Assessing the Integration of Tobacco Cessation Treatment

Into Lung Cancer Screening (LCS)

NCT03611881

ID: 2018P000539/PHS

Study Protocol and Statistical Analysis

Version date: 1/30/2024

Partners Human Research Committee

Detailed Protocol

TITLE: Integrating Tobacco Treatment into Lung Screening at PHS.

PI: Elyse R. Park, PhD, MPH

GRANT NUMBER: 1R01CA218123 - 01A1

VERSION DATE: 1/30/2024

I. BACKGROUND AND SIGNIFICANCE (including progress report and preliminary studies).

Public health burden of lung cancer. Lung cancer is the leading cause of cancer death in the U.S., accounting for 27% of cancer deaths.[1, 2] The prognosis for patients with lung cancer is generally poor, largely because only 15% are diagnosed at an early stage.[3,4] Racial and ethnic minorities and low socioeconomic status (SES) individuals have higher rates of lung cancer incidence, late-stage diagnosis, and higher mortality.[1]

Smoking and lung cancer. Cigarette smoking is responsible for 87% of lung cancer deaths[3,5,6] and is the leading cause of preventable death in the U.S.[7,8] Tobacco use is higher in individuals with less education and lower incomes, contributing to disparities in overall mortality in low SES individuals.[9-13] Lung cancer screening (LCS) has the potential to improve the earlier detection of malignancies. LCS and tobacco treatment must be made equally accessible for all patients to benefit, thus narrowing, not contributing to, the disparities gap.

Screening reduces lung cancer mortality. In 2011 the National Lung Screening Trial (NLST) demonstrated a 20% reduction in lung cancer mortality among current and former smokers (aged 55-74, 30+ pack-years of smoking) who were randomly assigned to 3 annual lung cancer screenings with low-dose computed tomography (LDCT) vs. those assigned to 3 annual chest X-rays.[14] The U.S. Preventive Services Task Force (USPSTF) recommends annual LDCT screening for high-risk individuals.[15] By NLST criteria, an estimated 8.6 million Americans are eligible for LCS;[16] LCS could save 18,000 lives annually.[16]

LCS provides a critical opportunity to promote cessation. Tobacco cessation services are strongly recommended as an adjunct to LCS.[17] Payers, including Medicare, cover LDCT for high-risk individuals. Medicare requires a shared decision making visit and documentation of cessation counseling. Radiology imaging facilities must make cessation assistance available and submit LDCT data to a Medicare-approved registry. Smoking cessation during LCS could help reduce disparities in access to treatment; not promoting cessation might send a message that screening obviates the need to quit.[18] Even if screening identifies a malignancy, quitting smoking could improve survival[6, 19, 20] and decrease treatment complications.[21-30]

Evidence-based tobacco cessation treatments exist. Clinical guidelines[5, 31] state that combining counseling and pharmacotherapy (e.g., nicotine replacement therapy (NRT)) is more effective than either alone.[5, 31] The challenge is delivering treatments to smokers; 70% want to

quit,[32] but <30% use available treatments.[5,32-34] State-based quitlines are the most accessible cessation resource. Quitlines offer free proactive behavioral support to smokers; 76% also send free NRT to eligible callers.[35] However, quitlines have limitations for smokers undergoing LCS because they 1) offer few resources for smokers not ready to quit, 2) provide only short-term counseling (e.g., ≤ 5 sessions and only short-term (≤4 weeks) NRT, and 3) do not tailor counseling to the salient issues of smokers undergoing LCS, as identified in our preliminary work.

Smokers undergoing LCS need tobacco treatment personalized to their quit readiness and risk perceptions. Many smokers undergoing LCS are not ready to make a quit attempt. The mean readiness to quit in NLST was 5.1 (1-10),[36] only half of smokers tried to quit in the year after their initial screen,[37] and only 20% were ready to quit within 30 days.[38] In Project Reach, the mean readiness to quit was similar (5.5). Quit rates in NLST[39,40] and other LCS studies[40-43] were not significantly higher than in the general population, but the effect on risk perception was complex.[39,44,45] Data are mixed as to whether negative screens provide false reassurance and reduce motivation to quit.[18,46] Smokers in Dr. Park's NLST sub-study perceived a benefit from quitting but were not confident in their ability to quit,[47] avoided thinking about risks, and used unhelpful avoidance strategies.[45] A smoking intervention in the context of LCS should address risk perceptions by (a) assuring that patients understand results and recommended follow-up, (b) helping correct erroneous beliefs about test results and lung cancer risk, and (c) helping patients process test result information in a motivating way. *We propose to test tobacco treatment which personalizes* counseling *based on motivation to quit and perceived risk.*

Smokers undergoing LCS are heavy smokers who likely need more intensive support. Initiating smoking early in life, heavy smoking, and having strong nicotine dependence are factors associated with less success in quitting, and these are common characteristics of smokers eligible for LCS. Over 40% of smokers undergoing LCS are heavy smokers (>20/day).[36] In our Project Reach, patients were older heavy smokers (mean age = 62, 41% smoking >1ppd) who had been smoking for an average of 46 years. Older smokers need more intensive interventions, but it is not clear what types of interventions would be most appealing and motivating for them.[48] Long-term heavy smokers also have social barriers to quitting (e.g., food insecurity) that may not be otherwise addressed.[49] Our work with low income older smokers suggests that addressing social barriers is key; use of systematic referral, a community resource and referral database, was significantly associated with quitting.[50] Reflecting the chronic nature of tobacco dependence, a chronic disease management strategy that sustains treatment over time is more effective than standard treatment[51] and may be appropriate for smokers having LCS. *We will test 3 intervention components*—counseling *length, medication duration, and systematic screening and referral to community-based services to address social barriers. All treatment will be 1) proactively offered, 2) delivered with MI, 3) personalized to quit motivation and risk perceptions, and 4) coordinated by a central care service.*

Challenges to offering cessation services at LCS sites. Integrating cessation services into LCS screening sites (typically high volume practices that lack cessation resources) is a challenge. Most LCS sites report screening patients' smoking status (99%) and advising to quit (91%), but fewer provide cessation counseling or referral (60%); only one-third recommend medications.[52] Following LCS, primary care clinicians do not often provide any cessation support.[53] The deployment of ***health information technology (IT) platforms*** can promote outreach and access at different points in the LCS process, using technologies like patient portals, informational videos, and video-conferencing. In our Project Reach evaluation, patients

expressed the need for time and repeated offers to engage in a cessation program. Given these barriers, it is imperative to offer cessation treatment at multiple points of LCS delivery. *We propose that the LCS process provide 3 systems-based patient-engagement opportunities that 1) integrate into the screening process, 2) include primary care and radiology, and 3) use a population health management perspective.*

II. SPECIFIC AIMS (Research Objectives)

Aim 1: To develop a centralized smoking cessation treatment (care coordination and intervention components) at 10 MGB LDCT-LCS screening sites.

Aim 2: To test the effectiveness of the intervention for smoking cessation in a randomized controlled trial using a factorial design to assess 3 intervention components:

(a) Duration of counseling contact (repeated proactive sessions delivered by a trained tobacco treatment specialist using phone or videoconferencing telehealth platform);
(b) Duration of NRT, and
(c) Referral to community-based resources to address social barriers.

Aim 3: To evaluate the reach, adoption, implementation, and maintenance of the intervention. The components of the LCS-tailored intervention are informed by our preliminary studies and conceptual frameworks.

III. SUBJECT SELECTION

Patients: Inclusion and exclusion criteria. Patients who are scheduled to undergo LDCT-LCS at a participating PHS LCS site, speak English or Spanish, and are current smokers are eligible. Current smokers will be defined as those who have smoked a cigarette, even a puff, in the last 30 days. Smokers will fulfill the Medicare coverage requirement (age 50-80 years, 20+ pack/years). Smokers do not have to be ready to quit smoking. We will exclude patients who are: (1) undergoing lung CT as part of a diagnostic or abnormal follow-up evaluation, (2) unable to give informed consent due to psychiatric or cognitive impairment as determined in consultation with study PI or treating clinician, (3) who do not have access to a telephone or cannot communicate by telephone, or (4) do not reside within the United States of America.

