ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A211401

REDUCING SURGICAL COMPLICATIONS IN NEWLY DIAGNOSED LUNG CANCER PATIENTS WHO SMOKE CIGARETTES

Varenicline and placebo provided and distributed by Alliance Research Base Pharmacy; IND holder: Exempt

ClinicalTrials.gov Identifier: NCT02856581

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Study Resources:

Expedited Adverse Event Reporting
[redacted]

Medidata Rave® iMedidata portal
[redacted]

OPEN (Oncology Patient Enrollment Network)
[redacted]

Biospecimen Management System
[redacted]

Protocol Contacts:

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Biospecimen Accessioning Processing
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Protocol-related questions may be directed as follows:	
Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox [redacted]
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox: [redacted]
Questions regarding specimens/specimen submissions:	appropriate Alliance Biorepository

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

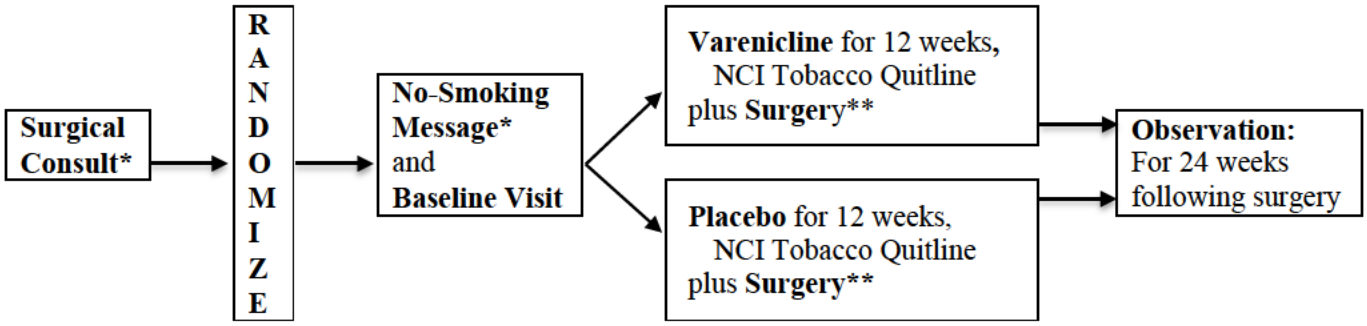
For regulatory requirements:	For patient enrollments:	For study data submission:
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at [redacted] and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN), which can be accessed at [redacted] Contact the CTSU Help Desk with any OPEN-related questions at [redacted]	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at [redacted] Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e., patient eligibility or treatment-related) see the Protocol Contacts, Page 2		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – [redacted]. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU website is located at [redacted].		

REDUCING SURGICAL COMPLICATIONS IN NEWLY DIAGNOSED LUNG CANCER PATIENTS WHO SMOKE CIGARETTES

Eligibility Criteria (see Section 3.2)

- Eligible patients will have either confirmed or suspected new diagnosis of lung cancer and have sought a surgical consult relating to this diagnosis.
- Surgery scheduled no sooner than 10 days after, and no more than 12 weeks after randomization.
- Have smoked daily or nearly every day in the previous 6 months up to the date of surgical consult AND have smoked at least one puff in the previous 7 days.
- Motivated to stop smoking, as indicated by a score of 6 or above on the Contemplation Ladder (see Appendix III)
- Cannot be currently using (past 30 days) any pharmacologic treatment using any nicotine delivery system (i.e., e-cigarettes and vape products) or be enrolled in a formal behavioral treatment program for tobacco dependence as determined during the surgical consult via patient report.
- No allergies to or not currently using varenicline.
- No suicidal thoughts as indicated by a positive (1+) response to question 9 on the PHQ9.
- No active untreated clinically significant psychiatric condition (psychosis, bipolar disorder, or depression).
- Not pregnant (see Section 3.2.9)
- No unstable angina, myocardial infarction, or coronary angioplasty within the past 3 months or an untreated cardiac dysrhythmia.
- No history of seizures.
- No unstable neurologic, hepatic, renal, cardiovascular, lymphatic, or metabolic disease.
- Not currently on renal dialysis or has a history of significant renal impairment.
- No recent history (past 3 months) of substance abuse (outside of tobacco) defined by NIAAA77 (see Section 3.2.14).
- No other household member or relative participating in the study.
- Patients must be able to complete study questionnaires in English.
- ≥18 years of age
- Calculated creatinine clearance ≥ 30 mL/min

Schema



Tobacco use will be assessed prior to registration, at randomization, and every six weeks during treatment and observation until 24 weeks after surgery

* The surgical consult, randomization, and Baseline Visit may take place on the same day. The surgical consult must precede randomization and the No-Smoking Message must be delivered following randomization.

** Surgery must occur after the target quit date (TQD) defined at baseline and can be performed no sooner than 10 days after randomization and no more than twelve weeks after randomization.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

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1.0 BACKGROUND

1.1 Rationale for Proposed Study

Can surgical teams capitalize on a teachable moment regarding the harmful effects of smoking that will reduce surgical complications among lung cancer patients who smoke? This study will introduce the management of a tobacco treatment intervention to health care providers who may not know what to do in managing lung cancer patients who smoke. By helping smoking surgical patients stop smoking, we are reducing harm by reducing post-operative complications. Therefore, this study will address both the prevention of worsening complications post operatively and hopefully reduction of smoking in lung cancer patients. This study will support the Alliance Prevention Committee's research priority aimed at tobacco harm reduction and cessation and will add to the NCORP research portfolio "Cancer control studies to reduce incidence and co-morbidity of cancer and its treatment and enhance quality of life". This study will address all four essential A's (Advise to Quit, Assess willingness to quit, Assist with quitting, and Arrange follow-up) recommended by the US Guideline model for treating tobacco use and dependence Guidelines (http://www.rcjournal.com/ contents/09.08/09.08.1217.pdf) [1].

1.1.1 Impact of Cigarette Smoking on Oncologic Treatment and Outcomes

Smoking is a significant risk factor for cancer, and smoking cessation efforts have been widely implemented among smokers as primary prevention of cancer development. In addition to its effects on carcinogenesis, smoking also impacts premalignant-to-malignant progression [2-8] and increases the risks for perioperative morbidity and mortality. Due to its effect on small vessels and oxygenation, smoking may also decrease the effectiveness of adjunctive treatments such as radiation and chemotherapy while at the same time increasing symptom burden. Smoking also increases the risk of secondary cancers [2-8]. Importantly, there has been an increasing body of evidence indicating that smoking can be a barrier to successful administration and completion of multimodality oncology treatments (including chemotherapy, radiotherapy, and surgery), and smoking can reduce both the quality of life (QOL) and long-term survival. Comparison of the 5-year survival of lung cancer between smokers and non-smokers has shown that only 33% of smokers survive 5 years compared to 70% of non-smokers [3-9].

Smoking causes temporary changes in the blood and tissue microenvironment (increased tissue CO2 and decreased O2 carrying capacity)[2] and in reparative cell functions, which can lead to delayed wound healing [2]. This can be responsible for prolonged recovery, which in turn, leads to an increase in the risks of hospital-acquired infections and other postoperative complications.[2-4] Smokers with gastrointestinal malignancies have a higher risk than non-smokers for surgical site infections (OR 1.25; 95% CI, 1.09–1.44), combined pulmonary complications (OR 1.60; 95% CI, 1.38–1.87), and reoperations (OR 1.20; 95% CI, 1.03–1.39)[10]. Complications of oncologic surgery (Appendix 1) can contribute to delays in the initiation of and lower ability to tolerate adjuvant therapy, further contributing to poor long-term cancer outcomes [11]. However, cigarette smokers diagnosed with cancer have not been a focus of smoking cessation efforts [12]. Cancer-directed treatments generally receive the bulk of attention after a cancer diagnosis, and smokers diagnosed with cancer represent a missed opportunity in smoking cessation and prevention of second cancers or recurrence of cancer.

1.1.2. Benefits of Smoking Cessation in Cancer Patients

Quitting smoking has beneficial health effects regardless of patient age.[13] Individuals who stop smoking significantly decrease their risk of lung cancer compared to current smokers.[7] For patients diagnosed with cancer, smoking cessation can improve cancer

treatment tolerance and effectiveness,[14, 15] overall survival,[13] prevention of second primary malignancy,[8, 16] and QOL.[17] Multimodal cancer therapy most often includes surgical procedures. Minimizing postoperative complications in oncology patients undergoing surgical procedures is of paramount importance both for minimizing treatment-related morbidities and for allowing a patient to go on to other components of the multimodal therapy. A reduction in complications has been observed within 4 weeks of smoking cessation.[18] Smoking cessation is beneficial at any time point relative to lung cancer surgery, but "current" smoking status at the time of surgery has been associated with a poor postoperative QOL.[19] A recent meta-analysis of 6 studies addressing smoking and surgical complications found that stopping smoking can reduce the relative risk of postoperative complications by 41% (95% CI, 15% to 59%; $P = 0.01$); each week of cessation prior to surgery increased this effect by 19%.[20] In addition, stopping smoking prior to chemotherapy and radiation therapy reduces the total symptom burden (sum of 12 symptoms scored on an 11-point Likert scale) of cancer treatment during treatment (smokers vs. nonsmokers: 46.3 vs. 41.2; $P < 0.05$) and at 6 months after treatment (27.7 vs. 21.9; $P < 0.05$).[21] Fewer than 10% of smokers actively seek treatment for tobacco dependence. Over 80% of providers in oncology practices provide brief smoking cessation counseling, but fewer than 30% ask about smoking in subsequent visits.[22] Barriers to smoking cessation among oncology patients include provider lack of confidence and patient lack of motivation.[22] Adjunctive use of a self-help guide for stopping smoking has been associated with improved motivation and has been found to be a predictor of long-term smoking cessation in oncology patients.[23, 24] Thus, effective methods for smoking cessation exist, but they have not been tested in the setting of a multicenter clinical trial targeting cigarette-smoking oncology patients who are scheduled for surgery.

1.1.3 Potential for Smoking Cessation Opportunities in Surgical Cancer Patients

Women smokers are 25.7 times more likely than women who never smoked to develop lung cancer. For men smokers, it's 25 times the risk of men who never smoked.[25] Among cancer patients who smoke, 85%-87% of cancer patients want to stop smoking.[26, 27] In one clinical trial, of the 263 cancer participants, the retention rate was approximately 84.5%.

Teachable Moment: Smokers with cancer presenting to a surgeon present a unique opportunity to intervene on smoking behavior. Opportunities in which patients have enhanced susceptibility to interventions on unhealthy behaviors are referred to as "teachable moments." Use of teachable moments can occur at office visits (associated with 2–10% success in smoking abstinence), notification of abnormal test results (7–21% success), pregnancy (10–60% success), and hospitalization and disease diagnosis (15–78% success).[28] Available evidence suggests that major surgery for a smoking-related cancer provides a significant and effective teachable moment for smoking cessation. A study of 5498 individuals demonstrated that older individuals (≥50 years) were more likely to quit smoking after a major medical procedure.[29] The steps in using a teachable moment to help smokers quit smoking include simple physician advice to quit, brief behavioral interventions provided by physicians or other clinicians, and pharmacotherapy.[30, 31] A recent randomized controlled trial testing the clinician-delivered message versus no message has shown randomizing within a site can be successful.[32]

Pharmacotherapy: Varenicline is a partial agonist/antagonist that binds with high affinity and selectivity at the α4β2 neuronal nicotinic acetylcholine receptors. It has been approved by the Food and Drug Administration (FDA) as a stop-smoking aid. Varenicline is presently the most efficacious pharmacotherapy for increasing smoking abstinence rates, with proven superiority over bupropion and suggested superiority over nicotine replacement therapy.[33, 34] In a head to head comparison of varenicline vs. bupropion the odds ratio (OR) at end-

of-treatment (12 weeks) were 3.85 (95% CI 2.69-5.50) for varenicline and 1.90 (95% CI of 1.38-2.62) for bupropion. The OR at end of study (6 months) was also significant with an OR of 2.83 (95% CI of 1.91-4.19) for varenicline and an OR of 1.69 (95% CI 1.19-2.42) for bupropion.[35] A recent systematic review of interventions for pre-operative smoking cessation has shown that of all the interventions tested in clinical trials, varenicline given pre-operatively was the only intervention with long term smoking cessation.[36] Although the safety and acceptability of varenicline among surgical patients with thoracic cancer has been previously tested,[37] the efficacy of varenicline in smokers who are diagnosed with cancer and are undergoing surgery has yet to be proven. Recent studies among non-cancer patients have confirmed that varenicline has the greatest efficacy for tobacco dependence treatment when combined with behavioral therapy,[38, 39] and is safe as well, dispelling previous concerns. [40-46] In addition, the results from an 18-study pooled analysis and a 5-study meta-analysis have been added to the label (currently in the process of being published in the literature).[47]

Behavioral Intervention (Tobacco Quitlines): According to the US guidelines, behavioral support is minimal intervention that all smokers should be receiving when trying to stop smoking. Behavioral support can be provided either as a stand alone or in conjunction with pharmacotherapy. Behavioral support can be provided in several different formats. Currently the two formats discussed in the US guidelines include face-to-face or by telephone. Telephone quitlines are one of the 10 key recommendations for effective tobacco dependence treatment.[1] The advantage of counseling via telephone quitline is that it can potentially provide wide-access to evidence-based cessation counseling while providing uniformity in the counseling approach, when utilizing a national quitline (vs. private or state quitline). Quitlines can include mailed materials, recorded messages, proactive and reactive contacts, and optional medication services.[48] A recent meta-analysis of 65 controlled studies, comprising of 73,000 participants, concluded that telephone quitlines provide an important approach in supporting smokers who are trying to stop smoking.[49]. The pooled odds ratio for a number of studies utilizing quitlines varies from 1.4 [50] to 1.6.[48] The US National Cancer Institute provided the very first telephone based quitline (early 1980's) as a component of the Cancer Information Service. A national referral service to the individual state/private quit lines is available through the use of 1-800-QUIT-NOW. The disadvantage of utilizing state or private quitlines in large national studies is that each state is privately funded and therefore clinical services can vary from providing medication, to only one initial consult, depending on available funding (see http://map.naquitline.org/). Utilizing a private quitline for the use of a large national research study can be expensive and many quitlines cannot support research since it would interfere with their clinical services. The NCI quitline (1-877-44U-QUIT) is a national federally funded service. They provide the smoker with counseling support, help develop a quit plan, provide follow up calls, mail quit materials (as needed), and answer questions concerning medications (medications are not provided). Using a toll free number, smokers across the United States can call in Monday through Friday 8 am to 8 pm (ET). These services are at no cost and services can be provided in both English and Spanish.

