surrounding the use of any medication, the risk of neuropsychiatric adverse events among these groups, particularly for depression, anxiety, hostility, suicidal ideation and suicide itself, may be no more than what is expected within a population of smokers who are attempting to quit. In contrast, the risks of continued smoking for cardiovascular disease, cancer, COPD and other chronic diseases are well established. Continued research on smoking cessation among those with psychiatric disorders is highly important, as such individuals have a disproportionately high smoking prevalence [3].

A currently on-going trial sponsored by Pfizer is directly examining the safety of varenicline vs. bupropion, nicotine patch and placebo among smokers with and without current psychiatric disorders. The results of this trial which will include 8000 smokers will provide a definitive answer to the question of varenicline safety but the empirical evidence thus far appears contradictory to the post-marketing reports of increased risk of neuropsychiatric symptoms during smoking cessation pharmacotherapy.

Augmentation: Varenicline 3 mg**. Only individuals who tolerate the starting 2 mg varenicline dosing regimen well but continue to smoke will be eligible for augmentation.** Two prior open label studies have shown promising results in the augmentation of varenicline treatment for smoking cessation. In both studies the dose was increased from 2 mg to 3 mg if patients **tolerated varenicline well but continued smoking.** In one study that included 73 patients who continued to smoke after 8 weeks of varenicline 2 mg treatment, 4 additional weeks of varenicline 3 mg treatment resulted in 40% abstinence rates. The increase in dosage was associated with adverse events in 22 patients (30%) [16], though they were mostly mild. Only 2 patients discontinued treatment due to adverse events (nausea, in both cases). More specifically, the reported events are as follows: nausea (22), abnormal dreams (17), vomiting (13), insomnia (12), and headache (7). No neuropsychiatric events were reported. A naturalistic study with an open label design conducted here at MD Anderson Cancer Center involved 88 cancer patients that received varenicline for 12 weeks. Of those, 44 patients received 2 mg/day for the whole 12 weeks and 44 got an increase to 3 mg per day (2 mg q.a.m. and 1 mg q.p.m.) between weeks 6 and 8. At the end of treatment, 4 out of the 44 patients (9%) in the 2mg control group and 11 out of the 44 patients (25%) in the experimental group (3 mg) achieved abstinence. Patients whose medication was increased to a higher dosage (3 mg) were significantly more likely than those who continued to received 2 mg varenicline to report 7-day abstinence at week 12 ($\chi 2 = 3.94$, $p = .05$, OR = 3.33, 95% CI: 1.12 – 11.45) [17]. No increase in neuropsychiatric side effects was noted. In both cases, the results suggest that the increase in dosage was not only incrementally and statistically beneficial in achieving abstinence, but was also **well-tolerated by the participants**.

Adverse Experiences Associated with Nicotine Replacement Therapy (NRT): All of the commercially available forms of nicotine replacement therapy (NRT), i.e. gum, transdermal patch, nasal spray, inhaler, lozenge and sublingual tablet, are effective as part of a strategy to promote smoking cessation, enhancing long-term abstinence rates as much as 50 to 70% [18]. The 2008 US clinical practice guidelines [5] state that the long-term use of nicotine patch with another form of ad lib NRT is more effective than nicotine patch alone and recommend that physicians consider this option. Recent reports indicate that recommended changes to NRT product labeling by the FDA include a removal of the warning that consumers should not use an NRT product if they are still smoking, chewing tobacco, using snuff or any other product that contains nicotine—including another NRT. The FDA suggests to consumers, “There are no significant safety concerns associated with using more than one over-the-counter (OTC) NRT at the same time, or using an OTC NRT at the same time as another nicotine-containing product—including a cigarette” [96].

