Published in final edited form as:

Contemp Clin Trials. 2017 September ; 60: 86–95. doi:10.1016/j.cct.2017.07.002.

Program for Lung Cancer Screening and Tobacco Cessation: Study Protocol of a Sequential, Multiple Assignment, Randomized Trial

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Keywords

Smoking cessation; lung cancer screening; adaptive interventions

INTRODUCTION

The landmark National Lung Screening Trial (NLST) showed that annual low dose computed tomography (LDCT) screening decreased the rate of lung cancer death by 20%.^{1–3} In response, the US Preventive Services Task Force (USPSTF)⁴ and other professional societies issued recommendations to screen persons at high risk, which is defined as adults aged 55–80 years who have a 30-pack-year or more smoking history and

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Declaration of interests

We declare no competing interests.

Clinical Trials Registration: [ClinicalTrials.gov](https://clinicaltrials.gov): NCT02597491

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currently smoke or have quit within the past 15 years (USPSTF Grade B recommendation).^{5–9} Approximately half of the patients undergoing lung cancer screening will be current smokers.⁶ Hence, screening current smokers at high risk for lung cancer creates a clinical imperative to establish efficient and effective systems to treat smokers on a large scale.

Clinical trials have demonstrated the efficacy of a variety of behavioral, pharmacological, and combination treatment strategies for smoking cessation.¹⁰ However, these treatments yield low rates of long-term abstinence (5–20%) depending on the population of smokers and intensity of treatment.¹⁰ Research suggests that it is possible to identify the individuals who are not likely to quit early (during treatment), and those who quit in the short-term who are likely to remain abstinent long-term even with less support.¹¹

One approach to improving the long-term abstinence rate is an *adaptive intervention* (AI) which guides the provision of additional treatment for individuals showing early signs of failure to quit *and* guides how best to maintain long-term abstinence among individuals who show early signs of success.¹² The premise that intervention needs to adapt systematically to the changing needs and experiences of the individual provides a framework that closely resembles clinical practice and is consistent with the management of chronic disorders such as smoking.¹³ In order for adaptive interventions to be useful to practicing clinicians, they must provide clear decision rules that explicitly identify the construct(s) used to tailor the treatment to an individual (including how and when to measure them), and how to link such construct(s) to specific treatment options.¹²

To date, there is scant evidence to guide the development of adaptive interventions in tobacco cessation. Our prior research has raised three important treatment questions: (a) Do individuals who fail to quit after receiving 8 weeks of telephone coaching and nicotine replacement therapy (NRT) (i.e., standard combined behavioral and pharmacologic treatment) benefit from the provision of prescription medications? (b) Do individuals who quit within 8 weeks require additional intensive standard combined treatment for one year or can we reduce treatment intensity (e.g. quarterly) for one year? (c) How does the time at which a smoker is identified as responding or not responding to treatment (e.g., early (week 4) or later (week 8)) affect his/her response to further treatment?^{11,13} In particular, it may be better to modify treatment for non-responders early, but better to modify treatment for responders later. Given the high rate of relapse following initial treatment, these are critical knowledge gaps.

We present the study design and intervention protocols of the **P**rogram for **L**Ung Cancer Screening and **T**Obacco Cessation (PLUTO) trial that aims to answer the preceding three questions to develop a two-phase, one-year long adaptive intervention among high risk smokers screened for lung cancer.

METHODS

PLUTO Study Design Overview

The PLUTO trial will enroll 1,000 participants and will employ a **sequential, multiple assignment, randomized trial** (SMART) design⁴⁻⁶ (see Figure 1). All participants, current smokers at high risk for lung cancer and meeting other inclusion/exclusion criteria, are provided tobacco longitudinal care (TLC) which includes a combination of intensive telephone coaching (relapse-sensitive call protocol) and NRT for one year, with a minimum of monthly contact.¹³ All individuals will be randomized with equal probability to the duration of the initial phase of TLC treatment: 4 vs. 8 weeks. At the end of initial treatment, participants will be assessed for complete response vs. incomplete response to TLC for purposes of considering the second phase of treatment. At the end of the initial phase of TLC treatment, *incomplete responders* (i.e., any smoking, even a puff, in the last 7 days) will be randomized to continue TLC or TLC plus an expanded toolbox of treatment options, adding pharmacist-administered medication therapy management (TLC+MTM). MTM includes the prescription drug options bupropion and varenicline. At the end of initial phase of TLC treatment, *complete responders* will be randomized to continue TLC or TLC with less intensive quarterly contact (TLC-Quarterly). All participants receive longitudinal treatment for one year, however the treatment components, treatment intensity, and timing of treatment availability will vary.

While alternative study designs are also appropriate for informing the development of adaptive interventions, we chose the SMART design because it allows us to (1) compare different components of an adaptive intervention, (2) test different intervention strategies embedded within the trial design (Table 1), and (3) explore ways to develop a more personalized AI.

Primary Aim

The primary aim of this study is to test whether incomplete responders to initial phase of TLC treatment benefit from the addition of MTM. The primary outcome will be 6-month prolonged abstinence measured 18 months after the beginning of TLC. We hypothesize that among *incomplete responders*, long-term abstinence rates will be higher in smokers randomized to TLC+MTM compared to TLC.