1.1.4 Genetics of Nicotine Addiction

Genetic variants in nicotinic receptor genes represent the strongest known genetic risk factors for nicotine addiction. The genetic variant rs16969968, which causes an amino acid change in *CHRNA5*, the gene encoding the α5 nicotinic receptor subunit, strongly contributes to nicotine addiction and heaviness of smoking.[51, 52] This variant also contributes to smoking-related diseases (lung cancer and chronic obstructive pulmonary disease).[52-54] In a genome-wide association meta-analyses including over 73,000

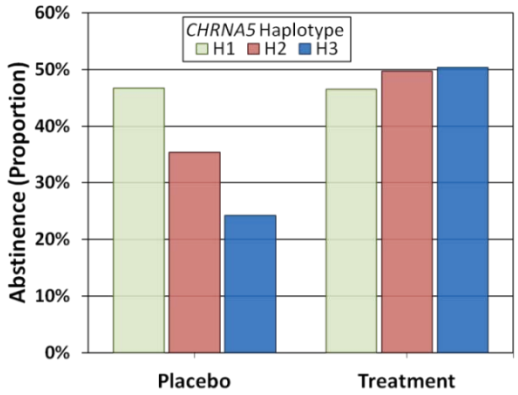
subjects, the chromosome 15 locus that includes the nicotinic receptor subunit gene cluster (*CHRNA5*, *CHRNA3*, and *CHRNB4*) had a highly significant association between rs16969968 and cigarettes per day ($P = 5.57 \times 10^{-72}$).[55-57]

Nicotine Metabolism Genes Contribute to Heavier Smoking: Conversion of nicotine to cotinine accounts for 70–80% of initial nicotine metabolism and is performed by cytochrome P450 2A6 (CYP2A6), which is located in the cytochrome p450 gene cluster on chromosome 19.[58-60] Variation in *CYP2A6* and nicotine metabolism efficiency is robustly associated with smoking phenotypes, especially cigarette consumption.[55, 61-64] *CYP2A6* is highly polymorphic, and genome-wide association meta-analyses have identified variants in the *CYP2A6* region associated with the number of cigarettes per day.[52, 57] Individuals with reduced-function alleles have significantly slower rates of nicotine metabolism, and several studies have reported an influence of nicotine metabolic rate upon cessation, with faster metabolism associated with lower abstinence and higher withdrawal symptoms.[65-67]

Nicotine Addiction and Smoking Cessation: The ultimate public health significance of understanding the biological underpinnings of nicotine addiction comes from translating that knowledge into improved treatment for smoking cessation. A critical step in translation is to determine whether genetic variants associated with nicotine addiction influence smoking cessation. Until recently, genetic studies of smoking cessation have been mixed, finding little evidence of replicable associations.[57, 68, 69]

We found that *CHRNA5-CHRNA3-CHRNB4* variants predict age of smoking cessation, age of lung cancer diagnosis, and response to smoking cessation treatments. In a recent meta-analysis, we found that the CHRNA5 variant rs16969968 is a marker of delayed smoking cessation and accelerated lung cancer diagnosis. The median age of smoking cessation for those with the high-risk variants (AA) at rs16969968 is 56 years versus 52 years for those with the low-risk variants (GG). Similarly, those with the high-risk variants have a 4-year earlier age of lung cancer diagnosis (61 years) compared to those with the low-risk variants (65 years) (Chen et al, in press, JNCI). This can be clinically significant given the high mortality following a diagnosis of lung cancer (50% die within a year of diagnosis and a 5-year survival rate of 16.6%). In clinical trials, those with high-risk genetic variants had more difficulty quitting without treatment, but this genetic risk was ameliorated by aggressive pharmacological treatment (Fig. 1) [70] (please also add reference Bergen et al, 2013)

Figure 1: Response to Pharmacotherapy Varies by Haplotypes*



- *CHRNA5* haplotypes were associated with failed smoking cessation in the placebo group (Wald $\chi^2 = 7.02$, df = 2, $P = 0.03$)
- *CHRNA5* haplotypes were not associated with smoking cessation outcomes in the treatment group ($P = 0.48$)
- The interaction of haplotypes and treatment on abstinence is significant (Wald $\chi^2 = 8.97$, df = 2, $P = 0.01$)

* *CHRNA5* haplotypes based on rs16969968 and rs680244 (N = 1073); H1 = G-C (21%); H2 = G-T; (44%) H3 = A-C (35%)

From Chen et al., 2012[70]

These results revealed a statistically significant interaction between the genetic variants and pharmacologic treatment. The clinical impact of this genetic and treatment interaction is exemplified by the number needed to treat (NNT), the number of patients who must be treated to prevent one additional bad outcome (e.g., relapse). For example, if a drug has an NNT of 10, it means one would need to treat 10 people with the drug to achieve smoking abstinence in one person. In this smoking cessation trial,[70] the overall NNT to prevent one relapse was 7, supporting the established effect of pharmacotherapy. However, the NNT varied widely depending on haplotype: the NNT was 4 for smokers with the high-risk haplotype (H3) versus >1000 for smokers with the low-risk haplotype (H1). This large difference in NNT was the first finding that genetic variants in the chromosome 15 region interact with treatment for smoking cessation.

Given the existing evidence that this CHRNA5 variant predicts accelerated risk for lung cancer and favorable response to cessation pharmacotherapy, these findings underscore the potential clinical and public health importance of rs16969968 in CHRNA5 in relation to smoking cessation treatments.

1.2 Significance and Innovation of this Study

The adverse health consequences of smoking are profound,[71-75] and capitalizing on the unique teachable moment surgeons have available for smokers after cancer diagnosis may reduce post-operative complications. Further, if post-operative complications can be reduced or ameliorated, the cost of care, length of time in the hospital, and quality of life aspects of the cancer experience can be improved. Observational evidence indicates that smoking cessation prior to cancer surgery reduces complications such as pneumonia, failure to wean from ventilator, re-intubation, and prolonged hospital stays [10]; however, the optimal approach to achieving abstinence in this population is not known.

The innovation of this study is that it directly engages the surgical team in cancer control studies by taking advantage of the unique teachable moment that the surgical team has with the patient pre-operatively. Controlling for the definition of abstinence, the duration of abstinence relative

to surgery, the surgical team's message, and the smoking cessation intervention in a large population, will help us identify the parameters that will yield both the highest success rates for quitting and the best perioperative outcomes with respect to morbidity and QOL.

The correlative genetic component of this trial may differentiate patients who are likely to respond strongly to pharmacologic treatment from those who receive little benefit. This will allow us to better target treatments and will contribute to our goal of using genetic information to develop personalized medicine.

1.3 Study Overview

This will be a randomized clinical trial. The primary goal is to assess the effect of smoking cessation treatment on surgical complications. We will also report the impact of alternative treatments on QOL and post-operative care. According to the US Guidelines[1], although counseling and medication are effective when used alone, the combination of both is more effective than either alone. Thus clinicians should encourage smokers who want to quit, to use both counseling and medication in trying to quit smoking (#7 of the 10 key guideline recommendations). In this study, 626 cancer surgery patients will be randomized 1:1 to a "protocolized" smoking cessation program (varenicline plus a brief no-smoking message from the surgical team and behavioral support provided by a telephone smoking quitline [NCI's 1-877-44U-QUIT]), or to placebo plus a brief no-smoking message from the surgical team and behavioral support provided by the telephone smoking quitline). Surgery must occur after the target quit date (TQD) defined at baseline and can be performed no sooner than 10 days after randomization and no more than twelve weeks after randomization. The study will remain open to accrual until 626 patients have had surgery and are followed for 24 weeks after surgery for surgical complications. The primary outcome will be the rate of surgical complications, as identified from an investigation of the American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP). Secondary outcomes include QOL, post-operative care (length of hospital and high dependency unit stay), and rates of smoking abstinence. All study participants will have the option of enrolling in the correlative genetic study. This correlative study will look at important genetic variants in nicotinic receptor gene cluster (*CHRNA5-CHRNA3-CHRNB4*) and nicotine metabolism (*CYP2A6*) that have been shown to impact successful smoking abstinence. This will include a blood draw at baseline, and tobacco use outcome will be determined by salivary cotinine at baseline and every six weeks after surgery for 12 weeks, with a final measurement at 24 weeks.

1.4 Feasibility, Accrual Time, and Study Duration

A survey of legacy ACOSOG thoracic surgeons and the Alliance Community Oncology Committee members has shown that the vast majority of sites that see these patients would be interested in accruing patients for this study. From accrual estimates provided by sites in this survey, we anticipate accruing 150 evaluable patients per year. In the opinion of these surgeons, this study is highly feasible to accrue quickly. We conducted a follow-up survey asking surgical practices to describe in detail the manner in which the workflow for the study would be carried out. This survey provides us with example templates to guide potential participating sites. Given these data and our past experience with accruing patients to smoking cessation studies, we anticipate that our accrual estimate is conservative. In previous NCCTG trials accrual rates of as high as 25 patients per week were achieved, albeit in mixed treatment practices. As already indicated, however, we have done multiple surveys of Alliance surgical practices who indicate strong support for the study, with specific accrual expectations and workflow details. Hence the sites are unusually well prepared and aware of the needs to accrue to this study and are eagerly awaiting the trial opening. That likelihood of rapid accrual, plus the involvement of surgeons in the prevention aim, is a major selling point for the trial. This study accrual will close when

626 study patients have undergone surgery; therefore, we anticipate patient accrual to be completed in approximately 4 years and 2 months.

2.0 OBJECTIVES

Because of the considerable discussion surrounding the goals of this study, we include the following declarative and definitive statements:

I. The goal of this study is to examine the impact of alternative interventions for smoking cessation on the reduction of surgical complications.

II. Smoking cessation is an intermediate and concomitant secondary outcome that is not the focus of this study, because it already is well known that smoking cessation interventions reduce smoking incidence in cancer patients.

2.1 Primary objective

To determine if varenicline plus a behavioral intervention consisting of a brief clinician-delivered intervention and tobacco quitline follow-up, decreases postsurgical complications through 24 weeks after surgery when compared to placebo plus the behavioral intervention in lung cancer patients who undergo surgery and are motivated to stop smoking.

2.2 Secondary objectives

2.2.1 To compare changes from baseline to 12 and 24 weeks after surgery in the patient quality of life (LASA-12) domains between the intervention (varenicline) and control group (placebo).

2.2.2 To compare changes from baseline to 6, 12 and 24 weeks after surgery in the patient quality of life related domains (LASA) for the PHQ-9 and SEQ12 between the intervention and control groups.

2.2.3 To compare the proportion of patients 12 weeks and 24 weeks after surgery who endorse ("Was It Worth It") each treatment (intervention vs. control groups).

2.2.4 To compare post-operative care (as measured by length of hospital and high dependency unit stay) between the intervention and control groups.

2.2.5 To compare treatment adherence between the intervention and control groups.

2.2.6 To compare rates of smoking abstinence between the intervention and control groups as a covariate of the primary outcome only.

2.3 Correlative science objectives

2.3.1 To evaluate the predictive role of the nicotinic receptor gene cluster (*CHRNA5-CHRNA3-CHRNB4*) and *CYP2A6* genotypes in smoking cessation among lung cancer patients undergoing surgery.

2.3.2 To evaluate the potential moderating effect of these cessation-relevant genotypes on smoking cessation treatment between the intervention and control groups.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.
- Patients who cannot swallow oral formulations of the agent.

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following pages.

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday four weeks later would be considered Day 28.

___ **3.2.1** Eligible patients will have either confirmed or suspected new diagnosis of lung cancer and have sought a surgical consult relating to this diagnosis.

___ **3.2.2** Surgery must be scheduled no sooner than 10 days after randomization and no more than twelve weeks after randomization

___ **3.2.3** Have smoked daily or nearly every day in the previous 6 months up to the date of surgical consult AND have smoked at least one puff in the previous 7 days.

___ **3.2.4** Motivated to stop smoking, as indicated by a score of 6 or above on the Contemplation Ladder (see Appendix III).76

___ **3.2.5** Within the 30 days before registration, no use of: 1) any pharmacologic treatment for smoking cessation, including buproprion or nicotine replacement therapy; 2) any nicotine delivery system (i.e., e-cigarettes and vape products); or 3) be enrolled in any formal behavioral treatment program for tobacco dependence as determined by patient report.

___ **3.2.6** No allergies to and not currently using varenicline.

___ **3.2.7** No suicidal thoughts as indicated by a positive (1+) response to question 9 on the PHQ9.

___ **3.2.8** No active untreated clinically significant psychiatric condition (psychosis, bipolar disorder, or depression).

___ **3.2.9** Negative pregnancy test (serum or urine) done ≤7 days prior to registration, for women of childbearing potential only.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

___ **3.2.10** No unstable angina, myocardial infarction, or coronary angioplasty within the past 3 months or an untreated cardiac dysrhythmia.

___ **3.2.11** No history of seizures.

___ **3.2.12** No unstable neurologic, hepatic, renal, cardiovascular, lymphatic, or metabolic disease.

___ **3.2.13** Not currently on renal dialysis or has a history of significant renal impairment.

___ **3.2.14** No recent history (≤ 90 days) of substance abuse (outside of tobacco) defined by NIAAA [77] as:

- If male, drinking >14 alcoholic beverages per week for past 1 month.
- If female, drinking >7 alcoholic beverages per week for past 1 month.
- Use of cocaine, heroin, club drugs (i.e., MDMA/"ecstasy"), methamphetamine, or hallucinogens (e.g., LSD) at any time during the past 1 month.
- Use of marijuana on a weekly basis for the past 1 month.

___ **3.2.15** Patients must be able to complete study questionnaires in English.

___ **3.2.16** ≥18 years of age

___ **3.2.17** No other household member or relative participating in the study.

___ **3.2.18** No known history of any condition or factor judged by the investigator to preclude participation in the study or which might hinder study adherence.

___ **3.2.19** Calculated creatinine clearance ≥ 30 mL/min.

Creatinine clearance (CrCl) will be calculated using the Cockroft-Gault equation as follows:

$$\text{CrCI (ml/min)} = \frac{(140\text{-age}) \times \text{actual wt (in kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

For females, use 85% of calculated CrCl value

4.0 PATIENT REGISTRATION

4.1 CTEP/DCP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account [redacted] In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, Rave, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) [redacted] Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at [redacted] For questions, please contact the RCR Help Desk by email at [redacted]

4.2 CTSU Site Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in

the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Site Registration Documents

Site registration forms may be downloaded from the A211401 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to [redacted] and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the Alliance link to expand, then select trial protocol #A211401
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

4.2.2 Requirements for A211401 Site Registration

IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal [redacted] (members' area) → Regulatory Tab → Regulatory Submission Portal

When applicable, original documents should be mailed to:

[redacted]

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] in order to receive further instruction and support.

4.2.4 Checking Your Site's Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to [redacted] and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration Requirements

Informed consent: The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

Patient completed booklets: Patient questionnaire booklets are to be ordered prior to the registration of any patients. Patient completed booklets can be ordered by downloading and completing the CTSU supply request form (located under the site registration documents section of the A211401 CTSU site) and faxing the form to the CTSU data operations center at [redacted]. The questionnaires found in the booklets are listed in Appendices II-IX. The example questionnaires in the Appendices are for reference only and not for patient completion.

Institutional Credentialing: Surgeons and institutional staff participating in this study must have undergone training outlined in Section 15.0. Training must be confirmed by the study chair before any patients may be enrolled to this study.

4.4 Patient Registration/Randomization Procedures

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at [redacted] and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at [redacted] or from the OPEN tab on the CTSU members' side of the website at [redacted]. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer

in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at [redacted] or at [redacted]. For any additional questions contact the CTSU Help Desk at [redacted].

4.5 Registration to Correlative and Companion Studies

There is one substudy within Alliance A211401. This correlative science study **must be** offered to all patients enrolled on Alliance A211401 (although patients may opt to not participate). This substudy does not require separate IRB approval. The substudy included within Alliance A211401 is:

- Pharmacogenetics of Smoking Cessation Treatment (POST), Alliance A211401-PP1 (Section 14.2)

If a patient answers "yes" to "My samples and related information may be used for the additional study described above," Question #1 in the model consent, they have consented to participate in the substudy described in Section 14.2. The patient should be registered to Alliance A211401-PP1 at the same time they are registered to the treatment trial (A211401). Samples should be submitted per Section 6.2.

4.6 Treatment Assignments and Blinding

Patients will be randomized 1:1 to receive one of two blinded treatments:

Intervention Group: Participants will receive varenicline for 12 weeks plus a brief no-smoking message from the surgical team and behavioral support provided by a telephone smoking quitline (NCI's 1-877-44U-QUIT).

Control Group: Participants will receive placebo for 12 weeks plus a brief no-smoking message from the surgical team and behavioral support provided by a telephone smoking quitline (NCI's 1-877-44U-QUIT).

After the treatment assignment has been ascertained in the OPEN application, the patient's study medication code number will be displayed on the confirmation of registration screen.

The pharmacist or designated contact person at the treating site will maintain records that indicate the identity of the patient and their corresponding study medication code number.

5.0 STUDY CALENDAR

Pre-Study Testing Intervals

- To be completed ≤ 16 DAYS before registration: History and physical.
- To be completed ≤ 6 months before registration: Serum creatinine.