IV. SUBJECT ENROLLMENT

Recruitment. The study RA will recruit patients on the telephone at 3 points in the process of LDCT-LCS delivery: (1) after the test has been scheduled, (2) after the patient has completed their LCS, and (3) after the result has been communicated to the patient. At each point, a short video recruitment message (see Video Recruitment Message Overview document), explaining the purpose of the study will be disseminated to patients.

Recruitment Point 1: LDCT Scheduled. All orders for LDCT-LCS are made through the EHR, which requires clinicians to identify smoking status (current vs. former, packs per day, and years smoked) to complete the order. The study team will obtain a regular download from the EHR of newly scheduled LDCTs, along with the patient's smoking status. Study staff will proactively contact all smokers after the LDCT is scheduled. First, patients will be mailed an opt-out letter within a study packet, which includes a study pamphlet and a detailed information sheet about

the study. The opt-out letter will include a link to a short video recruitment message, embedded in a REDCap survey and hosted on the Partners approved video platform. Patients will be contacted by a research assistant (RA) within approximately two business days after the study recruitment materials have been disseminated to reinforce attendance at the LDCT-LCS appointment and describe the study. Interested patients will be screened for eligibility, read a standard script to elicit verbal informed consent, and the RA will administer a baseline survey if verbal consent is obtained. The survey may be completed verbally, digitally through a REDCap link, or if patients require a hard copy of the survey, they may be sent it in the mail. Patients who wish for more time to consider about participating the study will be asked for permission to re-contact them at the time of the LDCT test. If they decline, the study team will not approach them at later recruitment points.

Recruitment Point 2 Pre-COVID: LDCT Exam. In March 2020 due to the COVID pandemic we stopped all ipad use in the clinics. RP2 procedures from April 2019-March 2020 are described below: All patients who arrive for LDCT screening will be given an iPad from front desk staff to facilitate study enrollment. The iPad will have a live data feed from the study's database, allowing it to determine if the patient is already in the study or has refused further contact. If the patient had already enrolled in the study at Point 1, the iPad will play a short video message reinforcing the importance of continuing with the program and study. If patients have consented to the study but have not completed the baseline survey, the iPad will play a short video message reminding them to complete the survey and offer them the opportunity to have the survey resent to them. If the patient had not enrolled at Point 1 and had permitted further contact, the iPad will present questions in the form of a REDCap survey to identify patient eligibility for the study. Eligible patients will then receive a short video recruiting them to the study, and will inform them that they will be contacted soon after the screening test by an RA who will explain the study and offer participation. After leaving the LDCT facility, eligible patients will be contacted by the RA who will use the same workflow as described at Point 1 (i.e., screen, consent, administer baseline survey). If the patient is ineligible for the study, the iPad will play a short video encouraging smoking cessation. If patients arriving for the LDCT test had refused further contact at Point 1, they will receive brief advice to quit, representing usual care, via the iPad but no contact about the study.

We will develop a live data feed on a secure Partners server to be used for patient tracking, real time randomization, and all data entry. Password protected iPads will communicate over the secure wireless network with the SQL database.

We will be providing $5 coffee cards to staff at the study sites for their assistance with the study.

Recruitment Point 2 Post COVID: LDCT Exam After leaving the LDCT facility, eligible patients will be contacted by the RA who will use the same workflow as described at Point 1 (i.e., screen, consent, administer baseline survey

Recruitment Point 3. LDCT Result. After the patient has received the result, patients who have not previously enrolled or refused further contacts will be sent a short video recruitment message tailored to the result via a secure, encrypted email including a secure REDCap survey link, or a letter with a URL to a secure REDCap survey. It will invite them to join the study, and

give brief cessation advice from Dr. Rigotti or Haas. Patients will then be contacted by the RA who will use the same workflow as described for Point 1 (i.e., screen, consent, administer baseline survey). Patients who enrolled at an earlier point will receive a short video embedded in a secure REDCap survey tailored to their test result to address why quitting and study participation remain important.

Hispanic/Latino patients that do not enroll will have MRNs shared with study investigators to be approach for protocol # 2019P002549.

Patients may also be contacted for research purposes from the team in the future.

Recruitment Summary: Our recruitment strategy is designed to require little additional effort at busy radiology sites, but make systematic and repeated recruitment offers to enable us to achieve maximal reach.[5,50,54,55,56,59] To provide data for our implementation evaluation (Aim 3), we will record the numbers and characteristics of patients who are identified, eligible, and enrolled at each time point. We will document reasons for ineligibility and refusal and document EHR-recorded sociodemographic and biological characteristics, medical history, and cancer history of refusers.

Randomization.Patients will be randomized at the time of enrollment (i.e., completed consent and baseline survey), stratified into 9 randomization strata (3 groups of LCS study sites and 3 recruitment points), to a LCS-tailored intervention treatment arm. The intervention arms will consist of 8 groups of equal proportions, based on a 3-factor fully crossed factorial design to efficiently test components that vary on counseling duration, NRT duration, and provision of systematic referral**.**

V. STUDY PROCEDURES

Data management. A centralized SQL database will be used for patient identification and recruitment, randomization, patient tracking, and data input. It will interface with all data collection efforts (RAs will enter in REDCap).

Intervention arm components

We will develop 8 versions of the multi-component intervention that differ in 3 critical treatment factors: duration of counseling contact (4 vs. 8 sessions), duration of free NRT (2 vs. 8 weeks), and offer of systemic referral to community based resources.[50]

(1) Counseling**.** Previous interventions conducted by the PIs are the basis for the personalized, algorithm-driven protocol for the short intervention; the longer intervention will be modified from Project CLIQ[50] and Dr. Park's tobacco treatment trial with cancer patients.[61] Patients randomized to the short and long duration counseling conditions will be offered 4 sessions. Those assigned to the long duration counseling will also be offered 4 additional sessions.

Tobacco Counseling Content. As in Project CLIQ and Reach, counseling sessions will be protocolized according to the 5As format for smoking cessation.[5] Counseling will incorporate patients' risk perceptions before and after the LCS results. The risk counseling content[63] emphasizes understanding the personal implications of risk beliefs and aims to reduce cognitive

biases (protective benefits of a negative screen). The counseling protocol elicits 1) contrasts between personal and comparative risk, 2) reasons underlying perceived risk, and 3) beliefs about the connections between risk, smoking, and lung cancer. Counselors will: 1) assess preferences for health information/numeracy; 2) explore the personal meaning of risk; 3) personalize negative and positive risk frames (need to quit, benefits of doing so); 4) emphasize personal magnitude of risk reduction; and 5) acknowledge ambivalence. The TTS will use Motivational Interviewing (MI) an empathic and supportive treatment style,[64] that can deliver personalized risk counseling, enhance motivation for behavior change, and is effective for patients not ready to quit[65] and medically and socio-economically vulnerable smokers MI is well suited for LCS patients because: 1) MI focuses on building self-confidence and resolving ambivalence; 2) MI tools (i.e., open-ended questions, affirmations, reflections, and summarizing statements) are effective when addressing sensitive topics; and 3) MI's strategy is effective when communicating about risk.[64] Undergoing LCS might increase or decrease smokers' risk perceptions, motivation to quit, and cessation efforts.[18,41, 44, 67, 68]

Counseling delivery. Patients will be given a choice of phone-based or videoconferencing-based virtual visits; we will track patient choices. Telephone-based counseling is effective with other medical populations[69, 70] and has been successfully used by Drs. Park, Haas and Rigotti. Technology use among seniors has rapidly increased over the past 5 years; smartphone use has quadrupled. [70] A videoconferencing option is innovative and feasible; over 67% of adults 65 years and older use the internet, almost half own a smartphone, and more than half have high-speed broadband at home.[72] A patient account will be created and RAs will assist patients in videoconferencing setup.