Secondary Aims

There are four secondary aims:

1. Among *complete responders* to initial phase of TLC treatment we will compare the effect of more intensive (at least monthly) follow-up to less intensive (quarterly) follow-up on long-term abstinence rates. More intensive follow-up is hypothesized to lead to improved long-term abstinence rates.
2. We will examine whether timing of assessment moderates the effect of treatment as timing of assessment may differentially affect incomplete versus complete responders. For incomplete responders, modifying treatment may be more effective earlier versus later because it is better to increase treatment intensity

earlier in smokers who are struggling. In contrast, for complete responders, it may be better to lower treatment intensity later when they are “more secure” in their quit attempt. This information will be helpful for treatment decision-making. Specifically, we hypothesize that incomplete responders identified after 4 weeks of treatment will benefit more from TLC+MTM compared to TLC than will those identified after 8 weeks of treatment. We also hypothesize that *complete responders* identified after 4 weeks of treatment will benefit more from TLC compared to TLC-Quarterly, but for *complete responders* identified after 8 weeks of treatment there will be no difference between TLC and TLC-Quarterly.

3. Among *incomplete responders* we will assess whether the number of days smoking in the 7 days prior to being identified as an incomplete responder moderates the effect of TLC+MTM vs. TLC. We hypothesize that the more days subjects report smoking, the more they will benefit from TLC+MTM relative to TLC.
4. Finally, we will analyze whether lung cancer screening results (e.g., nodule present or no nodule) moderate smoking abstinence outcomes to help identify ways to improve smoking cessation programs in the context of lung cancer screening.

The study was approved by the Institutional Review Boards at the University of Minnesota and the Minneapolis Veterans Affairs Health Care System (MVAHCS).

Conceptual Framework and Rationale for Adaptive Interventions in Smoking Cessation

Adaptive interventions are highly congruent with principles of chronic disease management.¹⁴ Chronic disease management typically involves the patient, practice, and health care system, and relies on multidisciplinary teams that provide intensive follow-up.¹⁵ Adaptive interventions are consistent with stepped care as a chronic disease management tool, as outlined in Figure 2. A stepped care model features 1) the least restrictive treatment for patients with respect to cost and personal inconvenience (i.e., initial treatment), and 2) monitoring with correction.^{16,17} More intensive treatments are generally reserved for patients who do not respond to initial treatments. Stepped care models often mimic clinical care and have been described for the case of smoking cessation^{18,19} as well as other behavioral disorders.^{16,17,20,21} Abrams et al. suggested a stepped care approach using treatment matching that might bypass low-intensity intervention for smokers at high risk of relapse.¹⁸ Stepped care relies on decision-making rules to define success and failure of treatment; however, there is a paucity of formal testing of such algorithms in the case of smoking cessation. The proposed set of interventions starts with initial treatment that has been shown to be both effective and efficient.²² Telephone coaching coupled with NRT, available over-the-counter, are the core components of many large scale effective smoking cessation treatment programs,^{22,10} including TLC, that have the considerable advantages of no requirement for face-to-face contact and relatively low costs. Decisions regarding subsequent treatment rest on how smokers respond to initial treatment. For those who are complete responders, treatment continues to involve counseling and NRT, but the frequency of follow-up could vary. For those who are *incomplete responders* treatment could continue

to involve counseling and NRT or it could expand to include a pharmacist consult to provide prescription medications and medication therapy management.

Study Setting and Participants

Lung cancer screening programs will identify patients who are eligible for lung cancer screening and potentially eligible for the trial using the electronic medical record (EMR) at two institutions, the University of Minnesota and the Minneapolis VAHCS. Patients undergoing lung cancer screening who are identified as current smokers in the EMR will receive information by mail about the trial, which will emphasize that smoking cessation is an integral part of the lung cancer screening program (whether or not smokers enroll in the trial). We will follow-up the invitation letter to potentially eligible current smokers with a telephone call for further explanation of the study and screening. Informed consent and enrollment for eligible patients will occur prior to or within 30 days of their LDCT.

Eligibility criteria are based on eligibility for lung cancer screening in individuals with interest in quitting. Inclusion criteria include: 1) scheduled or have an order for LDCT for lung cancer screening, 2) current daily smoker (defined as smoking a cigarette even a puff in the past 30 days and smoking on at least 5 of 7 days), 3) 55 to 79 years old, and 4) willing to choose a quit date within the next 12 weeks. Exclusion criteria include 1) unstable psychiatric disease, 2) cognitive impairment, 3) currently participating in formal smoking cessation treatment program and/or use of varenicline or bupropion specifically for smoking cessation, 4) no phone, or 5) non-English speaking.

Randomizations

Participants will be assigned to treatment groups using computer generated stratified, blocked randomization schemes for each of the two potential randomizations, available on a secure Web-based application. All randomizations will be stratified by gender, as there may be gender differences in response to smoking cessation treatment, and participating site to ensure equal distribution between treatment groups and sufficient numbers of female participants. Two block sizes in random order will be used to improve balance and to further protect the randomness of the treatment assignment.