	Prior to Surgery		Day of Surgery**	Post-Surgery***			
Visit week	**Prior to Registration†**	**Baseline***	**0**	**6**	**12**	**18**	**24**
Visit #	**1**	**2**		**3 (A)**	**4 (A, B)**	**5 (A, B)**	**6**
Tests and observations							
History & physical (weight, bp, pulse)	E	E		X			X
Height	X						
Serum creatinine	X						
Pregnancy test	C						
Concomitant therapies		X		X	X	X	X
Adverse events		X		X	X	X	X
Surgical adverse events				X(1)	X(1)	X(1)	X(1)
Suicidal ideation monitoring				X (2)	X (2)	X (2)	X (2)
Tobacco use assessment (Appdx IX)	X	X	X	X	X	X	X
Surgical team message		X					
NCI Smoking Quitline		X (3)		X (3)	X (3)		
Sample submission							
Salivary Cotinine Measure		X	X	X	D	D	X
Patient questionnaires							
Contemplation Ladder (Apdx III)	X			X	X		X
SEQ-12 (Apdx IV)		X		X	X		X
FTND (Apdx V)		X					
PHQ-9 (Apdx VI)	X (4)			X	X		X
LASA-12 (Apdx VII)		X			X		X
Was It Worth It Survey (Apdx VIII)					X		X
Drug and Behavioral Support Adherence Logs (Apdx X)		X		X	X		
Correlative study (optional)							
Whole blood	*To be collected at baseline, see Sections 6.2 and 14.0.*						

† Pre-study testing may be performed on the same day as the baseline visit (see also, Section 7.1).

* Baseline: After randomization and at the time the surgical message is discussed with the cancer patient. If performed within 7 days prior to baseline, the Tobacco Use Assessment need not be repeated.

** Surgery must occur after the TQD defined at baseline and can be performed no sooner than 10 days after randomization and no more than twelve weeks after randomization.

*** Post surgery visits can be +/- 14 days

A Patient-completed booklets for Weeks 12 and 18 should be given to patients at the Week 6 visit. Institutional staff should telephone patients within one week prior to Weeks 12 and 18 to remind them that they will either be completing these booklets by telephone at Weeks 12 and 18 or that they may bring the completed booklet to the clinic when they provide saliva samples for cotinine measurements (see Footnote D).

B May be done by telephone or in person (see footnote D).

C For women of childbearing potential. Must be done within 7 days prior to registration/randomization.

D Patients will be asked to come to the treating institution to provide saliva samples for cotinine measurement. A physician visit is not required.

E History and Physical may take place either at pre-registration or at the baseline visit.

1 See Section 9.1 and Appendix I.

2 Per Question 9 on the PHQ-9. See Section 8.2.3.

3 At the baseline visit, study staff will assist the patient in making the first contact with the NCI Quitline. At the 6- and 12-week clinic visits, patients will be asked if they utilized the Quitline since their last visit and data will be collected on its use.

4 Only the patient response to Question 9 is required at pre-registration in order to determine eligibility (see Section 3.2.7).

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at [redacted] and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login [redacted] using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at [redacted] or by contacting the CTSU Help Desk at [redacted] or by e-mail at [redacted].

A Schedule of Forms is available on the Alliance study webpage, within the Case Report Forms section. The Schedule of Forms is also available on the CTSU site within the study-specific Education and Promotion folder, and is named Time & Events.

Patient-completed questionnaire booklets for this study are to be ordered prior to the registration of any patients (see Section 4.4). The questionnaires found in the booklets are listed in Appendices II-IX. The example questionnaires in the Appendices are for reference only and not for patient completion.

Booklets must be given to patients to complete and patients should be instructed to return the booklets to site staff either in person, by telephone, or by mail and site staff will enter patient responses into Rave.

6.2 Specimen collection and submission

Salivary cotinine testing will be performed on all patients enrolled to this study. **The submission of these samples for cotinine testing is required for all patients registered to this study.** Rationale and methods for the scientific components of this study are described in Section 14.1.

In addition, all participating institutions must ask patients for their consent to participate in the correlative substudies planned for Alliance A211401, although patient participation is optional. Biomarker and pharmacogenetic studies will be performed. Rationale and methods for the scientific components of this study is described in Section 14.2.

REQUIRED for all patients registered to A211401:

Visit	Baseline	Surgery	At 6, 12, 18 and 24 weeks	Ship to:
Saliva	X	X	X	Mayo BAP

For patients registered to A211401 PP1, submit the following:

	Baseline	Submit to:
	Number and volume of tubes to draw	
Plasma and buffy coat (EDTA Vacutainer)	2 x 10 mL	Mayo BAP

6.2.1 Specimen submission using the Alliance Biospecimen Management System

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: [redacted] using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS webpage to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: [redacted] For assistance in using the application or questions or problems related to specific specimen logging, please contact: [redacted]

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted specimens must be labeled with the protocol number (A211401), Alliance patient number, patient's initials and date and type of specimen collected (e.g., serum, whole blood).

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

Ship specimens on Monday through Thursday only. Shipping by overnight service to assure receipt is encouraged. Do not ship specimens on Fridays or Saturdays [unless lab specifies Saturday delivery].

All specimens should be sent to the following address:

[redacted]

6.2.2 Saliva sample collection and submission

For patients enrolled on study, saliva samples will be obtained to analyze for cotinine as described in Section 14.1. Samples may batched, but should be submitted at least every 3 months.

Saliva collection procedures for sites:

1. Confirm that SalivaBio Passive Drool Method collection kit is available. (Please find order information at [redacted].

   Kits may also be ordered from Fisher Scientific:

   [redacted]
2. Document the presence of any significant oral infection or injury.
3. Patient should rinse mouth well with water about 5 minutes prior to collection to remove any food residue. Repeat if needed. No food or liquid intake before saliva collection.
4. Patient saliva should be collected following the kit instruction to get about 0.5-1ml saliva and freeze saliva samples at -20° C within 30 minutes or sooner if possible.
5. Document time between collection and placement in freezer.
6. Saliva samples should be kept frozen at -20° C until shipping samples to the Mayo Clinic biorepository, who will then batch shipments (every 6 months) to G. Warren at the Medical University of South Carolina for quantitative cotinine analyses.

Label samples with the following identification:

1. Alliance study number (A211401)
2. Alliance patient ID number
3. Patient's initials (L, F M)
4. Date and time of specimen procurement
5. Sample type (i.e. saliva)

6.2.3 Blood sample submission

For patients who consent to participate, blood samples will be used for the biomarker and pharmacogenomics analyses described in Section 14.2. Samples may batched, but should be submitted at least every 3 months.

Collect 2 x 10 mL of peripheral venous blood in EDTA vacutainer tubes at the baseline visit.

Plasma: Centrifuge whole blood at 1,300 x g for 5 minutes at room temperature. Transfer 1 mL of plasma into each labeled 2 mL cryovial. Typically one can get 3 x 1 mL aliquots per 10 mL tube without disturbing the buffy coat (which will be saved for submission per the instructions below). Record the number of aliquots created on the Biospecimen Submission Form (BSF) Transfer plasma specimens to temporary storage at -80 °C until shipment. If there are no -80°C freezers available, keep the plasma samples on dry ice for up to 48 hours before shipment. Ship on dry ice to the Alliance Biorepository at Mayo clinic per Section 6.2.1.

Label samples with the following identification:

1. Alliance study number (A211401-PP1)
2. Alliance patient ID number
3. Patient's initials (L, F M)
4. Date and time of specimen procurement
5. Sample type (i.e. plasma)

Buffy coat: After the plasma has been removed from the vacutainer tube as described above, remove the buffy coat layer (approximately 1 mL per 10 mL EDTA tube) and transfer into 2 mL cryovial(s). Snap freeze specimen in LN2 or EtOH / dry ice bath OR place in - 80°C if the others are not available. Transfer specimen to temporary storage at -80°C until shipment. If there are no -80°C freezers available, keep the plasma samples on dry ice for up to 48 hours before shipment. Ship on dry ice to the Alliance Biorepository at Mayo clinic per Section 6.2.1.

Label samples with the following identification:

1. Alliance study number (A211401-PP1)
2. Alliance patient ID number
3. Patient's initials (L, F M)
4. Date and time of specimen procurement
5. Sample type (i.e. buffy coat)

7.0 TREATMENT PLAN/INTERVENTION

7.1 Study outline

It is understood that clinic practices may vary with respect to how patients eligible for this study are identified and treated. The following outline of study procedures has been provided to guide participating institutions with respect to the order of events for this trial.

Screening: It is expected that at the time patients are referred to the surgical clinic (e.g., from pulmonary or interventional radiology service, primary care physicians), they will be screened for this study. Alternatively, site staff may review internal medical records to identify patients eligible for the study who have not yet completed the surgical consult. Time permitting, pre-registration tests, observations, and questionnaires may be completed on the same day as registration/randomization and the Baseline Visit.

Surgical Consult: The surgical consult may be done as part of the screening process. It must be completed prior to registration/randomization. PLEASE NOTE: The No-Smoking Message can only be delivered AFTER registration/randomization, as this is part of the study intervention

Registration/Randomization: Patients must be registered/randomized following informed consent and prior to the Baseline Visit (see below).

Baseline Visit: The Baseline Visit will include the delivery of the No-Smoking Message by the Surgical Team Member, collection of saliva for cotinine measurement, baseline assessments per Section 5.1, and the completion of the baseline questionnaires.

7.2 Behavioral Intervention (Baseline visit)

Teachable Moment – No-Smoking Message from Surgical Team Member: This message will be given to all patients on study during the Baseline Visit, and can be delivered by the surgeon or by a designated surgical team member. This message contains the following key sections:

(1) There is no better time to quit than when you are having cancer surgery;

(2) Unique detriments of smoking in patients facing cancer surgery: a) tobacco-related carcinogenesis/pre-malignant to malignant progression; b) increased risks of perioperative morbidity or mortality; c) increased risk for surgical complications and wound healing time; d) possible decrease in the effectiveness of adjunctive cancer treatments and increased side effects of these treatments; e) increased risk of secondary cancers;

(3) The best time to stop smoking is now;

(4) We know it is difficult and many other health care professionals are ready to help you do this; and

(5) The study team will be in contact with you periodically throughout the course of the study.

QUITLINE: Quitlines are an approved and cost-effective smoking cessation behavioral intervention[76] Quitlines are recommended by the US Smoking Cessation Guidelines[1] for their wide reach in large populations. The quitline selected to be used in this study can continue to be used by each study site long after the study is complete as it is free of charge to all. Support will be provided by the National Cancer Institute Telephone Smoking Quitline, 1-877-44U-QUIT, (1-877-448-7848). This is a toll free telephone line within the United States and provides smoking cessation counseling Monday through Friday 8 am to 8 pm Eastern time. After randomization, the study staff will assist the patient in making the first contact with the quitline.

HANDOUT: All patients will also receive a handout with reminders of why they should stop smoking (message from surgeon) and quitline information.

7.3 Target Quit Date

Following the baseline visit, patients will receive the full 12 week supply of drug. The target quit date (TQD) is to be determined during the baseline visit and should occur prior to the planned date of surgery. It must be at least 10 days after randomization. While it is understood that is rare for surgery in this patient population to be delayed, in order to allow for flexibility in exigent circumstances, the maximum time from randomization to the TQD will be 12 weeks.

7.4 Pharmacologic Intervention (Varenicline)

The initiation of the one-week dose escalation period of varenicline/placebo treatment will be considered Day 1 and the target quit date (one week later) will thus be Day 8 of therapy. Patients will be provided with instructions on the proper use of the medication (i.e., time of day to take the medication).

During Week 1, the dosing will be one of the 0.5 mg varenicline/placebo pills per day for the first 3 days followed by two 0.5 mg pills a day (morning and evening) for the next 4 days.

Weeks 2-12: Day 8 is the target quit day and on this day the patient will take two 0.5 mg pills twice daily (morning and evening). Patients will stay on this dose for 11 weeks.

Agent	Dose	Route	Day	
Varenicline/Placebo	0.5 mg	Oral	Days 1-3	1 pill per day
Varenicline/Placebo	0.5 mg	Oral	Days 4-7	1 pill twice per day – Minimum of 8 hours apart
Varenicline/Placebo	0.5 mg	Oral	Days 8-84	2 pills twice per day – Minimum of 8 hours apart (4 pills per day total)

Dosing should occur with 240 mL of water and it is recommended that patients eat prior to dosing to decrease gastric upset. It is recommended that there be at least 8 hours between the morning and evening dosing. If a dose is missed, the patient should take it as soon as s/he remembers. If it is almost time for the next dose (within 6 hours), the patient should skip the missed dose and take the next one as scheduled. Patients should not take a double dose of varenicline/placebo.

Participating institutions should have a suicide ideation monitoring and response procedures in place. An example of such procedures has been provided in Appendix XI.

8.0 DOSE AND TREATMENT MODIFICATIONS, UNBLINDING

8.1 Ancillary therapy, concomitant medications, and supportive care

8.1.1 Patients should not receive any other agent which would be considered treatment for smoking which can impact the primary endpoint. This includes, any nicotine replacement products (patch, gum, nasal spray, inhaler), bupropion, naltrexone,

8.1.2 Adjuvant chemotherapy and radiation therapy with curative intent for patients enrolled to this study is permitted.

8.1.3 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

8.1.4 Diarrhea management is per the discretion of the treating physician. Diarrhea could be managed conservatively with medications such as loperamide.

8.1.5 Alliance Policy Concerning the Use of Growth Factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based, Clinical Practice Guideline. J Clin Oncol 24(19): 3187-3205, 2006.

8.2 Dose Modifications

The following general guidelines apply to all adverse events except suicidal ideation or personality change (see Sections 8.2.7 and 8.2.8). Addition information regarding insomnia and nausea is provided in Sections 8.2.5 and 8.2.6.

- All missed doses should be considered as skipped and not delayed. That is, the duration of treatment must not continue past the original 12-week stop date.
- Patients may be re-challenged only one time for grade 3 events. That is, if a particular adverse event recurs after a dose reduction and rechallenge, varenicline/placebo will be permanently discontinued.
- If treatment is skipped for more than four weeks due to toxicity, permanently discontinue varenicline/placebo.

8.2.1 Dose Levels

Dose Level 0	0.5 mg x 2 tablets twice daily
Dose Level -1	0.5 mg x 2 tablets once daily
Temporary discontinuation	

8.2.2 For Grade 1 or 2 adverse events possibly related to varenicline, will be followed per physician's discretion. Also, At the physician's discretion, varenicline/placebo dose may be continued, reduced to Dose Level -1, or be temporarily discontinued.

Re-challenge:

- If varenicline/placebo dose is reduced or temporarily discontinued, patients may be re-challenged at the physician's discretion to the next higher dose level the adverse event remains at grade 2 or better.
- If varenicline/placebo was temporarily discontinued and the patient was successfully rechallenged to Dose Level -1 and the adverse event remains at grade 2 or better after an additional week, the dose of varenicline/placebo may be resumed at Dose Level 0 at the discretion of the treating physician.

8.2.3 For Grade 3 adverse events possibly related to varenicline, patients will temporarily discontinue varenicline/placebo and will be assessed weekly until toxicity resolves to Grade 2 or better. Assessments may be done by telephone per institutional practices.

Re-challenge:

- If the adverse event has resolved to grade 0, the patient should restart varenicline/placebo at Dose Level -1.

- If the adverse event has improved to grade 1 or 2, patients may be re-challenged at the physician's discretion to Dose Level -1. If the adverse event remains at grade 2 or better after an additional week, the dose of varenicline/placebo may be resumed at Dose Level 0 at the discretion of the treating physician

8.2.4 For any Grade 4 adverse events, permanently discontinue varenicline/placebo.

8.2.5 Insomnia: If the reported adverse event is persistent sleeplessness, the patient may be instructed take his/her medication earlier in the day (8 hours after morning dose). If reducing to Dose Level -1, patients should skip the evening dose.

8.2.6 Nausea: If the reported adverse event is persistent nausea with morning medication, patients should be advised to do the following:

- Take varenicline/placebo on a full stomach (after eating).
- Drink an 8-ounce glass of water after taking the pill.
- Eat a banana.