(2) Nicotine Replacement Therapy (NRT) duration. The tobacco cessation counselor will promote medication use, describe all FDA-approved options, offer free NRT patches to smokers with no contraindication, and assist smokers who choose other medications to obtain prescriptions from their clinicians in the Partners System. Although use of medication will be promoted, it is not required for study participation. NRT dose will be determined by daily cigarette use: 21 mg/d patch for ≥10 cig/day,14 mg/d patch <10 cig/day. Patients in the short duration arm will receive one 2-week kit. Patients in the long duration arm will receive one 4-week kit and are eligible for one additional 4-week refill, using a tapering dose schedule, for a total NRT duration of 8 weeks. The tobacco cessation counselor, in consultation with Drs. Rigotti or Haas, will adjust the NRT dose to control withdrawal symptoms and minimize adverse effects. NRT will be mailed at no cost to patients. NRT has been safely distributed through quitlines in this way, and this approach was used safely in our recent work.[50] The tobacco cessation counselor will use a protocol to screen for NRT eligibility and discuss any eligibility questions or adverse effects with Drs. Haas or Rigotti. NRT kits will include instruction and patient information sheets in English or Spanish written for a 6th grade reading level. NRT can be initiated at any point during the 8 weeks of the trial and can start before a quit date, a newer treatment strategy that is associated with improved outcomes.[62] Use of NRT will be supported during each tobacco cessation counseling call.

(3) Systematic screening for social barriers to care. If randomly assigned to receive this resource, the tobacco cessation counselor will encourage patients to address social barriers to cessation by receiving a personalized referral from a web-based tool named Aunt Bertha (https://www.auntbertha.com/) to systematically screen and provide local free or low cost referrals for social barriers to care. This approach was used successfully in CLIQ and was found to be significantly associated with cessation.[50] A branching logic questionnaire to evaluate social needs, suggests services near their residence or other desired location that may help them, and

then selects the referrals that meet their needs. Once services are selected, the tobacco cessation counselor can mail/encrypted email/text the selected referrals to patients.

Research staff will use a Partners approved text messaging service to contact patients whom have consented to be sent study text messages.

Treatment fidelity

Treatment fidelity will be monitored using recommendations by the Treatment Fidelity Workgroup of the NIH Behavior Change Consortium (BCC). The BCC cites monitoring 5 areas to promote reliability of behavioral interventions: Design (review tobacco counseling documentation weekly), Training (ongoing: a randomly selected 15% of session recordings will be reviewed by Dr. Park for MI and protocol adherence), Treatment Delivery (recordings and documentation of session content), Receipt of Treatment (session review of topics covered) and Enactment of Treatment skills/knowledge (patients set treatment goals and progress).

Assessments

Baseline**:** At enrollment, data will be collected from the patient either on the phone by the RA or on an iPad via REDCap, as described above. Additional baseline information will be obtained from the EHR (see assessment plan below for specific data collected). Patients will be offered a $20 incentive to complete the survey.

Outcome assessments*:* Patient-reported outcomes will be assessed at 3 and 6 months post-enrollment by telephone, email or mail and recorded in REDCap. Individuals will be offered a $20 incentive to complete each outcome assessment. To minimize patient burden, the survey will be piloted and kept to approximately 10-15 minutes. Other outcome measures will be obtained from the EHR. Prior to a patient's 6 month survey, we will be sending out promotional items such as notepads, reusable bags, stress balls, and hand sanitizer.

Additional questions will be added to the 6-month survey to assess participants' knowledge about electronic cigarettes, the addictiveness of electronic cigarettes in comparison to combustible cigarettes and other nicotine replacement products, their perception of the risk and benefits of electronic cigarettes, their interest in trying electronic cigarettes and their financial and employment status. Participants will also be asked about their willingness to be contacted for future research about switching from cigarettes to electronic cigarettes. These questions will be administered to those participants who haven't completed their 6-month survey yet . Participants will be offered a $30 incentive in addition to the current $20 incentive to complete the survey with the additional questions. The additional $30 in compensation will be given to those who qualify (i.e. those who are still smoking) and complete the additional questions.

Participants will be compensated an additional $30 for completing the additional questions due to the increased effort and time it will take to answer the questions. The survey will take nearly double the time, so we found it fair to increase the remuneration to reflect the additional time and effort. A future amendment will be submitted to reach back out to those who have already completed their 6-month

survey to also give them the opportunity to complete a survey with the additional questions and earn an additional $30.

All participants in the Screen ASSIST smoking cessation trial who reported having smoked a cigarette in the past 7 days at the trial's final 6-month follow-up assessment will be sent a letter informing them of the opportunity to participate in an additional survey. The opt-out letter will inform them that a study team member will be calling them with an invitation to complete an additional survey about e-cigarettes. The opt-out letter will also provide participants with the opportunity to call or email a study team member if they are not interested in participating. A study team member will reach out to participants a week after the opt-out letter has been sent to ask about their willingness to complete the survey.

Participants who already completed the additional questions during their 6-month survey will not be sent the opt-out letter

The additional survey will assess participants' knowledge about electronic cigarettes, perception of electronic cigarette benefits and risks, willingness to use electronic cigarettes as a substitute for combustible cigarettes and will ask about their willingness to be contacted for future research about switching from cigarettes to electronic cigarettes.

Participants who agree to complete the survey will be provided with the options to complete the survey over the phone with a study team member or to have the survey emailed or texted out to them after a study team member has received their consent. Participants who are eligible for and complete the additional survey will receive a $30 gift card.

We will aim to have 400 participants complete this survey.

Verification of smoking cessation: Due to COVID-19 and after discussion with the NCI Project officer, we will no longer be sending biochemical verification to patients. Patients who self-report 7-day abstinence at 3 and 6 months follow up will be considered non-smokers. Those who are enrolled prior to his change will continue to be sent biochemical verification and offered a $20 incentive for each sample.

Biochemical verification of smoking cessation: Patients who self-report 7-day abstinence at 3 and 6 months follow-up will be asked to provide a saliva sample to assay for cotinine. Individuals will be offered a $20 incentive for each sample.

Biochemical verification process**: (This process ceased in March of 2020 due to the COVID pandemic)**The study RA will send to patients who report 7-day cigarette abstinence at 3 and 6 months follow-up a saliva cotinine collection kit and pre-paid packaging for return to the J2 laboratory (J2 Laboratories is a premier forensic drug and alcohol testing and clinical diagnostic laboratory located in Tuscon, AZ that has successfully partnered with the study team for previous saliva cotinine testing). The saliva sample will be tested for cotinine, which is a chemical the body makes from nicotine. The test will determine the study participant's exposure to cigarette smoke and nothing else. The cotinine and expired CO samples collected for the purposes of this study will not be stored for future uses not described in the protocol. Saliva samples will be destroyed after they are assayed for cotinine. After each results transfer, participants' data will be purged from the test company's files. The saliva cotinine collection kit will be marked only with the patient's unique study identification code, and will include: 1) instructions for successfully completing a sample; 2) an information sheet detailing the time and

date of the collection, 3) a brief survey reporting recent patient smoking history. The pre-paid packaging will include a FedEx package and pre-paid airbill for the subject to return their saliva sample directly to the lab. The lab will provide MGH directly with pre-paid airbills to be provided to participants. The return address on the airbill includes only the location of the research offices at MGH; no identifiable patient data will be provided to the lab. The J2 lab will send MGH a notice immediately upon receipt of a sample, and again upon testing with the results of the sample. Notices from the lab will be shared with MGH via email or a secure fax machine, and all attachments (invoices, testing results) include no identifiable information and are password protected.