The first randomization will occur 4 weeks after the first telephone call from the quit coach to the participant (i.e., the outreach call) and will determine whether assessment of response to treatment is at 4 weeks or 8 weeks.

At 4 or 8 weeks, depending on the outcome of the first randomization, participants will undergo a second randomization. Treatment conditions available at the time of the second randomization will depend on whether they are an *incomplete* or a *complete responder* to initial treatment. *Incomplete responders* will subsequently be randomized to TLC or TLC +MTM and *complete responders* will be randomized to TLC or TLC-Quarterly.

Interventions

The intervention period will be one year for all participants, regardless of whether they respond to treatment or not, and regardless of randomized treatment group(s) (Figure 1). All

participants will receive the same initial phase of TLC treatment, and subsequent treatment options will vary starting at 4 or 8 weeks, depending on the outcome of the first randomization. The focus of all counseling will be to develop a personalized quit plan and use a combination of behavioral and pharmacological therapy to completely stop smoking, but the frequency of coaching, medications available, and timing of identifying treatment response as complete/incomplete will vary by treatment group.

Initial Phase of TLC Treatment—Seven scheduled counseling calls will take place during the first 8 weeks using a front-loaded, relapse sensitive schedule shown to be effective in other trials: outreach, quit-day, 1–3 days post-quit, and 1, 2, 4 and 8 weeks.⁷⁴ The outreach call will last 30–60 minutes and confirm the quit date and choice of NRT. Call content will include problem-solving, skills training, social support, NRT use, and relapse prevention. NRT combination therapy (patch+gum or patch+lozenge) will be available (free, delivered by mail); monotherapy will be used if there are problems with specific modes of delivery. NRT choices will be modeled on common clinical practice and based on the principles that participants 1) receive NRT unless they have a contraindication, and 2) will choose NRT type and dose based on intensity of withdrawal symptoms, experience, and participant preference.

For those not ready to immediately set a quit date within the next four weeks, counselors will call every two weeks (or earlier if a participant is willing) and utilize motivational interviewing strategies to enhance motivation and encourage selection of a quit date.

At 4 or 8 weeks, depending on outcome of the first randomization, *incomplete responders* may continue to receive TLC or TLC+MTM. *Complete responders* may continue TLC or receive TLC-Quarterly.

Other TLC Components—TLC is based on a chronic care model for tobacco treatment, including recycling treatment tools that worked in the past and relapse prevention. Chronic disease management includes continuity of care,²³ stepped care improvement (vs. extinction) of symptoms, and self-management. The TLC protocol¹³ includes contingencies for whether participants are abstinent, have relapsed (but to a reduced number of cigarettes), have resumed the original amount of smoking, or have not quit at all and, therefore, is an adaptive intervention itself. After the initial phase of TLC treatment, participants will receive a minimum of one call per month during the year. The TLC infrastructure, described below, is the backbone of the phase 2 year-long tobacco intervention.

For participants who are abstinent, counselors will use relapse prevention strategies including 1) identification of future high risk situations and skills to handle them; 2) methods to maintain abstinence such as lifestyle changes; 3) building self-efficacy, satisfaction with cessation, and social support; and 4) issues of weight and exercise.

For participants who relapse (this is anticipated to be a large proportion of our sample over the one-year treatment period), counselors will urge them to make a new quit attempt as soon as they are willing. If participants are not interested in making another quit attempt, counselors will explain that smoking reduction is an alternative, and provide positive

reinforcement for this choice as a step toward quitting. Counselors will stress a goal of at least 50% reduction from the baseline amount of cigarettes smoked (and less than 15 cigarettes per day), emphasizing that more reduction is better than less at any level of smoking. Strategies such as delaying smoking, eliminating cigarettes in specific situations, and scheduled reduction will be discussed. For participants choosing smoking reduction, counselors will aim to call every 2 weeks, but the schedule will be determined by participants' progress and receptivity to frequency of phone sessions.

For participants who choose to neither make a quit attempt nor reduce smoking, calls will be made monthly and they will be asked at each contact if they want to set a quit date or reduce. The counselor will also use motivational interviewing techniques with consideration for the participants' individual concerns about quitting^{24,25} and target cognitive factors to promote setting a quit date, such as self-efficacy and outcome expectations.

NRT can be used for repeat quit attempts or to maintain smoking reduction. Participants who continue to smoke can use the same NRT as when they tried to quit, use an alternative form of NRT, or increase the dose of NRT. Choices between these options will be based on past experience, intensity of nicotine withdrawal symptoms, and smoker preference. NRT recommendations for reducers include 1 piece of 4 mg gum to substitute for one cigarette, or a 21 mg. patch (for those who smoke more than 10 cigarettes per day).

TLC-Quarterly—In TLC-Quarterly, counselors will call participants every 3 months (rather than every month) for one year. During the call they will assess smoking behavior and, if the participant has relapsed and willing to set a quit date, switch back to the original TLC schedule. Calls will focus on setting a new quit date, maintaining reduction, or starting to reduce, with all steps oriented toward eventually becoming completely abstinent. For participants who are not smoking, call content will be the same as in TLC, the only difference being frequency of contact. Therefore, TLC-Quarterly will be more resource-efficient, but may miss opportunities to recycle back to more intensive treatment.