If reducing to Dose Level -1, patients should skip the morning dose**..**

8.2.7 Suicidal ideation: Varenicline is known to cause suicidal ideation, patients must be screened for suicidal ideation at Weeks 6, 12, 18, and 24. If a patient responds with a positive (1+) response to question 9 on the PHQ9, s/he will be evaluated by a physician using the CTCAE.

Any patient with CTCAE grade 2 or higher suicidal ideation will immediately discontinue treatment with varenicline/placebo and be referred to a mental health professional in accordance with institutional guidelines. For reference, the CTCAE grades 1 through 4 for suicidal ideation are provided below:

Grade 1: Increased thoughts of death but no wish to kill oneself

Grade 2: Suicidal ideation with no specific plan or intent

Grade 3: Specific plan to commit suicide without serious intent to die which may not require hospitalization

Grade 4**:** Specific plan to commit suicide with serious intent to die which requires hospitalization

8.2.8 Personality Change: Any patient with CTCAE grade 3 or greater personality change will discontinue treatment with varenicline/placebo and be referred to a mental health professional in accordance with institutional guidelines. For reference, the CTCAE grades 1 through 4 for personality change are provided below:

Grade 1: Mild personality change

Grade 2: Moderate personality change

Grade 3: Severe personality change; hospitalization not indicated

Grade 4: Life-threatening consequences, threats of harm to self or others; hospitalization indicated

8.2.9 Somnambulism: Any patient experiencing sleep walking will discontinue treatment with varenicline.

8.2.10 Pregnancy: Varenicline/placebo will be immediately permanently discontinued for any patient who becomes pregnant during the treatment period of the study.

8.3 Unblinding Procedures

Unblinding can be done only in cases of an emergency. Follow the directions below to unblind patient treatment. Please note that if a treatment assignment is unblinded, the patient must discontinue protocol therapy.

Emergency Unblinding Procedures:

Examples of emergencies include 1) a life-threatening unexpected adverse event that is at least possibly related to the investigational agent and for which unblinding would influence treatment decisions; or 2) medication error, such as accidental overdose. Expected adverse events are listed in the "Toxicities" section below.

Contact the Alliance Executive Officer on call by calling [redacted], pressing 1 to speak with an operator, and then asking for pager ID 8625 to return the call.

The institution must provide the following information to the Alliance Executive Officer:

- Alliance study ID (i.e., "A211401")
- Alliance patient ID number (e.g., "999999")
- Patient initials (e.g., "L, FM")
- Institution name
- Name and telephone number of treating physician
- Name and contact information of person requesting the unblinding procedure
- Name and contact information of person to inform of treatment assignment
- Reason for emergency unblinding

Please remember that an emergency unblinding request may be authorized only by an Alliance Executive Officer, and emergency unblinding applies only if unblinding would influence management of the medical situation.

After the Executive Officer deems unblinding is warranted, the treatment assignment will be provided to the contact person at the treating site.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. The CTCAE is available at [redacted] Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

9.1 Routine adverse event reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, Adverse Event: Baseline, Adverse Event: Solicited and Adverse Event: Other are used for routine AE reporting in Rave.

Attribution of Depression: When reporting depression, the following guidelines should be used for determining attribution to varenicline/placebo:

- If depression existed before the patient started drug, and the severity has not changed, then the event should not be reported as at least possibly related to varenicline/placebo.
- If depression started or worsened after the patient started drug (regardless of smoking status), the event should be reported as at least possibly related to varenicline/placebo.
- If depression starts 7 days or more following cessation of drug, then the event should not be reported as related to varenicline/placebo. because the half-life of the drug is less than 7 days.

Solicited Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and at 6, 12, 18 and 24 weeks after surgery.

CTCAE v4.0 Term	CTCAE v4.0 System Organ Class (SOC)
Personality change*	Psychiatric disorders
Suicidal ideation*	Psychiatric disorders

* Although the black box warning in the prescribing information has been removed (in December, 2016), patients will be monitored for neuropsychiatric events including hostility or changes in behavior or thinking that are not typical for the patient, or for suicidal ideation or suicidal behavior. See Sections 8.2.7 and 8.2.8.

Collection of surgical adverse events: For the purpose of determining the primary endpoint of the study, the following surgical adverse events **must be** collected at 24 weeks after surgery.

• 30-day mortality • 30-day re-hospitalization • 1-year mortality • Anastomotic failure • Anesthesia-related respiratory complications • Bleeding (transfusions > 5 U) • Coma (> 24 hours) • Deep venous thrombosis/ thrombophlebitis • Failure to wean from the ventilator • ICU readmission • Impaired bone healing • Implant loss (breast reconstruction)	• Increased postoperative pain • Renal insufficiency/failure • Return to operating room • Sepsis/septic shock • Stroke/cerebral accident • Surgical infection (organ space) • Surgical site infections • Urinary tract infections • Increased postoperative surgical stay • Increased scarring and asymmetry • Intubation (unplanned)/re-intubation • Lower rates of successful digital replantation (microsurgery)	• Myocardial infarction • Pneumonia • Prolonged intubation • Prolonged ventilator support • Pulmonary complications • Pulmonary embolism • Reduced skin flap survival • Vascular complications • Vein graft failure • Venous thromboembolism • Ventilator (> 48 hours) • Wound healing (delayed) • Wound infection (sternal) • Wound infections (superficial and deep)

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.
b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the Investigational Drug Branch (IDB), the Alliance Central Protocol Operations Program, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at: [redacted] All appropriate treatment areas should have access to a copy of the CTCAE. All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS).

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

Note: A death on study requires <u>both</u> routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

9.3.1 Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE ≤ 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour;
5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report ≤ 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exclusions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND:

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- Grade 3/4 hematosuppression and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results. All other grade 3, 4, or 5 adverse events that precipitate hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS.
- All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors. In CTCAE version 4.0, the new malignancies (both second and secondary) may be reported as one of the following: (1) Leukemia secondary to oncology chemotherapy, (2) Myelodysplastic syndrome, (3) Treatment-related secondary malignancy, or (4) Neoplasms benign, malignant and unspecified-other. Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.
- Treatment expected adverse events include those listed in Section 10.0 and in the package insert.
- CTEP-AERS reports should be submitted electronically.
- Pregnancy loss is defined in CTCAE as "Death in utero." Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.
- A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

10.0 DRUG INFORMATION

10.1 Varenicline Tartrate (Chantix®; Champix®)

Varenicline (Chantix™) is minimally metabolized by the liver, and 92% is excreted by the kidney unchanged.

Varenicline tartrate (Chantix™) is a nicotinic receptor partial agonist that binds with high affinity and selectivity at the α4β2 neuronal nicotinic acetylcholine receptors.

Procurement

Varenicline and matching placebo will be provided by Pfizer Inc. and shipped by the Alliance Research Base Pharmacy.

"Varenicline" and "Placebo" will be supplied as 0.5 mg tablets for oral administration. Bottles will be labeled as "Varenicline or Placebo" so that the local investigators will be blinded as to the actual contents of the bottles.

After receiving IRB approval for this study, each participating institution will order a starter supply of varenicline/placebo from the Alliance Research Base Pharmacy by faxing the Alliance Clinical Drug Order/Return Form to:

The A211401 Varenicline/placebo Order Form can be found on the A211401 study page of the Alliance and CTSU websites.

Each bottle will be identified by a unique code number and are not to be designated for use by a specific patient until they have been assigned to a patient by the Alliance Registration Office personnel. After the treatment assignment has been ascertained in the OPEN application, the patient's study medication code number will be displayed on the confirmation of registration screen.

The treating institution should not have to request additional supplies after a starter supply has been sent. The pharmacy and the Alliance registration office will work together to re-supply each location.

Outdated or remaining drug product should be destroyed on-site per procedures in place at each institution.

IND Status

IND Exempt: Varenicline is IND exempt as used in this trial. This exemption has been determined by attestation that neither the investigator nor sponsor intends to seek a new indication for use or to support any other significant change in the labeling or product advertising for varenicline; this investigation will use an approved route of administration and dosage of varenicline and has no factors that increase the risk of the product; this investigation will be in compliance with 21CFR parts 56, 50, and 312.7; and neither the investigator nor sponsor will promote or represent that varenicline is safe or effective for the context that is under investigation in this study.

Formulation

Commercial varenicline capsular, biconvex tablets contain 0.5 mg (white to off-white, debossed with "Pfizer" on one side and "CHX 0.5" on the other side). Each 0.5 mg varenicline contains 0.85 mg of varenicline tartrate equivalent to 0.5 mg of varenicline free base. The following

inactive ingredients are included in the tablets: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, Opadry® White (for 0.5 mg), Opadry® Blue (for 1 mg) and Opadry® Clear.

Storage and Stability

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) (see USP Controlled Room Temperature).

Administration

Varenicline/placebo will be administered at a dosage of 0.5 mg once daily for 3 days, increasing to 0.5 mg twice daily for days 4 to 7, and then to the maintenance dose of 0.5 mg 2 tablets twice daily for up to 12 weeks of treatment. Patients should be instructed to take medication after eating and with a full glass of water.

Drug Interactions

Varenicline is not known to interact with any medications and has no contraindications aside from previous allergic reactions to varenicline.

Other smoking cessation therapies: Safety and efficacy in combination with other smoking cessation therapies has not been established. Coadministration of varenicline and transdermal nicotine resulted in a high rate of discontinuation due to adverse events.

Effect of smoking cessation: Pharmacokinetics or pharmacodynamics of certain drugs may be altered due to smoking cessation with CHANTIX, necessitating dose adjustment.

Pharmacokinetics

a) Absorption: Varenicline is rapidly absorbed across the gastric mucosa, reaching a peak plasma concentration (C_{max}) in about 4 hours. After multiple oral doses, steady state is reached within 4 days. Bioavailability is unaffected by food or time-of-day dosing (food reduces the incidence and severity of nausea, a common side effect).

b) Distribution: Varenicline exhibits linear pharmacokinetics after single or repeated doses. Plasma protein binding is low ($\leq$ 20%).

c) Metabolism: Varenicline undergoes minimal metabolism.

d) Excretion: Elimination half-life of varenicline is approximately 24 hours. Ninety-two percent of varenicline is excreted unchanged in the urine. Renal elimination of varenicline is primarily through glomerular filtration along with active tubular secretion possibly via the organic cation transporter, OCT2.

Adverse Events

The most commonly reported adverse effects (>5% and twice the rate seen in placebo-treated patients) of varenicline are nausea (29.4% vs. 10% placebo), insomnia (14.3% vs. 12.4% placebo), abnormal dreams (13.1% vs. 3.5% placebo), headache (12.8% vs. 12.6% placebo), and constipation (9% vs. 1.5% placebo). Nausea is generally mild (72%) to moderate (23%) in intensity, becomes less severe with continued drug use, and causes 2.3% of the subjects to discontinue treatment.

Drug Warnings: The FDA previously required a boxed warning on the varenicline label to alert physicians and subjects to behavior change risks. The labeling warned of the risk of behavioral changes such as: depression, hostility, aggression, suicidal thoughts, suicide, and vehicular crashes. Subjects and family members will be given clear instructions on discontinuing varenicline and alerting study staff in the event such behavior changes occur. This is detailed in the DSMP.

As a result of the black box warning for varenicline, a number of studies have recently (2010-2015) focused on the safety of varenicline in various populations. Studies have included both individual studies with hospitalized smokers and meta-analysis of past randomized clinical trials. The common result in all these studies/reviews is that varenicline is safe and no significant increase in psychiatric conditions was observed in any of these cases. These studies include:

- In 2010, Tonstad reviewed 10 clinical trials comparing varenicline to placebo in over 3091 smokers. Psychiatric disorders (excluding sleep disorders or disturbances) was 10.7% in varenicline and 9.7% in placebo (RR=-1.02 – ns). No cases of suicidal ideation or behavior in the varenicline arms in all 10 trials;[99]
- In 2011, Park et al., conducted a study with 49 smokers who had lung cancer who met with a thoracic surgeon and were given varenicline and counseling or just counseling. The OR was 3.14 (not significant). This study did demonstrate that varenicline is safe (only nausea and abnormal dreams were higher in varenicline arm), and feasible (smokers with lung cancer did adhere to varenicline treatment);[37]
- In 2012, Wong et al., conducted a study with 286 patients who were randomized to varenicline or placebo perioperatively. Relative Risk (RR) was 1.45 for varenicline to help smokers stop smoking. The only significant event was nausea (13.3 vs 3.7, p=0.004);[100]
- In 2013, Nayan et al., reviewed 10 randomized clinical trials and 3 prospective clinical studies of smoking intervention in oncology patients. The interventions included NRT, bupropion and varenicline. The odds ratio (OR) of all interventions was 1.31 to 1.54 (not significant) depending on follow up period. But when the interventions were delivered perioperatively, the OR was significant at 2.31, thereby demonstrating that surgery does present the teachable moment in oncology patients;[101]
- In 2014, Carson et al., conducted a study with 392 hospitalized smokers who were randomized to varenicline vs. placebo for 12 weeks. No increase in psychiatric events were noted, the only increase was nausea (16.3% in varenicline patients vs. 1.5% in counseling alone);[102]
- In 2015 two studies took place, both with very large number of smokers:

  Thomas et al. – meta-analysis of 39 randomized trials (10,761 pts.) using varenicline vs. placebo to evaluate the incidence of neuropsychiatric events. No increase of suicide, attempted suicide, suicidal ideation, depression, irritability, aggression, or death. There was evidence of reduced anxiety and increase in sleep disorders, insomnia and abnormal dreams and fatigue.[103]

  Kotz et al. – A review of 753 general practices in England which identified 164,766 smokers who received prescription to stop smoking (106,759 NRT; 6557 bupropion; 51,450 varenicline). Neither bupropion nor varenicline showed any increase in cardiovascular or neuropsychiatric events (including depression and self-harm) compared to NRT (Hazard Ratio (HR)= 0.80), cerebral infarction (HR=0.62), heart failure (HR=0.61), arrhythmia (HR=0.73) or self-harm (HR=0.56).[104]

Weight Gain: Varenicline does not attenuate weight gain after stopping smoking.

Abuse Potential: The manufacturer's data, available in the package insert, suggests that varenicline is not likely to be abused. The FDA did not classify varenicline as a controlled substance.

Pregnancy Risk: Varenicline is FDA Pregnancy Class "C" drug defined as "Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus." Since we do not know the potential benefits, we cannot determine the risk-benefit ratio and will, therefore, exclude pregnant individuals at the beginning and during the study. Not enough medical information exists to know what the risks might be to a breast-fed infant so we will exclude individuals who are breast-feeding.

Nursing Guidelines

1. Be aware of black box warning regarding behavior changes, including depression, hostility, aggression, suicidal thoughts, and vehicular crashes. Warn patients of this risk and instruct patients to report any changes in mood or behavior to the study team.
2. Patients may experience nausea. Nausea may improve with time. Treat symptomatically and monitor for effectiveness.
3. Warn of difficulty sleeping and/or unusual dreams.
4. Headache may occur. Treat symptomatically and monitor for effectiveness.
5. Patients may experience mild constipation, encourage increased fluid intake and treat symptomatically as necessary.

10.2 Placebo (Supplied)

Investigators ordering and/or dispensing supplied agents at any time for study treatment must be currently registered with PMB, DCTD, NCI. A registered investigator must co-sign for other non-registered personnel prescribing the supplied agents

A matching placebo will be provided. It will be identical in appearance to the varenicline.

11.0 MEASUREMENT OF EFFECT

All of the following measures relate to the secondary endpoints.

The primary endpoint of surgical complication incidence rates at 24 weeks after surgery will be measured as described in Appendix X.

11.1 Patient reported measures

For the purposes of this study, patients should be reevaluated every 6 weeks. In total, the time for the patient to complete these forms is approximately 16 minutes at Baseline, 10 minutes at Week 6, 10 minutes at Week 12, and 13 minutes at Week 24.

11.1.1 Tobacco Use Assessment (Appendix IX): We will record the patient's self-reported smoking status including current use, use during the past 7 days, use since time of last self-report, and use since Target Quit Date (TQD) as appropriate. This form will collect vitals, smoking status, contact made with the tobacco quitline. This will take approximately 3 minutes to complete.