Patients who return a sample that is designated insufficient for testing by the lab will be offered the opportunity to complete additional samples. Patients who report use of NRT or e-cigarettes within the last week will be offered the opportunity to instead complete an expired air CO sample. The study RA will be trained in safe and proper use of the CO monitor and test results interpretation. As CO samples must be completed in-person, and with the aim of decreasing patient burden, samples will be completed at an existing clinic visit in accordance with patient preferences. We have successfully used these methods in previous work, with excellent return results (88%).[58,60, 61]

.

Exit interviews: A sample of 72 patients (approximately 10% of anticipated 6-month survey completers) will be asked to participate in an in-depth individual interview, with one of the study staff, after completing the final survey. Sampling selection will be stratified by intervention group (approximately 9 per group). A semi-structured interview guide will be developed for telephone interviews. All patients will be asked about 1) smoking and quitting behaviors, 2) the enrollment process (e.g., timing, video recruitment messages, iPad use), 3) coordination with the LCS process, 4) understanding of their test results, and 5) adherence to LCS recommendation. Patients will be also asked for feedback on the intervention components (counseling content and duration, medication dose and access, and the community resources referral process) and about their overall satisfaction with the tobacco cessation counseling received. The sample size was determined to allow for 9 patients in each strata; analyses will compare results by strata. Interviews will last about 60 minutes, and patients will be provided $20 remuneration.

Interviews will be audio-recorded, transcribed and analyzed. To ensure coding reliability, discrepancies will be resolved through discussion and comparison to raw data. Coding will continue until a high level of reliability (Kappa = $\geq$0.80) is established. Utilizing the mixed methods convergent design approach), qualitative data will be compared and contrasted to baseline and follow-up survey data.

Organizational Readiness. Site characteristics and site readiness will be measured at each study site. Employees will undergo local training and then each attending employee will answer the readiness items, identified by the SCALE collaboration. Data will be collected anonymously, and employees will be consented through a waiver of documented informed consent. Responses to these items will be collected at baseline and at the end of the intervention phase of the study.

Research staff may also use a Partners approved text messaging service to contact patients who have agreed to be sent text messages during the consent process. This will be used to maximize outcomes from study videos, follow up surveys, and study reminders.

The Area Deprivation Index (ADI) is a measure for social economical status. We plan on using ADI to control for social and economical factors that are not otherwise reported. We plan on using census.gov to import a csv file of participant addresses which will return the 2020 census block group for those addresses. Names and study details will not be included in the process. By knowing the census block group of an address, we can then link that address to the 2020 ADI score.

VI. BIOSTATISTICAL ANALYSIS

Assessment Plan

Outcomes

Primary smoking outcome: 7-day point-prevalence tobacco abstinence at 6-month follow-up.

Secondary smoking outcomes (1) self-reported 7-day abstinence at 3-,and 6- months follow-up; (2) significant reduction (>50% decrease from baseline in cigarettes/day[81]); and (3) >24-hour intentional quit attempt at 3-,and 6-months follow-up.

Measures

Moderators

Sociodemographic and biological characteristics [baseline only]. *EHR:* Sex, age, primary insurance, language preference for sessions and study materials. *Survey:* Race/ethnicity, education level, employment, and religiosity. Medical history [baseline and follow-up]. *EHR:* Comorbid tobacco-related disease, ambulatory visits, alcohol consumption. Screening result. *EHR:* Lung RADS score, results of any diagnostic tests (CT or biopsy). Smoking characteristics [baseline and follow-up]. *Survey:* Current cigarettes/day, number of years smoked, e-cigarette use, past and current use of cessation medication and other tobacco products, 24-hour intentional quit attempt, nicotine dependence (2-item Heaviness of Smoking Index from the Fagerström Test for Nicotine Dependence [FTND] which have predictive validity with the overall FTND[82, 83]).

Proximal Outcomes/Mediators

All proximal outcomes/mediators will be assessed via survey at baseline and follow-up. Smoking beliefs. Readiness to quit (1 item 10-point 'contemplation ladder [84,85]), importance and confidence to quit (1 item 10-point scales), 4 item perceived lung cancer risk, and 2 item perceived benefits of quitting.[47,57] Health and screening beliefs. Self-reported overall health status (1 item from the SF-36 survey[86]), 2 item perceived benefits of screening.[47,57] Emotional symptoms. Anxiety and depression symptoms (PROMIS Anxiety and Depression 4a short-forms), worry about lung cancer (1 item about level[87, 88]). Environmental factors. Living with a smoker in the household, 1 item 4-point scale about rules about smoking in the household[89], environmental workplace/hobby exposure and social support (PROMIS emotional and informational 4a short forms).[88]

Analysis plan

All analyses will be intent-to-treat; we will classify patients who are lost to follow-up and those who do not provide a sample as current smokers.[92] We will explore whether the mechanism of missing data is missing at random by comparing patient characteristics between those who complete follow-up vs. those who do not. We will perform sensitivity analysis: 1) limited to those who have complete data, and 2) multiple imputation for missing data.[93]

Factorial design

In a factorial research design, two or more independent variables are concurrently examined within the same trial.[94, 95] The three proposed factors will be crossed with one another to create a total of eight experimental conditions. An equal number of subjects will be randomly assigned to each condition, using a random number generator. This is not an 8-arm randomized controlled trial, but instead allows for an efficient examination of main effects for each variable over the entire sample of 640 subjects. This approach allows examination of three key treatment development questions in a much more time-efficient and economical manner by simultaneously performing three studies within the single trial. This achieves power to detect between-group differences that is equivalent to performing three separate randomized trials.[94]

Outcomes/analysis

Outcome measures will be assessed at baseline, 3-, and 6-months follow-up. At the outset, we will examine the frequency distributions of all variables. Data from all PHS sites will be pooled for analysis, after confirming there is no significant heterogeneity among sites or adjusting as needed. We will compare the baseline characteristics to assess whether randomization distributed covariates evenly. We will determine whether there is differential dropout in the groups and consider developing probability-of-completion weights to obtain unbiased estimates of treatment effect. The primary analysis will assess the effects of each intervention component in terms of its association with the **primary outcome** (cotinine-confirmed or self report of cessation at 6-months follow-up), **secondary smoking outcomes** and **proximal outcomes/mediators:** (a) short vs long counseling (conditions 1/2/5/6 vs. 3/4/7/8), (b) short vs long NRT (conditions 1/3/5/7 vs conditions 2/4/6/8), and (c) provision of systematic referral or not (conditions 1-4 vs. 5-8). Given the balanced complete factorial design,[94] each of the three main effect estimates will be based on the full sample size of 640. Cross-sectional analyses will be conducted for outcomes assessed at 3, and 6 months separately. For binary outcomes, chi-square tests will be used to compare the outcomes between groups for each follow-up time. For continuous outcomes two-sample t-tests or Wilcoxon rank sum tests, whichever more appropriate, will be used to compare between groups. A longitudinal analysis using Generalized Estimating Equations (GEE) techniques will also assess the overall impact of each component by including data from all follow-up time points. The secondary analysis will examine the interaction between components, which will provide insight into whether certain combinations of components are most useful. We will test the three-way and two-way interaction terms in the regression models. If there are component interactions, we will determine whether the components are synergistic or antagonistic. Exploratory analyses will examine the moderator effects on treatment effectiveness of the intervention components and groups. Of primary interest are sociodemographic characteristics (sex, race/SES, age), smoking characteristics (quit motivation, nicotine dependence), medical history, LCS-related factors (test results, and point of study entry), delivery modality selected (phone vs. video) and language of participation (English vs. Spanish). We will test the effects of these factors in multivariable logistic regression models to determine their association with the primary and secondary smoking outcomes. We will test for interactions between intervention and these factors to determine whether

intervention effects vary among subgroups. Those with significant interactions (p<.15) will be considered as candidates for identifying subpopulations.