Intensive Pharmacological Treatment: Medication Therapy Management—For incomplete responders randomized to MTM, the available toolbox will expand to include in-person consultation with a pharmacist, the prescription drugs bupropion or varenicline, or combination medications (bupropion + NRT). The participant is not obliged to use these medications, but the pharmacist will assess readiness to quit and promote their use. Varenicline in combination with NRT will not be recommended because this combination is not currently standard of care.

The first pharmacist-participant encounter will occur in the clinical setting and will follow an algorithm that includes a systematic process of collecting patient and medication-related information such as past experiences with medications and contraindications. Pharmacists will follow a protocol to develop a patient-specific medication action plan. The pharmacists will prescribe medications under a collaborative practice agreement (University of Minnesota) or a defined clinical scope of practice (VA). The action plan includes a list of self-management actions necessary to achieve the patient's specific health goals that will be congruent with TLC counselor recommendations. The participant and the pharmacist will

record actions and track progress towards health goals (the participant on paper forms/self-help manual, the pharmacist in the EMR). The goal is for the first visit to occur within 2 weeks of randomization to MTM and typically last about one hour (however some participants may decline referral). There will be a range of 3–6 follow-up calls. Follow-up calls are typically 5–10 minutes and are conducted over a 12-week period, but can last until the end of the one year treatment period depending on participant interest and progress. The TLC counselor will continue to interact with the participant by telephone during MTM, but the pharmacist will have responsibility for medications while they work with the participant. Counselors can access the EMR to read progress notes related to MTM visits/calls.

Treatment Fidelity—Weekly study meetings will be conducted to maintain treatment fidelity and to review counseling calls and telephone care protocols. Counselor calls will be audiotaped and 10% will be randomly reviewed to assess quality and treatment fidelity and debriefing sessions with counselors will be conducted. MTM treatment fidelity will be monitored using standardized progress note templates in the EMR.

Complete Response vs. Incomplete Response Defined—All participants will be assessed for treatment response by the quit coaches at the end of initial treatment (4 or 8 weeks), which will be conducted separately from the data collection procedures. There will be no financial incentives for treatment response assessment or participation in intervention activities. Response will be determined by 7-day point prevalence: an *incomplete responder* is defined as any smoking, even just a puff, during 7 days preceding the date of assessment, whereas a *complete responder* is defined as no smoking during the 7 days preceding the date of assessment. If participants are not available for a call at the point of their assessment, they will automatically be considered an *incomplete responder*. Research outcomes (primary and secondary) are listed below, but complete response vs. incomplete response assessments by coaches at the end of initial treatment is not included.

Data Sources and Data Collection

Data sources will include telephone surveys, the EMR, counselor records, and saliva (to biochemically verify abstinence). Based on prior experience, we will provide financial incentives for completion of research data collection activities only: \$25 for baseline, \$20 for each of the 4, 8, 12 week and 6, 12, and 18 month telephone surveys, and \$50 for subjects who return a saliva sample at 18 months. Follow-up data collection time points will be anchored by the date of the initial outreach call. Short windows around each time point will maximize response rates. We will collect multiple phone numbers and contact information for a family member or friend to maximize retention. Research assistants involved in data collection will be blind to treatment assignment and will not have counseling responsibilities. The measures that we will collect at each time point are shown in Table 2.

Measures

Demographics—Measures from the National Health Interview Survey (NHIS) will capture the following demographic characteristics: age, gender, race, ethnicity, education, annual household income, employment status, and family history of lung cancer (Table 2).

Physical Health—Health status will be measured by the 6-item Physical Components Summary (PCS) subscale of the Short Form Health Survey (SF-12).²⁶ Medical co-morbidities will be evaluated using the Charlson Index.²⁷ Pain will be measured by the pain intensity, interference with enjoyment of life, and interference with general activity (PEG) scale, which includes one pain intensity and two pain interference questions.²⁸ Chronic obstructive pulmonary disease (COPD) symptoms will be assessed using the five-item Chronic Obstructive Pulmonary Disease Population Screener (COPD-PS).²⁹

Mental Health and Alcohol Use—Depression will be assessed by the Patient Health Questionnaire (PHQ-9),³⁰ and anxiety will be assessed using the Generalized Anxiety Disorder 7-item (GAD-7) scale.³¹ Alcohol use will be measured using the Alcohol Use Disorders Identification Test (AUDIT-C),³² which includes 3 measures that assess hazardous drinking patterns.