11.1.2 Contemplation Ladder (Appendix III)[77]: The Contemplation Ladder is a visual analog comprised of 11 rungs and 5 anchor statements (item 0, 2, 5, 8, 10), representing stages of change. The response options (0) to (3) correspond with *pre-contemplation*, (4) to (6) represent *contemplation*, (7) and (8) refer to *preparation*, (9) and (10) represent *action and maintenance*, respectively. It is a brief measure of motivation or readiness to change, where (0) is the least motivated and (10) is the most motivated. This measure will be used to screen out those who are not motivated to change (scoring a 5 or below) and therefore lower likelihood of responding to the intervention and completing the study. Two recent studies

of smokers with co-morbid conditions showed the average hospitalized smoker enrolled scored a 6 and above and they found that 70-80% of the enrolled subjects scored an "8" or above.[78, 79] This will take approximately 1 minute to complete.

11.1.3 Smoking Self-Efficacy Questionnaire (SEQ-12; Appendix IV)[80]: Two six-item subscales measuring confidence of smokers in their ability to remain tobacco abstinent in the face of internal stimuli (e.g., feeling depressed) and external stimuli (e.g., in company of smokers). This will take approximately 5 minutes to complete.

11.1.4 Fagerström Test for Nicotine Dependence (FTND; Appendix V)[81]: Predicts smoking abstinence and is correlated with biochemical measures of tobacco dependence. This will take approximately 3 minutes to complete.

11.1.5 Patient Health Questionnaire-9 (PHQ-9; Appendix VI)[82]: A valid diagnostic and severity measure for depression, with scores ≥10 indicating moderately severe depression. The PHQ9 is used to help guide the investigator during the study enrollment process and to help the investigator monitor the patient with respect to depression after randomization. The study investigator will determine if the person is still eligible for study enrollment. This will take approximately 2 minutes to complete.

11.1.6 Linear Analogue Self-Assessment (LASA; Appendix VII)[83]: Single-item LASA items have become the most widely-used assessment in all NCI-sponsored cancer control studies.[84] Normative data have been obtained from various clinical populations enrolled in NCCTG clinical trials and from healthy participants.[85, 86] This will take approximately 3 minutes to complete.

11.1.7 "Was it Worth It?" Survey (Appendix VIII)[87]: This is an end-of-study survey to ask the patient if the entire experience was worth it for them. This will take approximately 2 minutes to complete.

11.1.8 Drug and Behavioral Support Adherence Logs (Appendix X): Each patient will be provided with an adherence log which is specific to his/her treatment phase. In this log, they will provide details of their daily pharmacotherapy intake, contacts made to/from the telephone quitline, amount of cigarettes smoked (if any), and any other comments the patient feels is pertinent. This will take approximately 5 minutes to complete.

11.2 Biochemical confirmation using salivary cotinine

Biochemical confirmation will be used in the cotinine analysis in saliva. Cotinine analyses are two of five validated methods to analyze and verify smoking in patients during smoking cessation.[93-95] Salivary cotinine will be analyzed using the commercially available quantitative enzyme linked immunosorbent assay (ELISA),[96] which we have used in several prior studies.[97, 98] Using salivary cotinine will allow for testing of clinically useful measures. All saliva will be shipped to the Medical University of South Carolina, Charleston, SC per Section 6.2.2. The correlative analyses will be performed in the laboratory of Dr. G. Warren at MUSC.

11.3 Definitions of analysis variables

Formal definitions of variables used in analyses can be found in the Statistical Considerations section of the protocol.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Treatment

Patients should be treated with varenicline/placebo for 12 weeks.

If the patient discontinues varenicline/placebo before completing 12 weeks of therapy, patients should be followed for the duration of the study period (6 months).

12.2 Definitions and Follow-up Requirements

Definition of ineligible patients: A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible. Patients who are deemed ineligible may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient were to continue protocol treatment. Notification of the local IRB may be necessary per local IRB policies.

Definition of clinical follow-up: The follow-up period where the study participant is no longer receiving treatment, but is still following the study calendar for tests, exams, and correlative endpoints (e.g., specimen collection, quality of life, disease assessments as required by the study).

Baseline data must be submitted per Section 5.0 for patients deemed ineligible or canceled. See also the Forms Packet for full details of data submission requirements

12.2.1 Follow-up for Ineligible Patients

Study participants who are registered to the trial but deemed ineligible must complete follow-up requirements.

Baseline, on-study, endpoint (e.g., relapse or progression), off treatment, and survival data submission required.

12.2.2 Follow-up for Patients Never Receiving Protocol Intervention

Study participants who receive the study intervention (varenicline/placebo and behavioral module), but never go on to have the surgery, can complete study intervention if they wish. Data on outcome and complications (adverse events) will continue to be collected, but these patients will not be included in the analysis of the primary endpoint.

Study participants initiate the study intervention (varenicline/placebo and behavioral module), go on to receive surgery, but wish to stop study intervention thereafter, will continue to have data on outcome and complications (adverse events) collected. These data will be used in the analysis of the primary endpoint.

Study participants who were registered/randomized but never received varenicline/placebo will be considered “canceled” and baseline data must be submitted per Section 5.0..

12.3 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design

This is a randomized, double-blind, placebo-controlled, phase III trial evaluating varenicline vs. placebo for reduction in post-surgical complications through 24 weeks after surgery in lung cancer patients who undergo surgery and are motivated to stop smoking. A parallel group design will be utilized for this two-arm study: varenicline vs. placebo. Both arms will also include a brief no smoking message from the surgical team and the NCI Quitline.

13.1.1 Study Populations

Intent-to-Treat (ITT) Population: Consists of all randomized patients who had surgery. The ITT population will be used for the efficacy evaluation at each of the planned analyses. Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned at randomization. Patient with missing values will be considered to have complications.

Safety Population: Consists of all patients who were randomized, had surgery, and who have at least one post-baseline safety assessment. The safety population will be used in the safety data summaries Note that a patient who had no adverse events (on the Adverse Event CRF) constitutes a safety assessment. Patients who have received at least one dose of study drug but have no post-treatment safety data of any kind would be excluded.

13.2 Study Endpoints

13.2.1 Primary Endpoint

The primary endpoint will be the incidence for any of the following complications from surgery within 24 weeks after surgery: 30-day mortality, 30-day re-hospitalization, pulmonary complications, ICU readmission (an upgrade from any inpatient status [floor or intermediate care status] to full intensive care nursing acuity because of a serious deterioration in physical condition that warrants closer physician monitoring or nursing care), wound infection (NOS), anastomotic failure. These complications were identified as being sufficiently numerous from an investigation of the national surgical database (ACS-NSQIP). They will be defined using the General Thoracic Surgery Database (GTSD) for study purposes. These complications will be considered equally important in determining complication rates. Patients who have any of these individual morbidities will be considered to have a perioperative complication. Patients without any of these individual morbidities will be considered to not have a perioperative complication.

Formal definitions for all complications of the primary and secondary endpoints are found in Appendix X. We have reviewed the elements of the primary endpoint with the Community Oncology Committee and the Alliance lung cancer surgeon working group and surveyed potential participating sites for a description of the workflow for treatment administration and data collection to ensure that all the elements can be recorded across the Alliance sites.

13.2.2 Secondary Endpoints

- QOL-related domains as measured by the LASA-12, PHQ-9, SEQ-12, and Was It Worth It assessments.
- Post-operative care as measured by length of hospital and high dependency unit stay. Length of stay will include only the time from surgery until the patient is released from the hospital.

- Expanded complication rate defined as any of the complications listed in Appendix I that are not being examined as part of the primary endpoint. This is included to account for the possibility that other complications, which do not occur with high frequency in the ACS-NSQIP data base, actually occur in our study.
- Treatment adherence rates related to visits, medication compliance, quitline usage, and surgeon teachable moment delivery.
- Smoking abstinence rates as measured by self-report and salivary cotinine testing.

13.3 Primary analysis

Surgical complication incidence rates at 24 weeks after surgery will be compared between the intervention vs. control groups using a Fisher's exact test.

Logistic regression models will supplement the univariate analysis, using complication incidence as the dependent variable and will include smoking status at the time of surgery as an independent variable and also adjust for age, gender, FTND, time between randomization and surgery, and presence of adjuvant chemotherapy and/or radiation therapy. A separate logistic model will be created including treatment arm instead of smoking status. We will also explore the collinear relationship between arm and smoking status to see whether they can be included together in the logistic models.

13.4 Additional Analyses

We will compare changes from baseline in patient quality of life related domains (LASA-12, PHQ-9, SEQ12) between the intervention and control groups using analysis of covariance and linear mixed model repeated measures analysis for each assessment domain. Specifically, we will analyze each LASA domain with a separate ANCOVA model using the change from baseline to 12 weeks post-surgery as the dependent variable, followed by a similar analysis using the change from baseline to 24 weeks post-surgery. Each LASA question corresponds to a separate domain. For the PHQ-9 and SEQ12, we will use the scale scores in a repeated measures analysis involving data from all time points (baseline, 6, 12, and 24 weeks). For the PHQ-9 there is one overall score and for the SEQ12 there are two scales (internal stimuli and external stimuli).

The WIWI survey will be analyzed by comparing the proportion of patients at the end of the treatment period (i.e., 12 weeks after surgery) and at 24 weeks after surgery who endorse each treatment (intervention versus control) via Fisher's exact testing.

These QOL-related domain variables will be included in the modeling process of the primary and other secondary analyses as potentially concomitant confounding covariates so as to produce more efficient estimates from the models. Sensitivity analysis for potential differences between groups demonstrated via the ANCOVA and repeated measures models will be assessed using Generalized Estimating Equations models to account for the correlation of repeated measures on the same patient.

We will compare post-operative care (length of hospital and high dependency unit stay) between the intervention vs. control groups using separate logrank testing of Kaplan-Meier estimates for length of hospital stay and length of high dependency unit stay and supplemented by Cox models to control for concomitant covariates. The assumptions underlying the Cox model will be tested for veracity.

For the expanded complication rate, we will utilize the same analysis approach as the primary endpoint analysis for all complications listed in Appendix I. We will also compare the incidence rates of each specific type of complication between arms.

We will also measure treatment adherence. The number of study visits completed by each patient during the treatment phase will be summarized and compared between groups using the rank

sum test. Patient self-report will be used to collect adherence data on the use of the quitline and the medication adherence for the patients receiving the multi-faceted smoking cessation intervention. To assess medication compliance, patients will report to the study staff at each visit the amount of study medication used each day. In addition, patients will return unused medication at each study visit and study staff will maintain drug accountability logs to account for dispensed and returned medication. The amount of study medication taken by each patient will be calculated weekly. Adherence data on teachable moment delivery from the surgical team will be collected by the study staff at the time of the message delivery. These data will be summarized using simple descriptive statistics to indicate the degree of treatment adherence that is achieved for the multi-faceted smoking cessation intervention.

Rates of smoking abstinence will be compared between arms using Fisher's exact test and logistic regression models. Abstinence definitions are based upon the Society for Research on Nicotine and Tobacco (SRNT) Working Group recommendations.[88] The major advantage of point prevalence estimates is that they are widely reported in the literature and can be verified biochemically. However, point prevalence abstinence does not account for slips/lapses that might occur between follow-up periods. Prolonged abstinence is defined as smoking abstinence sustained after an initial 2-week grace period[88] and accounts for initial lapses. However, prolonged abstinence cannot be verified biochemically short of daily biochemical confirmations and, ultimately, must rely on self-report. Research suggests that self-reports among smokers in general tend to be accurate, and misreporting rates are generally very low.[89] We allow for a 2-week grace period after TQD based upon the SRNT Working Group recommendations.[88] Prolonged smoking abstinence will be adjudicated if the following criteria are met: 1) Self-reported smoking abstinence since 2 weeks after the TQD. This will be identified by a negative response to the question, "Since xx/xx/xxxx, which was 2 weeks after your TQD, have you smoked any tobacco, even a puff, for 7 consecutive days or at least once each week on 2 consecutive weeks?" and 2) No failed biochemical confirmation of self-reported smoking abstinence at any previous outcome assessment. Point prevalence smoking abstinence will be adjudicated if both of these criteria are met: 1) Self-reported smoking abstinence for the last 7 days. This will be identified by a negative response to the question, "Have you smoked any tobacco, even a puff, in the past 7 days?", and 2) Salivary cotinine less than 15 ng/mL. Relapse will be defined as smoking on 7 consecutive days or smoking at least once each week on 2 consecutive weeks.[88]

13.5 Correlative and companion substudy analyses

13.5.1 Correlative substudy analysis (A211401)

Salivary cotinine is an evidence-based biochemical method to confirm tobacco use that significantly increases the accurate identification of current smoking. Data demonstrate that 30-40% of cancer patients who smoke do not accurately report smoking status even using structured assessments (97-98). As a result, quantitative cotinine analyses (96) will be used to increase the accuracy of identifying current smoking, which will in parallel be used to evaluate changes in study outcomes using a more accurate methodology. For this study, a cutoff of 15 ng/mL will be used to define biochemically confirmed current smoking (>15) according to recommendations from the Society for Nicotine and Tobacco Research (95).

13.5.2 Pharmacogenetic companion substudy analysis (A211401-PP1)

For the correlative analysis, we will examine whether cigarette smokers undergoing surgery for cancer who have the high-risk variants of *CHRNA5-CHRNA3-CHRNB4* will have higher abstinence rates, as determined by the tobacco use assessment and continine levels, than those with the low-risk variants of *CHRNA5-CHRNA3-CHRNB4*. We will examine this genetic effect in the overall group and in each treatment arm. We will also examine whether

intervention effect varies with *CHRNA5-CHRNA3-CHRNB4* (i.e. a genotype X intervention interaction). A series of logistic regression models will be used to examine main effects of genotype and intervention before testing genotype x intervention interactions, with age, sex, and intervention arm as covariates. Similarly, we will examine whether smokers with *CYP2A6*-defined fast nicotine metabolism will have lower abstinence and higher withdrawal symptoms at 12 weeks after surgery and at 24 weeks after surgery (end of study) , compared with smokers with slow metabolism. We will examine whether the effect of varenicline varies with participant's *CYP2A6*-defined nicotine metabolism status. Fisher exact tests will be used, supplemented by logistic regression models similar to what is described for the primary analysis. We will examine if these cessation-relevant genotypes (*CHRNA5-CHRNA3-CHRNB5, CYP2A6*) modify the effect of the intervention vs. control groups. These correlative analyses will not be adjusted for multiple comparisons, since the magnitude of the associations is of more interest than the statistical significance for whether or not there is any association.

13.6 Power/Sample Size

The primary statistical endpoint for this study is the incidence of surgical complications as described in Sections 13.1 and 13.3. Patients that have any of these individual morbidities will be considered to have a perioperative complication. Patients without any of these individual morbidities will be considered to not have a perioperative complication.

In a study of 635,265 non-cardiac surgical cases treated in 200 centers throughout the United States, the incidence rate of the perioperative complications listed above from the National Surgical Quality Improvement Program (NSQIP) data was in the range of 25–30%. They further found that smokers undergoing non-cardiac surgery had an estimated 40% increased odds of developing major morbidity and mortality within 30 days of surgery over never smokers, representing a modest difference of between 10%-12% in the actual percentage of patients with major morbidity.[90] One report focused on the limitations of NSQIP in identifying adverse events following major cancer surgery. NSQIP does not abstract the complications considered most important by many surgical subspecialists (e.g., anastomotic leak).[91] Therefore, the true impact of smoking on adverse surgical events may be greater in this trial.

For the purposes of this power calculation then, we will assume a 30% perioperative complication incidence rate in the control group.[104] The study design is a randomized clinical trial intended to estimate the incidence rate of perioperative complications in patients who are smoking at the time of enrollment. The primary statistical analysis will be a comparison of the perioperative complication incidence rates from the time of surgery to 24 weeks after surgery between the intervention and control groups. We will hence power the study to detect a 10% difference in perioperative complication rates between the intervention and control groups.

With a sample size of 626 patients (313 patients per arm), a Fisher exact test can detect a difference in the perioperative complication rate between the two treatment groups of 10% (20% versus 30% in the intervention arm and control arm, respectively) with 80% power using a Type I error rate of 5% and a two-sided alternative.