Cost

We will calculate the incremental cost per quit of the interventions over the 6-month follow-up period as follows: (total per-person costs of LCS-tailored intervention – total per-person costs of the lowest intensity comparator/(cessation rate with the LCS-tailored intervention – cessation rate with the lowest intensity comparator).[96] From these comparisons, we will also be able to construct a "league table" comparing the relative cost-effectiveness of different intervention components.[97] While the study is specifically powered to detect differences across factorial dimensions, we will develop incremental cost per quit estimates for all intervention comparisons that are proven effective, whether it be for individual factorial dimensions' main effects (counseling duration, NRT duration, or systematic referral), for specific permutations of the intervention components versus usual care or for intervention permutations versus each other. Costs of implementation included in our analyses will be: 1) personnel time related to intervention delivery (training, minutes of counseling, contact attempts, maintaining data and information systems), 2) NRT costs (medication, delivery), and 3) systematic referral to community resources. While systematic referral is free in Boston, access to similar services elsewhere in the country may not be, so this will be an element of our sensitivity analyses. We will also include patient time as an indirect cost. The TTS database will document all implementation costs. All intervention costs incurred will be included in the analysis, even for patients who do not complete their intervention course. Research costs will be excluded. The denominator for the cost analyses will be based on the primary outcome. Uncertainty in cost and effectiveness inputs will be incorporated into the incremental cost per quit comparisons using Monte Carlo methods allowing us to determine whether these ratios are significantly different from zero. The robustness of the cost-effectiveness ratio estimates will be further examined in sensitivity analyses in which each parameter is varied, singly and in combination, through plausible ranges. Sensitivity analyses will also consider how cost-effectiveness changes based on payment arrangements and stakeholder (provider, payer, and patient) perspectives to identify where incentives to adopt the interventions differ. For example, overhead costs such as counseling training and data/information systems are borne by the provider, and indirect costs are borne by patients, but treatment costs (counseling, NRT) and the cost of systematic referral-style resources may be borne by providers, payers, and/or patients (e.g., copayments). Assessing how assignment of costs to different stakeholders changes cost-effectiveness from different perspectives will be critical to understanding how to scale up the intervention to other LDCT screening settings and what payment policies will produce the best public health outcomes.

Sample size/ Power calculations

Reference rate	Relative Risk		
	1.4	1.45	1.5
16%	0.71	0.80	0.87
17%	0.74	0.83	0.90
18%	0.77	0.86	0.92
19%	0.80	0.88	0.93
20%	0.83	0.90	0.95
21%	0.85	0.92	0.96
22%	0.87	0.93	0.97

Power calculations are based on our primary analysis, which is to assess the effect of each intervention component (e.g., shorter counseling vs. longer counseling) on our primary outcome, 7-day point-prevalence tobacco abstinence at 6-month follow-up. This is a two-sample comparison between patients that receive one intervention component (e.g., longer counseling) and those that receive the other (e.g., shorter counseling). We conservatively estimate that 160 patients/month will have LCS, of whom 50% will be current smokers. Assuming a 50% enrollment rate, we aim to recruit a total N of 720 patients. This sample size allows us to allocate N=360 to each treatment component comparison (main effect). Our

outcome of interest will also be assessed at 3-month followup, which allows us to use a longitudinal generalized estimating equations approach wherein power is proprotional to the within-person correlation. We estimate the correlation between 3 month and 6 month smoking cessation to be 0.6. Assuming N=360 patients in each condition, a Type 1 error rate of 0.05, a 25% attrition rate by 6 month follow-up, and a 15% cessation rate for the reference group, we will have 92.3% power to detect a risk ratio of 1.6 (15% vs. 21%). Under those same conditions, but with a 10% cessation rate for the reference group, we will have 79.0% power to detect a risk ratio of 1.6 (10% vs. 16%). Given that this is full factorial design, we will have the same power to detect two-way interactions between components. Further, we will also have 77.9% power to detect a risk ratio of 2.0 in the difference between our most intensive set of treatments (longer counseling, longer NRT, and community support; N=90) and our least intensive set of treatments (shorter counseling, shorter NRT, and no community support; N=90) after six months, assuming a 15% reference rate and 25% attrition.

Reduction from initial power calculations

This study was initially powered conservatively to detect a smaller risk ratio of 1.4 and did not account for additional power provided through within-person correlation via repeated measurement of our outcome of interest. Initial power calculations, assuming a Type 1 error rate of 0.05, 25% attrition at 6 months, and no within-person correlation showed that our original N of 960 patients (N=480 per condition) gave us 85.0% power to detect a risk ratio of 1.4 with a reference rate of 15%. Updated power calculations accounting for within-person correlation of 0.6 show that this original N gives us 96.8% power to detect our target risk ratio of 1.6, assuming 25% attrition at 6 months and a 15% reference cessation rate.

Our previous power calculation assumed a 25% attrition rate at 6 months. We re-examined this assumption after halfway through the recruitment. Our new estimates are 12.7% attrition rate at 3 months and 15.9% attrition rate at 6 months. Based on these estimates, we further reduce the target recruitment from 720 to 640. Combining data from both 3-month (estimated N=559) and 6-month (estimated N=539) assessments, the effective sample size will be 768 after taking into account of within-person correlation using a conservative estimate of 0.6. The new sample size will have 70% power to detect a risk ratio of 1.6 (10% vs. 16%) and 81% power to detect a risk ratio of 1.7 (10% vs. 17%).

VII.. RISKS AND DISCOMFORTS (Stratify by common and uncommon)

Prior to enrollment, potential patients will be cautioned about the potential negative psychological and physical implications of joining the study and/or quitting smoking.

Psychological Risks

Individuals may find it stressful to answer questions and discuss their smoking behaviors. The risks associated with these discussions are minimal, especially when compared to the benefits of smoking cessation.

The potential risks to subjects include: 1) speaking with a counselor about smoking and/or cancer-related topics has the potential for increasing psychological vulnerability; 2) experiencing physical and emotional withdrawal symptoms from smoking cessation; and 3) potential side effects of using nicotine replacement therapy.

These risks will be described by the research assistant and will be clearly outlined in the consent script. Among enrolled patients, in the event that a patient is determined to be actively suicidal and at risk for self-harm at any of the study contact points, the study PIs will be immediately contacted and the appropriate clinical intervention effected. These procedures would be followed in the case of active suicidality or homicidality, as well as in the case of abuse, neglect or risk of harm to a minor or elder.

Toxicities and Side Effects

Nicotine Replacement Therapy (Nicotine Patch)

The transdermal nicotine patch has been an FDA-approved treatment for nicotine dependence since 1991, and in 1996, the patch was approved for over-the-counter sale. Up to 50% of patients using the nicotine patch will have a local skin reaction. Skin reactions are usually mild and self-limiting but may worsen over the course of therapy. Local treatment with hydrocortisone cream (1%) or triamcinolone cream (0.5%) and rotating patch sites may ameliorate such local reactions. In less than 5% of patients, such reactions require the discontinuation of nicotine patch treatment.

Nicotine is not an independent risk factor for acute myocardial events, but NRT should be used with caution among those in the immediate (within 2 weeks) postmyocardial infarction period, those with serious arrhythmias, and those with serious or worsening angina pectoris. Mild sleep disturbances, such as vivid dreaming or insomnia, have been reported for approximately 12% of patients wearing the transdermal nicotine patch for 24 hours.[98] Other less common side effects are nausea, dizziness, tachycardia, upset stomach, restlessness, and headaches.

As our patient population may have existing physical and psychological symptoms, we will make every effort to determine if any symptom reported has its onset concurrent with or is exacerbated by medication use. In cases of severe or intolerable symptoms, patients will be instructed to discontinue use of the study medication and to contact their physician.

VIII. POTENTIAL BENEFITS

There are substantial benefits for individual subjects participating in this research study. Quitting smoking reduces risk of developing cancer, as well as improving cancer treatment effectiveness for patients diagnosed during the LCS, reducing risk of recurrence and of developing new primary tumors, and may improve chances of survival. Conversely, continuing to smoke may result in diminished quality of life (e.g., elevated pain, shortness of breath). If they succeed in quitting, the greatest potential benefit is improved outcomes and quality of life (e.g. increased breathing capacity). The potential short-term (e.g. improved breathing) and long-term (e.g. improved treatment outcome) health benefits of this study are tremendous. In addition, all patients will receive counseling during a potentially difficult time, which can bolster their sense of support and self-efficacy. Patients will receive support and counseling that may assist them with medication adherence and increased rates of tobacco cessation and continued abstinence. Patients may receive access to community resource database to address sociocultural barriers to cessation. Therefore, the overall risk to benefit ratio is favorable.