Regulatory Focus—Regulatory focus captures two ways people approach the pursuit of personal goals: prevention focus (which emphasizes minimizing losses by being responsible and careful) and promotion focus (which emphasizes maximizing gains by pursuing opportunities and accomplishments). It will be assessed by having participants indicate the extent to which they agree or disagree with 18 self-describing statements. Responses to 9 statements will be combined to assess prevention focus (e.g., I take risks that could cause trouble for me) and responses to the other 9 statements will be combined to assess promotion focus (e.g., I like to begin new things).^{33,34}

Smoking History—Current smoking habits and smoking history will be measured, including past quit attempts, prior use of smoking cessation aids. Peak cigarettes per day, and use of e-cigarettes and marijuana will be assessed using the Population Assessment of Tobacco and Health (PATH) Scale. Cigarette Dependence Scale (CDS-5) will be used to measure dependence on cigarettes.³⁵

Social Support for Cessation—Social support will be measured by a version of the Partner Interaction Questionnaire modified based on our prior work.³⁶ Question stems are tailored at baseline to assess anticipated social support (e.g., “How frequently *do you expect* your partner or the person closest to ask you to quit smoking”) and at follow-up to assess received social support (e.g., “How frequently *has* your partner or the person closest to you asked you to quit smoking?”).

Smoking Cessation-Related Beliefs & States—Interest in quitting will be assessed using the Readiness to Quit Ladder.³⁷ Smoking urges will be measured using the Questionnaire of Smoking Urges (QSU) brief.³⁸ Self-efficacy for smoking cessation will be measured by asking participants to indicate their level of confidence in their ability to refrain from smoking in 7 different situations (e.g., “How confident are you that you could keep from smoking when you’ve had a difficult day?”).¹¹ Participants will also be asked about their overall confidence in their ability to quit smoking or remain quit based on their current quit status.³⁹ Withdrawal will be measured by the Minnesota Nicotine Withdrawal scale; a total score will be obtained by asking participants to indicate how much they have noticed or felt 9 emotions or conditions in the past 7 days (e.g., “In the past 7 days, how much have you

noticed or felt angry, irritable, or frustrated?”).^{40–42} Satisfaction with cessation will be assessed by having participants indicate their level of satisfaction with their effort to quit smoking and with what they have experienced as a result of quitting or reducing their smoking, if applicable.³⁹ At later data collection visits (weeks 12, 26, 52, and 78) participants will also be asked to indicate how 5 different aspects of their life are at the present time compared to prior to starting the program (e.g., “Are your relationships with family and friends that do not smoke better or worse compared to before you started this program?”).⁴³

Treatment Utilization and Satisfaction—Number of calls, duration of calls, and content discussed during counseling calls and MTM encounters will be tracked. Type of encounter (in-person consultation or follow-up phone consultation) will be tracked for MTM encounters. Dosages, quantity, product type, single or combination NRT usage, and dates of shipments for all instances where NRT is provided to the participant will be recorded. At each data collection visit, participants will be asked if they are currently using any smoking cessation medications (e.g., NRT, varenicline, bupropion).

Smoking Outcomes—The primary research outcome will be 6-month prolonged abstinence assessed at 18 months after randomization.⁴⁴ Smoking at least once on 7 consecutive days or at least once on 2 consecutive weeks in the six-month period defines non-abstinence. We will ask participants who report 6 months’ abstinence at 18-month follow up to submit a saliva sample for biochemical verification. We will use methods that have demonstrated a yield greater than 80% rate of return at 12 months in the past.⁴⁵ We will also request saliva samples from a random sample of non-quitters to estimate biochemical validation nonresponse bias. Those who are abstinent but using NRT will be asked to come for an in-person expired carbon monoxide measurement for validation.⁴⁶ Secondary outcomes include 30- and 7-day point prevalent abstinence and will be defined by asking, “Have you smoked a cigarette, even a puff, in the past 30 days?” and if yes, “Have you smoked a cigarette, even a puff, in the past 7 days?”, respectively.^{44,47} A granular assessment of tobacco use, quit attempts, and reduction, will be obtained at baseline and weeks 4, 8, and 12 using the Timeline Followback Method for a 30-day period.⁴⁸ At weeks 26, 52, and 78, participants will be asked to describe their monthly cigarettes per day on average, retrospective to the month of the last follow-up phone call.

Risk Perception for Lung Cancer—Risk perception for lung cancer and other smoking-related diseases will be assessed by administering 15-items taken from the Risk Perception Questionnaire from which composite scores for 4 distinct domains will be obtained: risk perception for smoking-related diseases (e.g., “How likely do you think it is that you will develop lung cancer in your lifetime?”), perceived severity of health consequences of smoking related diseases (e.g., “How serious would the health consequences be if you developed a smoking-related disease?”), worry about smoking-related diseases (e.g., “How often do you worry about lung cancer?”), and perceived benefits of quitting (e.g., “How much would quitting smoking increase your chances of living longer?”).⁴⁹

Lung Cancer Screening Outcomes—An EMR review will be conducted to retrieve the American College of Radiology (ACR) Lung-Screening Reporting and Data System (RADS) (Version 1.0 Assessment Categories) score assigned to each screening LDCT. A comprehensive review and data collection of any diagnostic work-up components and subsequent diagnoses and outcomes will be conducted.⁵⁰ These data will include details about additional diagnostic work-ups, for example number and type of appointments, imaging studies, and procedures such as biopsies, bronchoscopy, or surgery.