The prevalence of smoking among lung cancer surgical patients is roughly 42%.[91] We estimate that 90% of these patients will be motivated to quit and enroll on the study, given the relaxed eligibility requirements requiring only a desire to quit and teachable moment delivery by the surgeons. Hence we can expect to screen roughly three patients to enroll one. An adjustment is also needed for patients that enter the smoking cessation part of the study, but drop out before surgery. We expect that at most 20% of the patients entering the study will drop out after registering and before having surgery. To obtain a sample size of 626 smoking patients with a new diagnosis of lung cancer for which surgery is indicated, we will need to screen

approximately 1878 oncology patients undergoing surgery to enroll 783 smoking patients. Of these 783 patients, we expect 626 to undergo surgery. The study will remain open to accrual until 783 patients have been enrolled. If we take into consideration patient refusal, we would need to approach 2000 smoking oncology patients undergoing surgery to have 626 patients enroll in the study and undergo surgery.

13.7 Accrual rate and study duration

From accrual estimates provided by sites in this survey, we anticipate accruing 150 evaluable patients per year. Multiple surveys have been conducted to obtain realistic accrual expectations as well as detailed descriptions as to how patients will be accrued, treated, and assessed at each site. This study accrual will close when 783 study patients have been enrolled; therefore, we anticipate patient accrual to be completed in approximately 4 years and 2 months. If, after 400 patients have been enrolled to the study, the proportion of patients who fail to undergo surgery is ≤ 10%; then accrual to the study will be stopped when 700 patients have been enrolled, as this would produce the required 626 patients for the primary analysis.

13.8 Monitoring

This study will be monitored by the Alliance Data and Safety Monitoring Board (DSMB), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DSMB every six months as per NCI guidelines.

This study will be monitored by the Clinical Data Update System (CDUS) version 2.0. An abbreviated report containing cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.9 Adverse Event Stopping Rule

The stopping rule specified below is based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below. CTCAE v4.0 will be used to determine grading for these stopping rules.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (varenicline) (i.e., an adverse event with attribute specified as "possible", "probable", or "definite") that satisfies the following:

- If 3 or more patients in the first 15 treated patients or, if at any time after the first 15 patients are enrolled, 20% or more patients develop ≥ grade 4 non-hematologic adverse events felt to be at least possibly related to treatment, the study team will review the data to determine the proper course of action. These actions may include further adverse event monitoring, suspension of accrual, dose modification, or closure of the trial.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

13.10 Interim Analysis

Although the final analyses will utilize a 5% Type I error rate, we will use a more conservative interim bound of 0.001 for the *P* value for all interim analyses. Freidlin's[92] simulation studies have demonstrated that such a bound trivially impacts both the interim bounds and the final significance level. Interim analyses will be done in concert with the semi-annual Data Safety Monitoring Board (DSMB) reports. These interim analyses will report on the primary endpoint using all patients that have been on study for at least 3 months.

13.11 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race or ethnic origin. There is no information currently available regarding differential effects in subsets defined by race or ethnicity, and there is no reason to expect such differences to exist. Based on prior smoking cessation studies, we expect about 15% of patients will be classified as minorities by race and about 40% of patients will be male.

Racial Categories	**Ethnic Categories**				
	Not Hispanic or Latino		Hispanic or Latino		**Total**
	Female	Male	Female	Male	
American Indian/Alaska Native	9	6	0	0	15
Asian	5	2	1	0	8
Native Hawaiian or Other Pacific Islander	5	2	0	0	7
Black or African American	37	25	0	1	63
White	391	262	7	5	665
More Than One Race	15	10	0	0	25
Total	462	307	8	6	783

14.0 CORRELATIVE AND COMPANION STUDIES

There are two substudies within Alliance A211401. Measurement of saliva cotinine levels is a correlative substudy, which is mandatory for all patients registered to A211401. There is one pharmacogenetics companion substudy, which must be offered to all patients enrolled on Alliance A211401 (although patients may opt to not participate). The companion substudy included within Alliance A211401 is:

- Pharmacogenetics of Smoking Cessation Treatment (POST), Alliance A211401-PP1

14.1 Correlative substudy to measure saliva cotinine levels

14.1.1 Background

For patients enrolled on study, saliva samples will be obtained to analyze for cotinine. Salivary cotinine is an evidence-based biochemical method to confirm tobacco use that significantly increases the accurate identification of current smoking. In cancer patients who are asked about tobacco use in person, approximately 30-40% of current smokers misrepresent smoking status (97-98, Khuri et al.). In cancer patients who participate in phone based assessments, recent data demonstrate that 48% of adult smokers (REF) and up to 80% of childhood cancer survivors (REF) misrepresent smoking status. For this study, a cutoff of 15 ng/mL will be used to define biochemically confirmed current smoking (>15) according to recommendations from the Society for Nicotine and Tobacco Research (95).

14.1.2 Hypothesis/objective

This biomarker will be used to increase the accuracy of tobacco assessment as compared with self-reported tobacco use. The hypothesis is that biochemically confirmed tobacco use will increase the magnitude of difference in study outcomes as compared with self-reported tobacco use. This biomarker will be used for the following objectives:

Primary objective: To evaluate the effect of biochemically confirmed tobacco use on study outcomes

Secondary objectives:

To evaluate the accuracy of self-reported tobacco use among study participants

To evaluate if biochemically confirmed tobacco use correlates with a larger magnitude of difference in study outcomes as compared with self-reported tobacco use

To evaluate longitudinal accuracy of self-reporting among study participants at baseline and throughout the study

14.1.3 Methodology

Saliva will be collected in patients as described in 6.2 and patients will be identified as current smokers using a salivary cotinine cutoff of >15 ng/mL (95-96) analyzed by G. Warren at the Medical University of South Carolina. Parallel evaluations of study outcomes, behavior, and genetic linkages will be performed using self-reported tobacco use assessments and biochemically confirmed tobacco use assessments.

14.2 Pharmacogenetics of Smoking Cessation Treatment (POST), Alliance A211401-PP1

14.2.1 Background

Alliance 211401-PP1 will evaluate genetic effects on cessation outcomes and treatment response. Dr. Laura Bierut and Dr. Li-Shiun Chen will identify genetic predictors for cessation outcomes and treatment response. (See section 1.1.4 for more background information).

14.2.2 Hypothesis/objective

To evaluate if biochemically confirmation strengthens associations between genetic markers, behaviors, and study outcomes

To evaluate the predictive role of the nicotinic receptor gene cluster (*CHRNA5-CHRNA3-CHRNB4*) and *CYP2A6* genotypes in smoking cessation among lung cancer patients undergoing surgery.

To evaluate the potential moderating effect of these cessation-relevant genotypes on smoking cessation treatment between the intervention and control groups.

14.2.3 Methodology

Participants will provide a blood sample of 10ml (EDTA Vacutainer) for assessment of genotyping and nicotine metabolism by Washington University. Multiple genes have been shown to predict abstinence and response to cessation pharmacotherapy. The blood sample will be used to extract DNA and the plasma will be used for the biomarker, NMR (ratio of 3'hydroxycotinine/cotinine) which reflect CYP2A6 activity and nicotine clearance in smokers, and may predict smoking cessation. All blood samples will be collected, stored, and shipped to the Alliance biorepository and will subsequently be shipped to Dr. Laura Bierut at Washington University in St. Louis for genotyping and nicotine metabolism essays.

15.0 TEACHABLE MOMENT TRAINING

Surgeons and designated members of the surgeon's team will be trained and educated in the basics of smoking cessation counseling and delivery of the No-Smoking message to the surgical oncology patient. The training will be based upon a validated approach to clinician-delivered tobacco use intervention (Warner et al, Anesthesiology 114:847-855, 2011). Two different training modules will be required: One for the surgeon and one for the site staff (study coordinator/nurse). Modules will be on-line and asynchronous, and available on the Alliance Web site via a link on the study-specific web page. Sites will certify that the training was completed by notifying the study chair or co-chair via email. To supplement this training, there will also be a training exercise at the Fall Alliance meeting.

15.1 Surgeons

The module will emphasize the importance of brief surgeon advice to quit and the compelling rationale for smoking cessation to reduce perioperative complications.

The surgeon module will require approximately 5 minutes to complete

15.2 Study Staff

The module will demonstrate the brief behavioral intervention to be delivered by the study coordinator/nurse, including the elements addressed in Section 7.1.

The study staff module will require approximately 30 minutes to complete.

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17.0 MODEL CONSENT FORM

Study Title for Study Participants:

Smoking Cessation Prior to Surgery to Reduce Surgical Complications

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:

Reducing Surgical Complications in Newly Diagnosed Lung Cancer Patients Who Smoke Cigarettes

This study is conducted by the Alliance for Clinical Trials in Oncology, a national clinical research group supported by the National Cancer Institute. The Alliance is made up of cancer doctors, health professionals, and laboratory researchers, whose goal is to develop better treatments for cancer, to prevent cancer, to reduce side effects from cancer, and to improve the quality of life of cancer patients.

What is the usual approach to quitting smoking before having lung cancer surgery?

You are being asked to take part in this research study because you are a smoker who is scheduled to have surgery for your lung cancer. Many surgeons encourage patients to stop smoking before surgery in order to reduce the chance of having medical complications after the surgery.

What are my other choices if I do not take part in this study?

There are many way to stop smoking. You do not have to be in this study to receive treatment for smoking cessation. You may attempt other methods to quit smoking in addition to the methods used in this study. Your other choices may include:

- Nicotine replacement (for example, nicotine patches, gums, lozenges, nicotine nasal spray, or nicotine inhalers)
- Taking varenicline not on this study
- Taking a drug called bupropion

You should talk to your doctor about each of your choices before you decide if you will take part in this study.

Why is this study being done?

The purpose of this study is to see if post-operative complications can be reduced by helping patients stop smoking with a drug called varenicline (also called Chantix®) and using National Cancer Institute Tobacco Quitline for counseling. This study will see how well the drug varenicline helps you stop smoking by comparing it to a placebo. A placebo is a pill that looks like the study drug but contains no medication.

About 626 people will take part in this study.

What are the study groups?

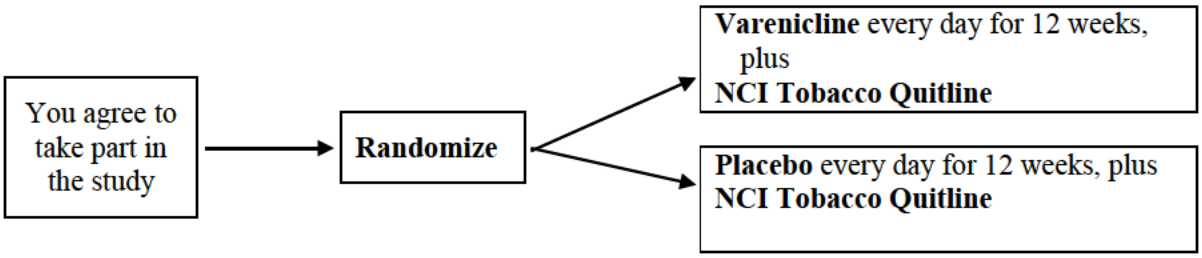
This study has two study groups.

- Group 1 will receive varenicline and access to the NCI Quitline
- Group 2 will receive a placebo and access to the NCI Quitline

The placebo is given in Group 2 so that participants in both groups receive similar-looking pills. This way, neither you nor your doctor can tell which group you are in, and that makes the study more objective. There is no plan to tell you whether you are receiving varenicline or placebo while you are on the study except in the case of an emergency.

A computer will by chance assign you to one of the two treatment groups being evaluated in the study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the other.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



After you are randomized, but before your surgery, you will start taking the varenicline/placebo to help you stop smoking. At the beginning of the study, you will receive one bottle varenicline/placebo tablets. For the first three days that you are taking varenicline/placebo, you will take one tablet every day. On Day 4 you will begin taking two varenicline/placebo tablets: One in the morning and another tablet in the evening. After the first week, you will continue by taking two varenicline/placebo tablets in the morning and two tablets in the evening for 11 weeks.

You should take varenicline with at least 8 ounces of water and after eating a meal.

Days 1-3	Days 4-7	Weeks 2-12
1 tablet Any time of day	1 tablet in the Morning and 1 tablet in the Evening	2 tablets in the Morning and 2 tablets in the Evening

How long will I be in this study?

You will take varenicline/placebo plus have access to the quitline for 12 weeks. You will be in this study until 24 weeks after your surgery. You will continue to have access to the NCI Tobacco Quitline after you have finished your participation in this study.

What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra tests and procedures that you will need to have if you take part in this study.

Before you begin the study:
You will need to have the following extra to find out if you can be in the study:

- Physical exam and medical history
- Vitals (height, weight, blood pressure and pulse)
- Blood test to measure kidney function, if you have not had one recently
- You will be asked to complete a short questionnaire about your motivation to quit smoking
- If you are a female of child bearing potential, you will be asked to have a pregnancy test.

On the first day of the study ("Baseline Visit"):
On the first day of the study, you will meet with your surgeon or member of the surgical team to discuss quitting smoking and to learn about the NCI Tobacco Quitline.

You will be asked to set a target quit date to quit smoking. You should start taking varenicline/placebo one week before the target quit date that you set. Your surgery will be scheduled to take place after that quit date, and must be at least ten days and no more than 12 weeks after the visit with your surgeon.

You will also be asked to complete questionnaires about your tobacco use history, your ability to stay smoke free, your mood/depression level and your quality of life. This should take about 10 to 15 minutes to complete.

On the day of your surgery: You will be asked to complete a brief (3 minutes) questionnaire about your tobacco use and provide a sample of your saliva to measure amount of cotinine in your body. Cotinine is produced by nicotine, which is found in tobacco.

6 weeks after your surgery: You will be asked to come to the clinic for a doctor's visit to see how you are doing physically and with your tobacco cessation efforts. You will be asked to complete

questionnaires at this visit. These should take about 15 minutes to complete. Finally, you will be asked to provide some of your saliva to measure the amount of cotinine in your body.

12 and 18 weeks after your surgery: You will be asked to complete a questionnaire either by telephone or in person to see how you are doing physically (week 12 only) and with your tobacco cessation efforts (on both weeks 12 and 18). You will be asked to come to the clinic (not a doctor's visit) to provide some of your saliva to measure the amount of cotinine in your body.

24 weeks after your surgery**:** You will be asked to come to the clinic for a doctor's visit to see how you are doing physically and with your tobacco cessation efforts. You will be asked to complete questionnaires at this visit and to provide some of your saliva to measure the amount of cotinine in your body.

The following table summarizes your visit schedule for this study:

	Before Surgery		**Day of Surgery**	**Weeks after surgery**			
	Before randomization	**On the day of the Baseline Visit**		**6***	**12***	**18***	**24***
Visit #	**1**	**2**		**3**	**4****	**5****	**6**
Pregnancy test	X***						
History & physical	X	X		X			X
Saliva measurement		X	X	X	X	X	X
Monitoring				X	X	X	X
Tobacco use questionnaire	X	X	X	X	X	X	X
Other questionnaires	X	X		X	X		X
Drug diary		X		X	X		

* These visits may be up to 2 weeks before or after the scheduled day of the visit on the calendar.

** You will be asked to come to the clinic to provide saliva samples for cotinine measurement. A doctor visit is not required and the questionnaires may be completed either in the clinic or by telephone.