IX. Data and Safety Monitoring (DSM) Plan

The PIs will be responsible for monitoring the safety and effectiveness of this trial, executing the DSM plan, and complying with reporting requirements. The final protocol will be reviewed by the Partners IRB. The PIs will supply a summary of the DSM report to the NIH on an annual basis as part of the progress report. This report will include descriptive reports of the patients' sociodemographic characteristics, expected and actual recruitment rates, retention rates in each treatment condition, quality assurance, and regulatory issues that arose since the last report, summary of adverse events and serious adverse events, and any protocol changes. This report will include the results of any effectiveness data analyses conducted. Throughout the study, adverse events and serious adverse events will be reported in a timely fashion to the IRB. The PIs are responsible for protecting the rights, safety, and welfare of the study patients and for ensuring that the study is conducted in accordance with the IRB-approved protocol and applicable regulations and requirements of the IRB.

Data monitoring plan: Study procedures and data collection will be piloted before the trial begins. Participant data collected using paper and pencil records (participant questionnaires, progress notes from smoking cessation counselors) will be stored in a locked filing cabinet in a locked room; electronic participant tracking databases will be stored on a secure server accessible only by IRB-approved members of study staff. Data collected on paper and pencil forms will be thoroughly cleaned and entered into an electronic database with a 10% check; discrepancies will be resolved by the investigator team through a monthly data review meeting. Data collected using REDCap will identify patients by their names, email address, date of birth, medical record number, and by study ID. Participants will be identified on study forms and in the database by their names, email address, date of birth, medical record number, and by study ID. To further prevent the loss of confidentiality, all electronic information stored on the main database within the MGH/Partners Healthcare System, Inc. firewall, is password protected, and is protected by anti-virus software. Only study staff will have access to the study data on Shared File Areas. Dr. Park will review the data for quality assurance and discuss data quality problems with the PIs. Data quality (including visits completed during the intervention window, data missingness, and recruitment rates) will be monitored monthly. Interim data analysis will be conducted throughout the trial and results will be reported in the annual NIH progress report. In addition, the RAs will participate in weekly study evaluation meetings to review any difficulties that arise with survey administration and the status of follow-up survey and biochemical collection.

If patients report significant complaints about our recruitment approach, the study RA will document all patient concerns and provide a detailed report to the IRB in real time about the nature of the complaint. Study staff will discuss with the PIs on how to adapt recruitment approaches to prevent future complaints, and include any changes required by the IRB.

Safety monitoring plan: The exclusion criteria are designed to prevent patients at a high risk of medical and psychiatric complications from participating in study. However, if unexpected conditions appear to be placing patients at a higher risk than anticipated, the exclusion criteria will be amended. Any medical complications, which are considered to be related to the study, will be reported to the site PI, who will report them to the subject's treating physician. The site PI will review the progress of all study participants on an at least monthly basis. Any adverse events related to study participation will be reported to the IRB.

The main safety risks for the study include the potential for psychological discomfort with

surveys and counseling as well as side effects from study medications. In order to protect against risk from pharmacotherapy usage, these steps will be taken:

(1) Medication is being provided only to patients who receive counseling sessions. At each call, patients are specifically asked about any side effects or problems. Study staff will be required to report any unexpected or questionable reports of adverse effects to the study PIs. These will be reviewed at the weekly study staff meeting. If more urgent, the PI will review immediately.

(2) The study physicians (Drs. Rigotti and Haas) will provide back up to study staff for all medical questions that arise during participant enrollment or study progress.

(3) The PIs will review any serious adverse events and report them appropriately to the IRB and NIH. Reports are to be submitted within 5 working days/7 calendar days of the date the investigator first becomes aware of the problem. Each will be reviewed by the PIs to ensure that the readmission is not related to study medication.

Data Sharing

De-identified data will be periodically shared with NCI for cross-project research within the SCALE study sites. Data will be shared through a secure online portal developed by Information Management Services, Inc. (IMS), in which each SCALE study site will only have access to the data uploaded by members of that site. IMS provides a firewall, VPN, and intrusion prevention system. Routine security checks of the IMS computer resources are made with security analysis software tools. The production network is housed in physically separate and secured computing facilities. Only authorized user ID and password protected access is allowed to the network. In addition, IMS has an NIH approved IT System Security Plan in place that meets the OMB Circular A-130 guidelines and the NIST guidelines for IT system security at the "moderate" level.
As part of the SCALE collaboration, a data transfer agreement written by the NCI legal office will be sent to each study site for review by each site's legal offices. Research proposals will be sent to the soon-to-be formed Steering Committee (in which NCI is a non-voting member) and vetted. When approved, NCI will send data to the researchers who are leading a given analysis; NCI may also conduct analyses with the approval of the Steering Committee. NCI will only send data to non-SCALE members when approved by the Steering Committee, except in very specific, limited circumstances described in the data transfer agreement.

We will send a limited data set to our collaborator at UMass Boston, Dr. Jaqueline Contrera Avila. Dr. Avila will assist us with the data analysis. Data will be stored behind the UMB firewall on a password protected computer, for adding safety the data will be stored the University OneDrive under a two-way steps verification.

Protection of Human Subjects

Prior to enrollment, potential patients will be cautioned about the potential negative psychological (stress and loss of positive experiences from smoking) and physical implications of quitting smoking. A clear risk/benefit ratio will be presented to each potential patient. These risks will be described by the research assistant and will be clearly outlined in the consent script. Patients will

be encouraged to discuss any concerns with their provider, prior to enrolling. Patients who need time to consider these risks will be given the option of calling back and/or enrolling at a later date.

There are three potential reasons for elevated psychiatric risk in our study patients. Lung cancer screening could be a vulnerable time for patients, patients may be uncomfortable talking about their smoking given the stigma of smoking and lung cancer, and withdrawal symptoms and cravings from quitting smoking.

In order to protect against psychiatric risks, we will not enroll anyone who is potentially psychiatrically unstable. Individuals found to be psychiatrically unstable at screening will be referred for psychological/psychiatric evaluation. Once patients are enrolled in the study, study staff will notify the MPIs if a patient seems distressed during the surveys or counseling. In addition, patients will be given the contact information for the study MPIs at the beginning of the study and told that they can contact with any concerns about their study participation. If a patient appears to be in high distress/risk the tobacco counselor will page Dr. Park, who will immediately contact the patient and utilize a suicide prevention assessment and protocol previously developed for smoking cessation studies with other vulnerable medical patient populations. This protocol assesses for risk to self or others, including whether the patient has suicidal thoughts, a suicide plan, and a means to complete their plan. If a patient is deemed high risk of suicide/homicide, confidentiality may be suspended. Patients in the midst of a psychiatric emergency will be required to go to the emergency room for evaluation (if they are unwilling, paramedics will be sent to their location). Suicidal patients who are able to contract for safety will be required to follow up immediately

The study staff will immediately discuss any patients whom they are concerned about with the Drs. Rigotti or Haas, both licensed internists, who will decide an appropriate course of action. In the event of a psychiatric emergency, confidentiality may be suspended. Patients will be informed of the limits of confidentiality at the beginning of the study.

X. REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA: A Cancer Journal for Clinicians.* Jan-Feb 2015;65(1):5-29.

2. American Cancer Society. Cancer Facts & Figures. Atlanta; 2016. doi:10.3322/caac.20121.

3. Rigotti NA. Clinical practice. Treatment of tobacco use and dependence. *New England Journal of Medicine.* 2002;346(7):506-512.