Sample Size and Power Analysis

Sample size for the proposed trial was chosen to ensure sufficient statistical power for the primary aim, which corresponds to a main effects analysis comparing TLC to TLC+MTM among the incomplete responders on the primary outcome, 6-month prolonged abstinence measured at 18 months after baseline. The sample size calculation for this primary comparison is equivalent to a standard two-arm power calculation, which is inflated by the inverse of anticipated rate of incomplete responders to first-line treatment.

Power for this comparison with a sample size of 1,000 is shown in Table 3 under different, plausible assumptions about the proportion of complete and incomplete responders to initial treatment, and the proportion of long-term abstinence in TLC vs. TLC+MTM. We considered a difference between treatment groups of 10% to be of interest. The hypothesized proportion of incomplete responders (65–75%) averaged across the two assessment time points is based on the 21-day and 3-month abstinence rates in a previous trial of TLC which were 58% and 68%, respectively, although we anticipate that positive responses will be lower in this older population compared to the cohort enrolled earlier.¹³ The hypothesized proportion of incomplete responders achieving prolonged abstinence among those randomized to TLC (10–20%) is similarly based on data from the TLC trial (20% and 19% of participants who were smoking at 21 days and 3 months, respectively, had prolonged abstinence at 18 months). Table 3a indicates we have sufficient power to detect a 10% difference and even reasonable power across many scenarios to detect a 7.5% difference using a 0.05-level significance level.

A sample size of 1,000 permits sufficient power to test Secondary Aims 1 which compares long-term abstinence among complete responders for TLC compared to TLC-Quarterly (see Table 3b). For these power calculations, we assume the proportion of complete responders achieving prolonged abstinence is between 20–40% based on the TLC trial in which 40% of participants who were complete responders at 21 days achieved prolonged abstinence. Power to test hypotheses concerning the interaction of amount of smoking following the quit date and second phase treatment (among incomplete responders, Secondary Aim 3) and timing of assessment and second phase therapy (among complete responders, Secondary Aim 2) were generally between 60–90% assuming that there was no difference in prolonged abstinence between second-line treatments among those with few days of smoking following the quit date and those randomized to week 8 assessment and a 0.10 significance level. For these Secondary Aims, we were willing to tolerate a higher type I error rate (10%) in exchange for higher power.

Statistical Analyses

All analyses will be by intention-to-treat, and include all participants randomized to intervention, regardless of whether they are lost to follow-up. We will address missing response data using multiple imputation and additional sensitivity analyses.

Primary Aim and Secondary Aim 1 Analyses—To evaluate the primary aim (a test of TLC+MTM versus TLC among *incomplete responders*), we will compare the proportion of participants with prolonged abstinence between those randomized to TLC (cells 3 and 7) and TLC+MTM (cells 4 and 8) (see Figure 1) using a two-sided Wald-type test⁵⁵ of the difference in proportions. A similar analysis will be done to compare the proportion of participants with long-term abstinence among *complete responders* randomized to TLC (cells 2 and 6) and TLC-Quarterly (cells 1 and 5). These “main effects” comparisons are equivalent to the analysis in a standard trial among nonresponders comparing TLC to TLC +MTM and a trial among responders comparing TLC to TLC-Quarterly, respectively.

We will supplement these unadjusted analyses of the effect of various interventions on the primary outcome with *multiple logistic regression* which includes demographics, baseline information, and other factors collected prior to the second randomization specified in the measures section. These factors will be selected using results from previous studies and based on expert clinical opinion, including age, gender, marital status, income category, quit attempt in previous year, cigarettes per day at baseline, measures of cigarette dependence, withdrawal symptoms, and psychiatric co-morbidity (see Table 2).

Secondary Aims 2 and 3 Analyses—To test the effect of pre-specified moderators of treatment decisions after response to initial phase TLC is assessed, we will fit a logistic regression model within the relevant subpopulation (incomplete or complete responders), which includes a main effect for the randomized second phase treatment group, the moderator, and moderator by treatment interactions. Specifically, we will test whether the effect of second phase treatment is moderated by either the time (4 or 8 weeks) of assessment for response to initial treatment or the and number of days of smoking in the 7 days before second phase randomization.

Secondary Aim 4 Analysis—We will use the Lung-RADS score as an ordinal measure of lung cancer screening findings. A Cochran-Armitage trend test⁵⁵ will evaluate if the proportion of smokers achieving long-term abstinence differs by the degree of screening abnormalities. Similarly, the Jonckheere-Terpstra trend test,⁵⁶ a generalization of the Kruskal-Wallis test for ordinal predictors, will assess if progress toward quitting (i.e., reduction in cigarette smoking) differs by Lung-RADS score.

Exploratory Analyses—T-tests, supplemented by covariate-adjusted regression models, will be used to compare the treatment decisions after response to initial phase TLC is assessed as described above but with *other secondary, continuous endpoints* including smoking reduction from baseline, quit attempts, and treatment satisfaction (see Table 1). Because many variables will be assessed repeatedly (e.g. interest in quitting, self-efficacy, withdrawal, smoking reduction), we will also fit longitudinal models of these outcomes and

potential mediators using generalized estimating equations to account for the correlation between repeated measures.