*** If you are a female of child bearing potential.

What possible risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that:

- You may be asked sensitive or private questions which you normally do not discuss

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

COMMON, SOME MAY BE SERIOUS In 100 people receiving varenicline, more than 20 and up to 100 may have:
• Nausea

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving varenicline, from 4 to 20 may have:
• Trouble getting to sleep or staying asleep (insomnia) • Having vivid, unusual, or strange dreams, nightmares • Headache • Constipation • Stomach pain, swelling, belching, passing gas • Vomiting • Upper respiratory problems such as bronchitis, coughing, sinus congestion • Dry mouth • Anxiety • Depression • New or worse heart or blood vessel (cardiovascular) problems

RARE, AND SERIOUS In 100 people receiving varenicline, 3 or fewer may have:
• Nervousness, agitation, anger, suicidal or thoughts of hurting someone else—If you, your family, or your caregivers notice agitation, hostility, depression, suicidal thoughts or changes in your behavior or thinking that are not typical for you, you should call your doctor right away. • Sleepwalking—If you or your family notice that this has happened you should call your doctor. • Heart attack • Stroke • Severe allergic reaction • Very bad skin reaction (Stevens-Johnson syndrome – red, swollen, blistered or peeling skin with or without fever) • Seizures–(this is most likely to occur in first month of treatment)

Alcohol consumption: You should decrease the amount of alcoholic beverages that you drink during treatment with varenicline until you know if the drug affects your ability to tolerate alcohol.

You should use caution when **driving or operating machinery** until you know how varenicline affects you. Varenicline may make you fell sleepy, dizzy, or have trouble concentrating, making it hard to drive or perform other activities safely.

If you successfully stop smoking, you may experience **nicotine withdrawal**. Effects of nicotine withdrawal include:

- Feeling angry, irritable, anxious,
- Having difficulty concentrating, sleep problems (insomnia or abnormal dreams)
- Feeling agitated or depressed, sometimes with thoughts of suicide.

The topics discussed in **interviews or in questionnaires** may cause you to feel embarrassed or uncomfortable. If this happens to you, please let your study doctor, nurse or other study staff know about your discomfort.

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. The varenicline used in this study could be damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

What possible benefits can I expect from taking part in this study?

The usual approach to performing surgery on people who smoke is to recommend that they quit prior to surgery. Quitting smoking has been shown to decrease surgical complications in other types of surgery. Although it is not possible to know if participation in this study will result in less surgical complications, it may help you quit smoking. Quitting smoking at any time has

numerous health benefits. This study will also help researchers learn things that will help people in the future with lung cancer who smoke or quit smoking.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

Varenicline/placebo will be supplied at no charge while you take part in this study. The cost of getting varenicline/placebo ready and giving it to you is not paid by the study, so you or your insurance company may have to pay for this.. It is possible that the varenicline/placebo may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The Alliance for Clinical Trials in Oncology
- Pfizer™, the pharmaceutical company supplying varenicline/placebo
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.

The Alliance has received a Certificate of Confidentiality from the federal government, which will help us to protect your privacy. The Certificate protects against the involuntary release of information about you collected during the course of the study. The researchers involved in this project may not be forced to identify you in any legal proceedings (criminal, civil, administrative, or legislative) at the federal, state or local level. However, some information may be required by the Federal Food, Drug, and Cosmetic Act, the U.S. Department of Health and Human Services, or for purposes of program review or audit. Also, you may choose to voluntarily disclose the protected information under certain circumstances. For example, if you or your guardian requests the release of information about you in writing (through, for example, a written request to release medical records to an insurance company), the Certificate does not protect against that voluntary disclosure.

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

ADDITIONAL STUDIES SECTION:

This section is about optional studies you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records and you or your study doctor will not know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say "no" to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

Optional Sample Collections for Laboratory Studies and Biobanking for Possible Future Studies

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part in this study, the study doctor for the main study would like to collect blood for research on determining who will react better to the intervention in helping them stop smoking.

In addition, the researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The additional research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by *the* Alliance and supported by the National Cancer Institute.

WHAT IS INVOLVED?

If you agree to take part, here is what will happen next:

1) About 2 tablespoons of blood will be collected from a vein in your arm at the baseline visit.
2) Your baseline blood sample and some related health information will be sent to a researcher for use in the study described above. Remaining baseline blood samples may be stored in the Biobank, along with samples from other people who take part. The samples will be kept until they are used up.

3) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the Alliance, and/or the National Cancer Institute, will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
4) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your baseline blood samples.
5) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

1) The most common risks related to drawing blood from your arm are brief pain and possibly a bruise.
2) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
3) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
4) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your samples are sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and Alliance staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom the Alliance sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

Please circle your answer to show whether or not you would like to take part in each option:

SAMPLES FOR THE LABORATORY STUDIES:

1. I agree to have my specimen collected and I agree that my specimen samples and related information may be used for the laboratory study described above.

   YES NO

SAMPLES FOR FUTURE RESEARCH STUDIES:

2. My samples and related information may be kept in a Biobank for use in future health research.

   YES NO

3. I agree that my study doctor, or their representative, may contact me or my physician to see if I wish to participate in other research in the future.

   YES NO

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study *and any additional studies where I circled 'yes'.*

Participant's signature_____

Date of signature_____

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____

APPENDIX I: SURGICAL COMPLICATIONS ASSOCIATED WITH CIGARETTE SMOKING [104]

30-day mortality 30-day re-hospitalization 1-year mortality Anastomotic failure Anesthesia-related respiratory complications Bleeding (transfusions >5 U) Coma (>24 hours) Deep venous thrombosis/thrombophlebitis Failure to wean from the ventilator ICU readmission Impaired bone healing Implant loss (breast reconstruction)	Increased postoperative pain Renal insufficiency/failure Return to operating room Sepsis/septic shock Stroke/cerebral accident Surgical infection (organ space) Surgical site infections Urinary tract infections Increased postoperative surgical stay Increased scarring and asymmetry Intubation (unplanned)/re-intubation Lower rates of successful digital replantation (microsurgery) Myocardial infarction	Pneumonia Prolonged intubation Prolonged ventilator support Pulmonary complications Pulmonary embolism Reduced skin flap survival Vascular complications Vein graft failure Venous thromboembolism Ventilator (>48 hours) Wound healing (delayed) Wound infection (sternal) Wound infections (superficial and deep)

APPENDIX II: PATIENT INFORMATION SHEETS

Patient Information Sheet
(Prior to registration)

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet contains:
    a. Tobacco Use Assessment
    b. Contemplation Ladder
    c. Patient Health Questionnaire PHQ-9

2. Directions on how to complete each set of questions are written on the top of each set.

3. You will be given the nurse's name and telephone number. You can call any time with any concerns or questions.

4. It is very important that you return the booklet to us, whether you finish the study or not.

Thank you for taking the time to help us.

Patient Information Sheet
(Baseline)

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet contains:
    a. Tobacco Use Assessment
    b. Smoking Self Efficacy Questionnaire (SEQ-12)
    c. Fagerström Test for Nicotine Dependence (FTND)
    d. Linear Analogue Self-Assessment (LASA-12)

2. Directions on how to complete each set of questions are written on the top of each set.

3. You will be given the nurse's name and telephone number. You can call any time with any concerns or questions.

4. It is very important that you return the booklet to us, whether you finish the study or not.

Thank you for taking the time to help us.

Patient Information Sheet
(Day of surgery)

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet contains the Tobacco Use Assessment.

2. Directions on how to complete each set of questions are written on the top of each set.

3. You will be given the nurse's name and telephone number. You can call any time with any concerns or questions.

4. It is very important that you return the booklet to us, whether you finish the study or not.

Thank you for taking the time to help us.

Patient Information Sheet
(Week 6)

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet contains:
    a. Tobacco Use Assessment
    b. Contemplation Ladder
    c. Smoking Self Efficacy Questionnaire (SEQ12)
    d. Patient Health Questionnaire (PHQ-9)

2. Directions on how to complete each set of questions are written on the top of each set.

3. You will be given the nurse's name and telephone number. You can call any time with any concerns or questions.

4. It is very important that you return the booklet to us, whether you finish the study or not.

Thank you for taking the time to help us.

Patient Information Sheet
(Week 12)

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet contains:
    a. Tobacco Use Assessment
    b. Contemplation Ladder
    c. Smoking Self Efficacy Questionnaire (SEQ12)
    d. Patient Health Questionnaire (PHQ-9)
    e. Linear Analogue Self-Assessment (LASA)
    f. Was It Worth It (WIWI)

2. Directions on how to complete each set of questions are written on the top of each set.

3. You will be given the nurse's name and telephone number. You can call any time with any concerns or questions.

4. It is very important that you return the booklet to us, whether you finish the study or not.

5. You will be asked to either complete the questionnaires by telephone or to bring the booklet with you to your next clinical visit.

Thank you for taking the time to help us.

Patient Information Sheet
(Week 18)

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet contains the Tobacco Use Assessment.

2. Directions on how to complete each set of questions are written on the top of each set.

3. You will be given the nurse's name and telephone number. You can call any time with any concerns or questions.

4. It is very important that you return the booklet to us, whether you finish the study or not.

5. You will be asked to either complete the questionnaires by telephone or to bring the booklet with you to your next clinical visit..

Thank you for taking the time to help us.

Patient Information Sheet
(Week 24)

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet contains:
    a. Tobacco Use Assessment
    b. Contemplation Ladder
    c. Smoking Self Efficacy Questionnaire (SEQ12)
    d. Patient Health Questionnaire (PHQ-9)
    e. Linear Analogue Self-Assessment (LASA)
    f. Was It Worth It (WIWI)

2. Directions on how to complete each set of questions are written on the top of each set.

3. You will be given the nurse's name and telephone number. You can call any time with any concerns or questions.

4. It is very important that you return the booklet to us, whether you finish the study or not.

Thank you for taking the time to help us.

APPENDIX III: CONTEMPLATION LADDER

Directions: Please complete the following concerning you readiness to quit smoking.

Each number below represents where various tobacco-users are in their thinking about quitting. Circle the number that indicates where you are now.

10 ⟶	*I am ready to quit now.*
9	
8 ⟶	*I have cut down or am seriously thinking of quitting.*
7	
6 ⟶	*I am thinking about cutting down or quitting.*
5	
4 ⟶	*I think I should quit but I'm not quite ready.*
3	
2 ⟶	*I think I need to consider quitting some day.*
1	
0 ⟶	*I am not ready to quit.*

APPENDIX IV: SMOKING SELF EFFICACY QUESTIONNAIRE (SEQ12)

The following are some situations in which certain people might be tempted to smoke.

Directions: Please indicate whether you are sure that you could *refrain* from smoking in each situation by placing an "X" in the appropriate box.

1. **When I feel nervous** *(check one)*

☐Not at all sure ☐Not very sure ☐More or less sure ☐Fairly sure ☐Absolutely sure

2. **When I feel depressed** *(check one)*

☐Not at all sure ☐Not very sure ☐More or less sure ☐Fairly sure ☐Absolutely sure

3. **When I am angry** *(check one)*

☐Not at all sure ☐Not very sure ☐More or less sure ☐Fairly sure ☐Absolutely sure

4. **When I feel very anxious** *(check one)*

☐Not at all sure ☐Not very sure ☐More or less sure ☐Fairly sure ☐Absolutely sure

5. **When I want to think about a difficult problem** *(check one)*

☐Not at all sure ☐Not very sure ☐More or less sure ☐Fairly sure ☐Absolutely sure

6. **When I feel the urge to smoke** *(check one)*

☐Not at all sure ☐Not very sure ☐More or less sure ☐Fairly sure ☐Absolutely sure

7. **When having a drink with friends** *(check one)*

☐Not at all sure ☐Not very sure ☐More or less sure ☐Fairly sure ☐Absolutely sure

8. **When celebrating something** *(check one)*

☐Not at all sure ☐Not very sure ☐More or less sure ☐Fairly sure ☐Absolutely sure

9. **When drinking beer, wine or other spirits** *(check one)*

☐Not at all sure ☐Not very sure ☐More or less sure ☐Fairly sure ☐Absolutely sure

10. **When I am with smokers** *(check one)*

☐Not at all sure ☐Not very sure ☐More or less sure ☐Fairly sure ☐Absolutely sure

11. After a meal *(check one)*

☐Not at all sure ☐Not very sure ☐More or less sure ☐Fairly sure ☐Absolutely sure

12. When having coffee or tea *(check one)*

☐Not at all sure ☐Not very sure ☐More or less sure ☐Fairly sure ☐Absolutely sure

APPENDIX V: FAGERSTRÖM TEST FOR NICOTINE DEPENDENCE

Directions: Please read each question below.
Check only one box for each question that best describes your response.

1. How soon after you wake up do you smoke you first cigarette? *(check one)*

- ☐ Within 5 minutes
- ☐ 6-30 minutes
- ☐ 31-60 minutes
- ☐ After 60 minutes

2. Do you find it difficult to refrain from smoking in places where it is forbidden, e.g. in church, at the library, in cinema, etc.? *(check one)*

- ☐ Yes
- ☐ No

3. Which cigarette would you hate most to give up? *(check one)*

- ☐ The first one in the morning
- ☐ Any other

4. How many cigarettes per day do you smoke? *(check one)*

- ☐ 10 or less
- ☐ 11-20
- ☐ 21-30
- ☐ 31 or more

5. Do you smoke more frequently during the first hours after awakening than during the rest of the day? *(check one)*

- ☐ Yes
- ☐ No

6. Do you smoke even when you are so ill that you are in bed most of the day? *(check one)*

- ☐ Yes
- ☐ No

APPENDIX VI: PATIENT HEALTH QUESTIONNAIRE – 9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?

1. Little interest or pleasure in doing things

- ☐ 0 – Not at all
- ☐ 1- Several days
- ☐ 2 – More than half the days
- ☐ 3- Nearly every day

2. Feeling down, depressed, or hopeless

- ☐ 0 – Not at all
- ☐ 1- Several days
- ☐ 2 – More than half the days
- ☐ 3- Nearly every day

3. Trouble falling or staying asleep, or sleeping too much

- ☐ 0 – Not at all
- ☐ 1- Several days
- ☐ 2 – More than half the days
- ☐ 3- Nearly every day

4. Feeling tired or having little energy

- ☐ 0 – Not at all
- ☐ 1- Several days
- ☐ 2 – More than half the days
- ☐ 3- Nearly every day

5. Poor appetite or overeating

- ☐ 0 – Not at all
- ☐ 1- Several days
- ☐ 2 – More than half the days
- ☐ 3- Nearly every day

6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down

- ☐ 0 – Not at all
- ☐ 1- Several days
- ☐ 2 – More than half the days
- ☐ 3- Nearly every day

7. Trouble concentrating on things, such as reading the newspaper or watching television

☐ 0 – Not at all

☐ 1- Several days

☐ 2 – More than half the days

☐ 3- Nearly every day

8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual.

☐ 0 – Not at all

☐ 1- Several days

☐ 2 – More than half the days

☐ 3- Nearly every day

9. Thoughts that you would be better off dead or of hurting yourself in some way

☐ 0 – Not at all

☐ 1- Several days

☐ 2 – More than half the days

☐ 3- Nearly every day

_____

For office coding _____+_____+_____+_____

= _____

_____

If you checked off <u>any</u> problems, how <u>difficult</u> have these problems made if for you to do you work, take care of things at home, or get along with other people? *(check one)*

☐ Not difficult at all ☐ Somewhat difficult ☐ Very difficult ☐ Extremely difficult

APPENDIX VII: LINEAR ANALOGUE SELF-ASSESSMENT

Directions: Please circle the number (0-10) best reflecting your response to the following that describes your feelings **during the past week, including today**

How would you describe:

1. your overall Quality of Life?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

2. your overall mental (intellectual) well being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

3. your overall physical well being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

4. your overall emotional well being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

5. your level of social activity?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

6. your overall spiritual well being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

7. the frequency of your pain?

0	1	2	3	4	5	6	7	8	9	10
No pain										Constant pain

8. the severity of your pain, on the average?

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

9. your level of fatigue, on the average?

0	1	2	3	4	5	6	7	8	9	10
No fatigue										Constant tiredness

10. your level of support from friends and family?

0	1	2	3	4	5	6	7	8	9	10
No support										Highest level of support

11. your financial concerns?

0	1	2	3	4	5	6	7	8	9	10
Constant concerns										No concerns

12. your legal concerns (will, advanced directives, etc.)?

0	1	2	3	4	5	6	7	8	9	10
Constant concerns										No concerns

APPENDIX VIII: WAS IT WORTH IT (WIWI) QUESTIONNAIRE

Participating in a clinical trial / research study is a personal choice and an individual experience. We would like to get your feedback on your experience in this research study. Please respond to the following questions as indicated.