4. NCI Surveillance, Epidemiology and ERP. Cancer of the Lung and Bronchus - Cancer Stat Facts. Natl Cancer Inst. 2017. https://seer.cancer.gov/statfacts/html/lungb.html. Accessed April 7, 2017.

5. Fiore MC, Jaen CR, Baker TB, al. e. *Treating Tobacco Use and Dependence: 2008 Update.* Rockville, MD: US Department of Health and Human Services. Public Health Service;2008.

6. *The Health Consequences of Smoking—50 Years of Progress. A Report of the Surgeon General.* Atlanta, GA: U.S. Department of Health and Human Services.;2014.

7. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. *JAMA.* 2004;291(10):1238-1245.

8. Schroeder SA. Shattuck Lecture. We can do better--improving the health of the American people. *N Engl J Med.* Sep 20 2007;357(12):1221-1228.

9. Haiman CA, Stram DO, Wilkens LR, et al. Ethnic and racial differences in the smoking-related risk of lung cancer. *N Engl J Med.* Jan 26 2006;354(4):333-342.

10. Kanjilal S, Gregg EW, Cheng YJ, Zhang P, Nelson DE, Mensah G, Beckles GL. Socioeconomic status and trends in disparities in 4 major risk factors for cardiovascular disease among US adults, 1971-2002. *Arch Intern Med*. 2006;166(21):2348-55.

11. Quitting Smoking Among Adults – United States, 2000-2015. Mmwr. Jan 6 2017;65(52):1457-1464.

12. Hiscock R, Bauld L, Amos A, Fidler JA, Munafo M. Socioeconomic status and smoking: a review. Ann N Y Acad Sci. 2011;1248:107-23.

13. Vidrine JI, Reitzel LR, Wetter DW. The role of tobacco in cancer health disparities. Current Oncology Reports. 2009; 11:475-481.

14. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. Aug 4 2011;365(5):395-409.

15. Moyer VA. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. Annals of internal medicine. Mar 4 2014;160(5):330-338.

16. Ma J, Ward EM, Smith R, Jemal A. Annual number of lung cancer deaths potentially avertable by screening in the United States. *Cancer.* Apr 1 2013;119(7):1381-1385.

17. Aberle DR, Abtin F, Brown K. Computed tomography screening for lung cancer: has it finally arrived? Implications of the national lung screening trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Mar 10 2013;31(8):1002-1008.

18. Zeliadt SB, Heffner JL, Sayre G, et al. Attitudes and Perceptions About Smoking Cessation in the Context of Lung Cancer Screening. JAMA Intern Med. Sep 1 2015;175(9):1530-1537.

19. Parsons A, Daley A, Begh R, Aveyard P. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. BMJ. 2010; 340:b5569.

20. Westmaas JL, Newton CC, Stevens VL, Flanders WD, Gapstur SM, Jacobs EJ. Does a recent cancer diagnosis predict smoking cessation? An analysis from a large prospective US cohort. J Clin Oncol. 2015; 33(15):1647-1652.

21. Garces YI, Yang P, Parkinson J, et al. The relationship between cigarette smoking and quality of life after lung cancer diagnosis. Chest. Dec 2004;126(6):1733-1741.

22. Gritz ER, Demark-Wahnefried W. Health behaviors influence cancer survival. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Apr 20 2009;27(12):1930-1932.

23. Park ER, Japuntich SJ, Rigotti NA, et al. A snapshot of smokers after lung and colorectal cancer diagnosis. Cancer. Jun 15 2012;118(12):3153-3164.

24. Kelemen LE, Warren GW, Koziak JM, Kobel M, Steed H. Smoking may modify the association between neoadjuvant chemotherapy and survival from ovarian cancer. Gynecol Oncol. 2016; 140(1):124-130.

25. Jung KH, Kim SM, Choi MG, Lee JH, Noh JH, Sohn TS, et al. Preoperative smoking cessation can reduce postoperative complications in gastric cancer surgery. Gastric Cancer. 2015; 18(4):683-690.

26. Shen T, Le W, Yee A, Kamdar O, Hwang PH, Upadhyay D. Nicotine induces resistance to chemotherapy in nasal epithelial cancer. Am J Rhinol Allergy. Mar-Apr 2010;24(2):e73-77.

27. Chen AM, Chen LM, Vaughan A, et al. Tobacco smoking during radiation therapy for head-and-neck cancer is associated with unfavorable outcome. International journal of radiation oncology, biology, physics. Feb 1 2011;79(2):414-419.

28. Zhang J, Kamdar O, Le W, Rosen GD, Upadhyay D. Nicotine induces resistance to chemotherapy by modulating mitochondrial signaling in lung cancer. Am J Respir Cell Mol Bio. 2009; 40(2):135-146.

29. Xu J, Huang H, Pan C, Zhang B, Liu X, Zhang L. Nicotine inhibits apoptosis induced by cisplatin in human oral cancer cells. Int J Oral Maxillofac Surg. 2007; 36(8): 739-744.

30. Zevallos JP, Mallen MJ, Lam CY, Karam-Hage M, Blalock J, Wetter DW, Garden AS, Sturgis EM, Cinciripini PM. Complications of radiotherapy in laryngopharyngeal cancer: effects of a prospective smoking cessation program. Cancer. 2009;115(19):4636-44.

31. US Preventive Services Task Force. Tobacco Smoking Cessation in Adults and Pregnant Women: Behavioral and Pharmacotherapy Interventions 2015.

32. Quitting Smoking Among Adults --- United States, 2001--2010. Mmwr. 2011;60(44):1513-1519.

33. Westmaas JL, Langsam K. Unaided smoking cessation and predictors of failure to quit in a community sample: effects of gender. Addictive behaviors. Aug 2005;30(7):1405-1424.

34. Shiffman S, Brockwell SE, Pillitteri JL, Gitchell JG. Use of smoking-cessation treatments in the United States. American journal of preventive medicine. Feb 2008;34(2):102-111.

35. 2013 Survey. http://www.naquitline.org/?page=2013Survey. Accessed September 20, 2015.

36. Clark MA, Gorelick JJ, Sicks JD, et al. The Relations between False Positive and Negative Screens and Smoking Cessation and Relapse in the National Lung Cancer Screening Trial: Implications for Public Health. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. Mar 6 2015.

37. Kumar P, Gareen IF, Lathan C, et al. Racial differences in tobacco cessation and treatment usage after lung screening: An examination of the National Lung Screening Trial. The Oncologist. Jan 2016;21(1):40-49.

38. Taylor KL, Cox LS, Zincke N, Mehta L, McGuire C, Gelmann E. Lung cancer screening as a teachable moment for smoking cessation. Lung Cancer. Apr 2007;56(1):125-134.

39. Park ER, Gareen IF, Jain A, et al. Examining whether lung screening changes risk perceptions: National Lung Screening Trial participants at 1-year follow-up. Cancer. Apr 1 2013;119(7):1306-1313.

40. Ashraf H, Saghir Z, Dirksen A, et al. Smoking habits in the randomised Danish Lung Cancer Screening Trial with low-dose CT: final results after a 5-year screening programme. Thorax. Jun 2014;69(6):574-579.

41. Cox LS, Clark MM, Jett JR, et al. Change in smoking status after spiral chest computed tomography scan screening. Cancer. Dec 1 2003;98(11):2495-2501.

42. Styn MA, Land SR, Perkins KA, Wilson DO, Romkes M, Weissfeld JL. Smoking behavior 1 year after computed tomography screening for lung cancer: Effect of physician referral for abnormal CT findings. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. Dec 2009;18(12):3484-3489.

43. van der Aalst CM, van den Bergh KA, Willemsen MC, de Koning HJ, van Klaveren RJ. Lung cancer screening and smoking abstinence: 2 year follow-up data from the Dutch-Belgian randomised controlled lung cancer screening trial. Thorax. Jul 2010;65(7):600-605.