The study design and assessment schedule will also provide an opportunity to assess the degree to which intervention impacts changes in cessation-related beliefs and feelings (e.g., self-efficacy, satisfaction, interest in quitting, withdrawal, urges; see Table 2) which are hypothesized mediators (behavioral mechanisms) for the effect of cessation treatment strategies. We will also examine whether the association between cessation-related beliefs and smoking outcomes vary across treatment strategies and whether baseline characteristics as well as experiences during treatment moderate these associations.^{57–59}

Importantly, the data collected as part of this trial will also permit us to *estimate the proportion of participants achieving prolonged abstinence within each of the 8 embedded interventions* and allow us to explore how to tailor the interventions based on an individual's characteristics through Q- and A-learning.^{60–73}

SUMMARY

PLUTO will conduct a sequential, multiple assignment, randomized trial to inform the choice and delivery of smoking cessation treatments for smokers in the setting of lung cancer screening, including for smokers who respond both *incompletely* (any smoking after quit date) and *completely* to first-line treatment (4 or 8 weeks of counseling with nicotine replacement therapy). Currently, there is little evidence to guide the development of adaptive interventions in tobacco cessation. SMART designs, such as the one we propose, are an ideal experimental design to assess different adaptive intervention strategies.

Adaptive interventions for smoking cessation in the context of lung cancer screening have high potential for dissemination and impact. The USPSTF recommends annual low-dose CT screening for patients at high risk Recommendation (Grade B)⁴; private insurance coverage is mandated for USPSTF Grade A or B recommendations. The Affordable Care Act (ACA) mandates coverage of preventative services including smoking cessation treatment. The ACA requires coverage of at least 2 quit attempts/year, 4 counseling sessions of at least 10 minutes, and all Food and Drug Administration (FDA) approved tobacco cessation meds for a 90 day treatment regimen when prescribed by a health care provider (7 medications: 5 forms of NRT, bupropion, and varenicline).⁷⁴ Effective smoking cessation treatment, delivered in the context of lung cancer screening programs, may augment the mortality benefit of imaging studies.

The novel tobacco treatment system we plan – identification of smokers by using the EMR and proactive invitation to treatment coupled with lung cancer screening – is an opportunity to engage a new cohort of smokers with mechanisms in place to implement delivery of care. Thus, the PLUTO trial takes advantage of a new clinical practice development: recommendation for annual lung cancer screening based on age and smoking history. Strengths are an innovative study design and sequential random assignment of treatment conditions in addition to the main comparative effectiveness outcome that allows more rigorous measurement of effects than a standard randomized controlled trial would afford.

The information about timing of assessment, optimal intervention components, and intensity of treatment are ripe for dissemination.

Acknowledgments

This study was funded by the National Cancer Institute (R01CA196873 and 2T32CA163184), National Institutes of Health. This material is the result of work supported with resources and the use of facilities at the Minneapolis VA HSR&D Center for Chronic Disease Outcomes Research. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs, the National Institutes of Health, or the United States government.

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Figure 1.
Study design overview

Figure 2.
Conceptual framework for adaptive interventions in smoking cessation

ACA	Affordable Care Act
ACR	American College of Radiology
AI	Adaptive Intervention
AUDIT-C	Alcohol Use Disorders Identification Test
BRFSS	Behavioral Risk Factor Surveillance System
CDS-5	Cigarette Dependence Scale
COPD	Chronic Obstructive Pulmonary Disease
COPD-PS	Chronic Obstructive Pulmonary Disease Population Screener
EMR	Electronic Medical Record
FDA	Food and Drug Administration
GAD-7	Generalized Anxiety Disorder 7-Item Scale
LDCT	Low-Dose Computed Tomography
MTM	Medication Therapy Management
MVAHCS	Minneapolis Veterans Affairs Health Care System
NHIS	National Health Interview Survey
NLST	National Lung Screening Trial
PATH	Population Assessment of Tobacco and Health Scale
PCS	Physical Components Summary
PEG	Scale Assessing Pain Intensity and Interference
PHQ-9	Patient Health Questionnaire
PLUTO	Program for Lung Cancer Screening and Tobacco Cessation
QSU	Questionnaire of Smoking Urges
RADS	Lung-Screening Reporting and Data System
SF-12	Short Form Health Survey
SMART	Sequential Multiple Assignment Randomized Trial
TLC	Tobacco Longitudinal Care
USPSTF	US Preventive Services Task Force

Figure 3.
Acronym glossary

Table 1

Embedded intervention strategies resulting from this experimental design.

	Initial Phase of Treatment	Time of Assessment of 7 Day Point Prevalence	Phase 2 Treatment for Complete Responders	Phase 2 Treatment for Incomplete Responders	Cells in Figure 1 Compliant with this AI
1	Initial Phase of TLC	4 weeks	Continue with TLC	Continue with TLC	1 & 3
2	Initial Phase of TLC	4 weeks	Continue with TLC	TLC+MTM	1 & 4
3	Initial Phase of TLC	4 weeks	TLC-Quarterly	Continue with TLC	2 & 3
4	Initial Phase of TLC	4 weeks	TLC-Quarterly	TLC+MTM	2 & 4
5	Initial Phase of TLC	8 weeks	Continue with TLC	Continue with TLC	5 & 7
6	Initial Phase of TLC	8 weeks	Continue with TLC	TLC+MTM	5 & 8
7	Initial Phase of TLC	8 weeks	TLC-Quarterly	Continue with TLC	6 & 7
8	Initial Phase of TLC	8 weeks	TLC-Quarterly	TLC+MTM	6 & 8

Table 2

Measures and data collection schedule.