Directions: Please answer each question by circling Y (for yes), N (for no), or U (for uncertain).

Was it worthwhile for you to participate in this research study? Y N U

If you had to do it over, would you participate in this research study again? Y N U

Would you recommend participating in this research study to others? Y N U

Directions: In the next two questions, please answer each question by circling one response.

Overall, did your quality of life change by participating in this research study?

It improved It stayed the same It got worse

Overall, how was your experience of participating in this research study?

Better than I expected The same as I expected Worse than I expected

If there was **one thing** that could have been done to improve your experience in this research study, what would it be?

_____

_____

Would you like to talk to someone about your concerns *(circle one response)*? Yes No

APPENDIX IX: TOBACCO USE ASSESSMENT

Visit Number ___ ___

Type of Visit: ☐ Phone Visit ☐ Clinic Visit

Missed visit: ☐ Please comment below if patient canceled and reason, if rescheduled, or if a no-show.

VITAL SIGNS

1. Height __ __ __.__ cm (*without shoes)*
2. Weight __ __ __.__ kg (*without shoes, with lightweight indoor clothes (no coats or jackets))*
3. Pulse ___ ___ ___ bpm
4. Blood Pressure: __ __ __/__ __ __ mm/Hg

TOBACCO-USE STATUS

REFERENCES:

a. Target Quit Day (__ __/__ __/__ __ __ __)
mm dd yyyy

b. 14 Days After TQD (__ __/__ __/__ __ __ __)
mm dd yyyy

5. a. Since 14 days after your TQD, have you used any tobacco on each of 7 consecutive days?
9☐ Not applicable 0☐No 1☐Yes
↓
1☐cigarettes 1☐cigars 1☐pipes 1☐smokeless 1☐other _____
↓
Date of First Use: ___ ___/___ ___/___ ___ ___ ___
mm dd yyyy

b. Since 14 days after your Target Quit Day, have you used any tobacco on at least one day in each of 2 consecutive weeks?
9☐ Not applicable 0☐No 1☐Yes
↓
1☐cigarettes 1☐cigars 1☐pipes 1☐smokeless 1☐other _____
↓
Date of First Use: ___ ___/___ ___/___ ___ ___ ___
mm dd yyyy

c. Have you used any tobacco since your last visit? 0☐No 1☐ Yes
↓
1☐cigarettes 1☐cigars 1☐pipes 1☐smokeless 1☐other _____
↓
Date of First Use: ___ ___/___ ___/___ ___ ___ ___
mm dd yyyy

d. Have you used any tobacco in the last 7 days? 0☐No 1☐ Yes

↓

1☐cigarettes/day? _____ if less than 1/day specify →_____
1☐pipe bowls/day? _____ if less than 1/day specify →_____
1☐cigars/day? _____ if less than 1/day specify →_____
1☐smokeless tobacco cans or pouches/week? _____ if less than 1/wk specify →_____
1☐other/week →specify type and amount _____ if less than 1/wk specify →_____

BEHAVIORAL INTERVENTION

6. Since your last visit, have you had the opportunity to speak with anyone in the NCI Tobacco Quitline?

0☐ No → Explain why not _____

Just a reminder that you can call the tobacco quitline at any time so that they can provide you with support during this time of trying to stop smoking. Would you like me to provide you with their toll-free number? 0☐ No 1☐ Yes → the number is 1-877-448-7848

Is there anything I can help you with?
0☐ No 1☐ Yes → explain_____

1☐ Yes → How many times have you connected with them since our last visit?___ ___ ___

What overall topic did you discuss?_____

Just a reminder that you can call the tobacco quitline at any time so that they can provide you with support during this time of trying to stop smoking. Would you like me to provide you with their toll-free number? 0☐ No 1☐ Yes → the number is 1-877-448-7848

Is there anything I can help you with?
0☐ No 1☐ Yes → explain_____

APPENDIX X: DRUG AND BEHAVIORAL ADHERENCE LOG

Date of Baseline Visit: _____

This log applies to: *(circle one)*	Weeks 1-6	Weeks 7-12

	Day		**Varenicline/ placebo dose taken** *Circle One)*	**Did you contact the tobacco Quitline on this day?** *(Circle One)*	**Number of Cigarettes Smoked**	**Comment**
Date:_____	**1**	AM	**Yes No**	**Yes No**		
Date:_____	**2**	AM	**Yes No**	**Yes No**		
Date:_____	**3**	AM	**Yes No**	**Yes No**		
Date:_____	**4**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**5**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**6**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**7**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**8**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**9**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**10**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			

	Day		Varenicline/ placebo dose taken *Circle One)*	Did you contact the tobacco Quitline on this day? *(Circle One)*	Number of Cigarettes Smoked	Comment
Date:_____	**11**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**12**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**13**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**14**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**15**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**16**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**17**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**18**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**19**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**20**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**21**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			

	Day		Varenicline/ placebo dose taken *Circle One)*	Did you contact the tobacco Quitline on this day? *(Circle One)*	Number of Cigarettes Smoked	Comment
Date:_____	**22**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**23**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**24**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**25**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**26**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**27**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**28**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**29**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**30**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**31**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**32**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			

	Day		Varenicline/ placebo dose taken *Circle One)*	Did you contact the tobacco Quitline on this day? *(Circle One)*	Number of Cigarettes Smoked	Comment
Date:_____	**33**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**34**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**35**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**36**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**37**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**38**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**39**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**40**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**41**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			
Date:_____	**42**	AM	**Yes No**	**Yes No**		
		PM	**Yes No**			

APPENDIX XI: GENERAL THORACIC SURGERY DATABASE DEFINITIONS

Complication	Definition
Air leak	Patient experienced a postoperative air leak for >5 days
Bronchoscopy for atelectasis	Postoperative atelectasis documented clinically or radiographically that needed bronchoscopy
Pneumonia	Defined according to the last CDC criteria: two or more serial chest radiographs with at least **one** of the following: • New or progressive **and** persistent infiltrate • Consolidation • Cavitation **and** at least **one** of the following: • Fever (>38°C or >100.4°F) with no other recognized cause • Leukopenia (<4000 WBC/mm^3) or leukocytosis (≥12,000 WBC/mm^3) • For adults ≥70 years old, altered mental status with no other recognized cause **and** at least **two** of the following: • New onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased functioning requirements • New onset or worsening cough, or dyspnea, or tachypnea • Rales or bronchial breath sounds Worsening gas exchange (e.g. O_2 desaturations [eg, PaO_2/FiO_2 ≤240], increased oxygen requirements, or increased ventilator demand)
ARDS	Adult respiratory distress syndrome defined according to the American-European consensus conference; all of the following criteria should be met: • Acute onset • Arterial hypoxemia with PaO_2/FIO_2 ratio <200 (regardless of PEEP level) • Bilateral infiltrates at chest radiograph or CT scan • No clinical evidence of left atrial hypertension or pulmonary artery occlusive pressure <18 mm Hg • Compatible risk factors
Bronchopleural fistula	Patient experienced a complete or partial dehiscence of the bronchial stump documented in the postoperative period (such as bronchoscopy or other operative intervention)

Pulmonary embolism	Patient experienced a pulmonary embolus in the postoperative period as documented by a V/Q scan, angiogram, or spiral CT
Initial ventilator support	Patient initially was ventilated >48 hours in the postoperative period; ventilator support ends with removal of endotracheal tube or, if the patient has a tracheostomy tube, until no longer ventilator dependent
Reintubation	Patient was reintubated during the initial hospital stay after the initial extubation; this may include patients who have been extubated in the operating room and require intubation in the postoperative period
Tracheostomy	Patient required a tracheostomy in the postoperative period whether performed in the ICU or the OR; prophylactic minitracheostomy on the day of operation should not be considered a complication
Atrial arrhythmia	New onset of atrial fibrillation/flutter (AF) requiring medical treatment or cardioversion; does not include recurrence of AF that was present preoperatively
Ventricular arrhythmia	Sustained ventricular tachycardia or ventricular fibrillation that has been clinically documented and treated by ablation therapy, implantable cardioverter defibrillator, permanent pacemaker, pharmacologic treatment. or cardioversion
Myocardial infarction	Evidenced by one of the following criteria: • Transmural infarction diagnosed by the appearance of a new Q wave in two or more contiguous leads on ECG • Subendocardial infarction (non Q wave) evidenced by clinical, angiographic, electrocardiographic signs • Laboratory isoenzyme evidence of myocardial necrosis
Empyema	Patient experienced an empyema requiring treatment in the postoperative period; diagnosis of empyema should be confirmed by thoracentesis; frank pus or merely cloudy fluid may be aspirated from the pleural space; the pleural fluid typically has leukocytosis, low pH (<7.20), low glucose (<60 mg/dL), high lactate dehydrogenase, and elevated protein and may contain infectious organisms
Wound infection	Patient experienced a wound infection in the postoperative period as evidenced by meeting two of the following criteria: • Wound opened with excision of tissue (I&D) • Positive culture • Treatment with antibiotics

Cerebrovascular complications	Occurrence of one of the following central neurologic postoperative events not present preoperatively: • A central neurologic deficit persisting postoperatively for more than 72 hours • A transient neurologic deficit (transient ischemic attack or reversible ischemic neurologic deficit) with recovery within 72 hours. • A new postoperative coma persisting at least 24 hours and caused by anoxic/ischemic and/or metabolic encephalopathy, thromboembolic event, or cerebral bleed
Recurrent nerve palsy	Patient experienced in the postoperative period a recurrent laryngeal nerve paresis or paralysis that was not identified during the preoperative evaluation
Delirium	Patient experienced a new onset of symptoms like illusions, confusion, cerebral excitement in the postoperative period
Renal failure	Defined as the onset of new renal failure in the postoperative period according to one of the following criteria: • Increase of serum creatinine to >2.0 mg/dL • Two times the preoperative creatinine level • A new requirement for dialysis postoperatively
Chylothorax	Patient experienced a chylothorax in the postoperative period that required persistent or new drainage and medical intervention (e.g. NPO, TPN) or reoperation. Chylothorax is defined by the clinical appearance of the pleural fluid or the presence of pleural fluid triglyceride levels >110 mg/dL with a cholesterol level <200 mg/dL
Unexpected admission to the ICU	An unplanned transfer of the patient to the ICU owing to deterioration in the condition of the patient requiring active life support treatment

APPENDIX XII: MAYO CLINIC NICOTINE RESEARCH PROGRAM CRISIS POLICY

This policy is provided as an example of suicide ideation monitoring and response procedures sites should have in place. For dose modification instructions for patients participating in this study, refer to Section 8.2 of the protocol.

Psychiatric Symptom Management

1. Suicidal Ideation

Assessment: Any study participant reporting suicidal ideation to a study coordinator or nurse will be psychiatrically evaluated immediately thereafter by either the site principal investigator or the on-call clinical investigator.

Procedures in place to deal with suicidal ideation: If the participant is unwilling to seek help, the individual will be advised that the Site Research Team is required to report that the subject is threatening to harm him/herself and the patient will be escorted to the Emergency Department of the local hospital by ambulance for an evaluation by the psychiatrist on call.

How and when study medication might be discontinued: At that time, the study medication will be stopped until further notice from the treating physician. If the medication is stopped permanently, the subject will be given the option of continuing in the study without the medication.

2. Depression

Assessment: To diagnose depression, most of the following signs and symptoms must be present most of the day, nearly every day, for at least two weeks: sleep disturbances, impaired thinking or concentration, significant weight loss or gain, agitation or slowing of body movements, fatigue, low self-esteem, less interest in sex, thoughts of death (suicidal ideation – see above). Accordingly, any study participant reporting depression or severe change in mood to a study coordinator or nurse will be psychiatrically evaluated immediately thereafter by either the principal investigator or the on-call clinical investigator.

Procedures in place to deal with depression:

- If it is determined that the current level of depression is likely to lead to self-harm or harm to others, the individual will be advised that the Site Research Team is required to report that the subject is threatening to harm him/herself and the patient will be escorted to the Emergency Department of the local hospital by ambulance for an evaluation by the psychiatrist on call.
- If it is determined that the emerging depression requires treatment, the subject will be referred to one of the following:
  - Primary provider (the physician will call the provider)
  - Local mental health facility
  - Community psychiatric services

How and when the study medication would be discontinued: If the site investigator notes new depression or an exacerbation of existing depression, the subject may be advised to modify the dose of the study drug. Based on the clinical assessment by the site investigator or one of the co-investigators the study medication may be stopped temporarily and then re-challenged at the target dose, reduced permanently, or discontinued permanently. If the study drug is permanently discontinued, the subject would still receive follow-up counseling according to the study protocol.

3. Less Common Psychiatric Symptoms

Assessment: In the case of emergency, diagnoses will be made immediately by the site investigator and/or the on-call clinical investigator.

Procedures in place to deal with anxiety:

- If it is determined that the current psychiatric symptom is likely to lead to self-harm or harm to others, the individual will be advised that the Site Research Team is required to report that the subject is threatening to harm him/herself and the patient will be escorted to the Emergency Department of the local Hospital by ambulance for an evaluation by the psychiatrist on call.
- If it is determined that the emerging psychiatric condition requires treatment, the subject will be referred to one of the following:
  - Primary provider (the physician will call the provider)
  - Local mental health facility
  - Community psychiatric services

How and when the study medication would be discontinued: If the site investigator notes a new psychiatric illness or syndrome or an exacerbation of an existing mental health condition, the subject may be advised to modify the dose of the study drug. Based on the clinical assessment by the site investigator or one of the co-investigators the study medication may be stopped temporarily and then re-challenged at the target dose, reduced permanently, or discontinued permanently. If the study drug is permanently discontinued, the subject would still receive follow-up counseling according to the study protocol.

4. Crisis Management of Maltreatment, Neglect, Violence:

In the event that the subject expresses thoughts or actively performs behaviors related to the mistreatment of vulnerable adults, domestic violence, workplace violence, child abuse, or neglect, the event(s) will be referred immediately by the nursing staff to the physician on duty. All events will be documented by nursing staff.

5. Homicidal Threat:

Hospital Security will be immediately called to report that the participant has threatened to harm another person or staff member.

- Staff who are threatened by a participant should take immediate precautions to protect themselves and others.
- The participant expressing homicidal ideation should be advised that we are required to take action to protect all individuals(s) being threatened.
- Participants who threaten to harm another individual will be assessed by study nursing staff who will then consult with the principal investigator or the on-call clinical investigator to determine the seriousness of the situation.
- Staff should attempt to locate a telephone number for the person being threatened. The person will be contacted as soon as possible and warned that such a threat has been made.

Contact Resources:

If a patient has expressed current symptoms of depression, active suicidal ideation, maltreatment, neglect, violence, and drug/alcohol issues signs and symptoms of severe depression, the following resources should be contacted in the order listed:

1. Principal Investigator for the study
2. Study Call Schedule (this includes physicians overseeing the residential treatment program and the outpatient clinical program).
3. Local Site Security, at any point they are needed for support.

Important facts to remember:

- If a participant will not cooperate or you have any concern for their safety or your own safety,
- Call Local Site Security.
- Please remember to document all events in the participant study record.
- The on-call clinical psychiatrist at local Hospital Emergency Room is an available resource.

APPENDIX XIII: VARENICLINE WALLET CARD

[Note to investigators: This convenient wallet-sized information card is to be completed and then provided for the patient to clip out and retain at all times.]

INFORMATION ON POSSIBLE DRUG INTERACTIONS You are enrolled on a clinical trial to help you stop smoking. This clinical trial is sponsored by the NCI. Quitting smoking may change how your body interacts with certain drugs that are processed by your liver. Because of this, it is very important to: ➢ Tell your doctors if you stop taking regular medicine or if you start taking a new medicine. ➢ Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	Quitting smoking may change levels of a specific liver enzyme called **CYP1A2**, and may change how certain medications are metabolized by your body. ➢ After you stop smoking, your study doctor will work with your regular prescriber to adjust medicines that are considered "substrates" of **CYP1A2** such as the blood thinner warfarin. ➢ Before prescribing new medicines, your regular prescribers should go to http://medicine.iupui.edu/clinpharm/ddis/table.aspx for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____.