In general, the patch and lozenge are tolerated well by those who use it. The most frequent side effects reported by those using the patch are listed below. These side effects tend to be mild and include: nausea, redness at the patch site and/or minor swelling, dizziness, difficulty sleeping, rapid heart rate, abnormal dreams, increased blood pressure, headaches, rash and/or itching. Similarly, the most common side effects reported by users of the lozenge are insomnia (reported in less than 5 percent of cases), nausea, hiccups, coughing, heartburn, and headache. A review of adverse effects based on 35 trials with over 9,000 participants did not find evidence of excess adverse cardiovascular events among participants assigned to nicotine patch, and the total number of such events was low [97]. Additionally, a review of safety in patients with cardiovascular disease found no evidence of an increased risk of cardiac events [98]. Similarly, an analysis of 187 smokers admitted to hospital with acute coronary syndromes who received nicotine patches showed no evidence of differences in short- or long-term mortality compared to a propensity-matched sample of smokers in the same database who did not receive NRT [99].

Augmentation: Double Patch and Lozenge**. Only individuals who tolerate the starting NRT dosing regimen well but continue to smoke will be eligible for augmentation.** Several studies have reported little or no increase in clinically significant adverse events associated with use of high-dose nicotine replacement therapy [100-102]. For example, in terms of individual adverse events, two prior studies [100,102] found higher rates of nausea or vomiting with higher nicotine doses (incidence rates of 28 and 24%) in the 42-mg groups. One study also reported more sleep disturbances [100] and another reported increased skin reactions [103] with higher doses, though these were not reported in all studies [102]. Several studies using **high**-dose NRT in individuals who had not yet quit smoking (or relapsed) reported no higher incidence of cardiac or other adverse events [100-103]. Importantly, the authors concluded that because cessation is so important and the risk of higher doses so small, it's worthwhile to use higher doses [102]. **In another recent review, the authors concluded that increasing nicotine dose in NRT products either through combination or high-dose patches should not be restricted to highly dependent smokers and that increased nicotine delivery resulted in few clinically significant adverse events [21]**.

Protection Against Risks: Varenicline and NRT are both FDA approved medications for smoking cessation. Our procedures closely follow those used in previous clinical trials involving several medications for smoking cessation and include medical and psychiatric screening. Our study physician will identify participants who have contraindications for use of either drug and we will monitor participants for adverse reactions while they are on medication.

The typical side effects are not usually serious in nature and often abate within a few days to weeks after starting medication or once the medication is withdrawn. Adverse effects and concomitant medications will be assessed at each of the post-baseline visits. The study physician will monitor participants' complaints of adverse events and, when necessary, adjust the dosage or discontinue medication, order additional lab tests, etc. Adverse experiences and medication assessments will continue until 30 days following completion of the drug regimen.

We have conducted several studies using varenicline and use it regularly in our clinical program, treating over 1800 patients with this medication since 2006. We have developed a detailed safety monitoring protocol used to assess on-going psychiatric symptoms, and provide appropriate medical monitoring. The monitoring calls for a structured clinical assessment and where appropriate medical intervention of all self-reported psychiatric symptoms such as depression, anxiety and suicidal ideation. This safety plan has been previously approved by our IRB and DSMB (MDACC protocols 2003-1024 and 2008-0850) and will also be used in this trial.

Data Quality and Integrity

Because of the ongoing monitoring of the project, study investigators and staff are responsible for ensuring that data quality assurance procedures are developed and maintained. Several procedures will be used to maintain the integrity of the data. All databases will be stored in a centralized location on one of the departmental servers, which is backed up daily, with access limited to specific users at the discretion of the PI. The PI will assure that audits of selected subsets of data are performed and that appropriate safeguards of participant privacy are maintained. Privacy safeguards will include appropriate password protection and physical security for all computer systems.

Additional quality assurance procedures include a data collection protocol documented in a protocol manual; a two-stage editing procedure for survey data collection consisting of the initial review of the data collection form by a project member immediately following data collection, and a second review by a project member who will record any significant deviations from the

protocol; and regular meetings between the study statistician, the PI, data managers, and other project staff to review problems and solutions, and discuss concerns. Data entry systems, whether via a CATI, or QDS, system, scannable forms, or hand entry with verification, specifically provide field checks, range checks for continuous variables and valid value checks for categorical variables; checks for legitimate dates and times and logical consistency. During data collection, we will issue reports weekly, or even following any new data entry, depending on the needs of the project. Queries and reports will be provided to the PI. Preliminary review will be initiated shortly after data collection begins to allow monitoring of data quality.

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