	T0	4W	8W	12W	6M	12M	18M	Instrument
Demographics								
Age, gender, race, education, income, lung cancer history <i>a, b</i>	x							NHIS ⁵¹
General health								
Physical health <i>a, b</i>	x					x	x	SF-12 ²⁶
Medical co-morbidities <i>a, b</i>	x							Charlson Index ²⁷
Pain <i>a, b</i>	x							PEG
COPD <i>a, b</i>	x			x		x	x	COPD-PS
Mental health and alcohol use								
Depression <i>a, b</i>	x							PHQ-9 ³⁰
Anxiety <i>a, b</i>	x							GAD-7 ³¹
Alcohol use <i>a, b</i>	x							AUDIT-C ³²
Smoking history								
Tobacco use: Cigarettes per day <i>a, b, d, e</i>	x	x	x	x	x	x	x	PATH ⁵²
Use of other tobacco products including e-cigs <i>a, b, d</i>	x	x	x	x	x	x	x	
Cigarette dependence <i>a, b</i>	x							CDS-5 ³⁵
Social support								
Social support for cessation <i>b</i>	x	x	x	x	x	x	x	Partner Interaction Q ³⁶
Personality								
Regulatory focus <i>b</i>	x							Regulatory Focus Scale ^{33,34}
Smoking cessation-related beliefs and states								
Interest in quitting <i>a, b, d</i>	x	x	x	x	x	x	x	Readiness to Quit Ladder ³⁷
Nicotine withdrawal <i>a, b, d</i>	x	x	x	x	x	x		MN Nic Withdrawal Scale ⁴⁰⁻⁴²
Smoking urges <i>a, b, d</i>	x	x	x	x	x	x	x	QSU-B ³⁸
Self-efficacy for smoking cessation <i>a, b, d</i>	x	x	x	x	x	x	x	Baldwin ³⁹

	T0	4W	8W	12W	6M	12M	18M	Instrument
Satisfaction with cessation <i>a, b, d</i>		x	x	x	x	x	x	Baldwin ³⁹
Smoking outcomes								
6M prolonged abstinence (primary outcome at 18 months) <i>d</i>					x	x	x	BRFSS ⁵³ , NHIS, ⁵¹ Hughes ^{44,47}
7-day, 30-day point prevalent abstinence <i>d</i>		x	x	x	x	x	x	
Relapse, slip <i>b, d</i>		x	x	x	x	x	x	
Cotinine verification smoking abstinence							x	Murphy et al ⁵⁴
Number of quit attempts <i>d, e</i>		x	x	x	x	x	x	
Number of days in last week smoking <i>c, d</i>	x	x	x	x	x	x	x	
Treatment utilization and satisfaction outcomes								
Treatment usage <i>d</i>		x	x	x	x	x	x	
Satisfaction with study treatment <i>e</i>							x	
Lung cancer screening outcomes								
CT scan results <i>f</i>	x						x	Lung-RADS Version 1.0 Assessment Categories ⁵⁰
Diagnostic work-up components <i>f</i>							x	
Screening outcomes/diagnoses <i>f</i>							x	
Perceptions of cancer risk								
Self-assessment of cancer risk <i>b, d, e</i>	x	x				x	x	Risk Perception Questionnaire ⁴⁹

^aVariable (at baseline) which will be adjusted for in regression models to assess the effect of second phase treatments

^bVariable (at baseline or at time of second phase randomization) which we may, post-hoc, assess if it moderates treatment.

^cPre-specified moderator (at time of second phase randomization) of second phase treatment

^dMediator of treatment effect (measured before 18 months but after randomization)

^eSecondary outcome assessed at 18 months

^fPre-specified baseline variable which is hypothesized to be associated with long-term outcomes

Table 3

Power to test a difference in the proportion of subjects achieving prolonged abstinence between second phase treatments among incomplete responders (a) and among complete responders (b). Calculations assume total N=1,000 and the use of a two-sided test with a 0.05 significance level for the primary aim and 0.10 significance level for the secondary aim.

(a) TLC vs. TLC+MTM among incomplete responders (Primary Aim)									
Proportion incomplete responders=75%				Proportion incomplete responders=65%					
		TLC responders				TLC responders			
TLC+MTM responders		10%	15%	20%	TLC+MTM responders	10%	15%	20%	
7.5% diff		85%	75%	68%	7.5% diff	79%	68%	61%	
10% diff		97%	93%	89%	10% diff	95%	89%	84%	

(b). TLC vs. TLC-Quarterly among complete responders				
Proportion incomplete responders=65%				
		TLC responders		
TLC-Q responders		20%	30%	40%
7.5% diff		73%	62%	57%
10% diff		91%	81%	75%