44. Townsend CO, Clark MM, Jett JR, et al. Relation between smoking cessation and receiving results from three annual spiral chest computed tomography scans for lung carcinoma screening. Cancer. May 15 2005;103(10):2154-2162.

45. Park ER, Streck JM, Gareen IF, et al. A qualitative study of lung cancer risk perceptions and smoking beliefs among national lung screening trial participants. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. Feb 2014;16(2):166-173.

46. Anderson CM, Yip R, Henschke CI, Yankelevitz DF, Ostroff JS, Burns DM. Smoking cessation and relapse during a lung cancer screening program. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. Dec 2009;18(12):3476-3483.

47. Park ER, Ostroff JS, Rakowski W, et al. Risk perceptions among participants undergoing lung cancer screening: baseline results from the National Lung Screening Trial. Ann Behav Med. Jun 2009;37(3):268-279.

48. Zbikowski SM, Jack LM, McClure JB, et al. Utilization of services in a randomized trial testing phone- and web-based interventions for smoking cessation. Nicotine Tob Res. 2011; 13(5):319-27.

49. Sorensen G, Barbeau E, Hunt MK, Emmons K. Reducing social disparities in tobacco use: a social-contextual model for reducing tobacco use among blue-collar workers. Am J Public Health. Feb 2004;94(2):230-239.

50. Haas JS, Linder JA, Park ER, et al. Proactive tobacco cessation outreach to smokers of low socioeconomic status: a randomized clinical trial. JAMA Intern Med. Feb 2015;175(2):218-226.

51. Joseph AM, Fu SS, Lindgren B, et al. Chronic disease management for tobacco dependence: a randomized, controlled trial. *Arch Intern Med.* Nov 28 2011;171(21):1894-1900.

52. Ostroff JS, Copeland A, Borderud SP, Li Y, Shelley DR, Henschke CI. Readiness of Lung Cancer Screening Sites to Deliver Smoking Cessation Treatment: Current Practices, Organizational Priority, and Perceived Barriers. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. Sep 7 2015.

53. Park ER, Gareen IF, Japuntich S, et al. Primary Care Provider-Delivered Smoking Cessation Interventions and Smoking Cessation Among Participants in the National Lung Screening Trial. JAMA Intern Med. Sep 1 2015;175(9):1509-1516.

54. Reid ZZ, Regan S, Kelley JH, et al. Comparative Effectiveness of Post-Discharge Strategies for Hospitalized Smokers: study protocol for the Helping HAND 2 randomized controlled trial. BMC public health. 2015;15:109.

55. Rigotti NA, Regan S, Levy DE, et al. Sustained care intervention and postdischarge smoking cessation among hospitalized adults: a randomized clinical trial. JAMA. Aug 20 2014;312(7):719-728.

56. Rigotti NA, Bitton A, Kelley JK, Hoeppner BB, Levy DE, Mort E. Offering population-based tobacco treatment in a healthcare setting: a randomized controlled trial. American journal of preventive medicine. Nov 2011;41(5):498-503.

57. Koblitz A, Kaufman A, Persoskie A, Ferrer R, Klein W, Park ER. Factor structure and stability of smoking-related disease risk perceptions in the National Lung Screening Trial. Approaches to Studying and Understanding Tobacco Risk Perceptions. Paper presented at: Meeting of the Society of Behavioral Medicine2013; San Francisco.

58. Park ER, Japuntich S, Temel J, et al. A smoking cessation intervention for thoracic surgery and oncology clinics: a pilot trial. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. Jun 2011;6(6):1059-1065.

59. Regan S, Reyen M, Lockhart AC, Richards AE, Rigotti NA. An interactive voice response system to continue a hospital-based smoking cessation intervention after discharge. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Apr 2011;13(4):255-260.

60. Rigotti NA, Park ER, Regan S, et al. Efficacy of telephone counseling for pregnant smokers: a randomized controlled trial. Obstetrics and gynecology. Jul 2006;108(1):83-92.

61. Park ER, Ostroff JS, Perez GK, Hyland KA, Rigotti NA, Borderud S, Regan S, Muzikansky A, Friedman ER, Levy DE, Holland S, Eusebio J, Peterson L, Rabin J, Miller-Sobel J, Gonzalez I, Malloy L, O'Brien M, de León-Sanchez S, Whitlock CW. Integrating tobacco treatment into cancer care: Study protocol for a randomized controlled comparative effectiveness trial. Contemporary Clinical Trials. 2016; 50:54-65.

62. Aveyard P, Begh R, Parsons A, West R. Brief opportunistic smoking cessation interventions:

a systematic review and meta-analysis to compare advice to quit and offer of assistance. Addiction (Abingdon, England). Jun 2012;107(6):1066-1073.

63. Han PK, Joekes K, Elwyn G, et al. Development and evaluation of a risk communication curriculum for medical students. Patient education and counseling. Jan 2014;94(1):43-49.

64. Miller W, Rollnick S. Motivational interviewing. New York: The Guilford Press; 1991.

65. Lindson-Hawley NT, hompson TP, Begh R. . Motivational interviewing for smoking cessation.2015.

66. Emmons KM, Puleo E, Park E, et al. Peer-delivered smoking counseling for childhood cancer survivors increases rate of cessation: the partnership for health study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. Sep 20 2005;23(27):6516-6523.

67. Ostroff JS, Buckshee N, Mancuso CA, Yankelevitz DF, Henschke CI. Smoking cessation following CT screening for early detection of lung cancer. Preventive medicine. Dec 2001;33(6):613-621.

68. Borrelli B, Hayes RB, Dunsiger S, Fava JL. Risk perception and smoking behavior in medically ill smokers: a prospective study. Addiction (Abingdon, England). Jun 2010;105(6):1100-1108.

69. Eakin EG, Reeves MM, Winkler E, et al. Six-month outcomes from living well with diabetes: A randomized trial of a telephone-delivered weight loss and physical activity intervention to improve glycemic control. Annals of behavioral medicine : a publication of the Society of Behavioral Medicine. Oct 2013;46(2):193-203.

70. Wu TC, Lyerly MJ, Albright KC, et al. Impact of Telemedicine on Access to Acute Stroke Care in the State of Texas. Ann Clin Transl Neurol. Jan 1 2014;1(1):27-33.

71. Pew Research Center. Tech Adoption Climbs Among Older Adults. Published May 17, 2017. Accessed June 20, 2017. http://www.pewinternet.org/2017/05/17/tech-adoption-climbs-among-older-adults/

72. Pew Internet and American Life Project. 2014; http://www.pewinternet.org/fact-sheets/health-fact-sheet/. Accessed December 20, 2014.

73. Hughes JR, Keely JP, Niaura RS, Ossip-Klein DJ, Richmond RL, Swan GE. Measures of abstinence in clinical trials: issues and recommendations. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. Feb 2003;5(1):13-25.

74. Perkins KA, Karelitz JL, Jao NC. Optimal carbon monoxide criteria to confirm 24-hr smoking abstinence. Nicotine Tob Res. 2013;15(5):978-982.

75. Scheuermann TS, Richter KP, Rigotti NA, Cummins SE, Harrington KF, Sherman SE, Zhu S-H, Tindle HA, Preacher KJ, Consortium of Hospitals Advancing Research on Tobacco (CHART). Accuracy of self-reported smoking abstinence in clinical trials of hospital-initiated smoking interventions. Addiction. In press.

76. Etter J.-F. Financial incentives for smoking cessation in low-income smokers: study protocol for a randomized controlled trial, *Trials* 2012: 13: 88.

77. Cheung Y. T. D., Leung J. P. K., Cheung C. K. C., Li W. H. C., Wang M. P., Lam T. H. Motivating smokers at outdoor public smoking hotspots to have a quit attempt with a nicotine replacement therapy sample: study protocol for a randomized controlled trial, *Trials* 2016: 17: 355.

78. Velicer WF, Prochaska JO. A comparison of four self-report smoking cessation outcome measures. Addictive behaviors. Jan 2004;29(1):51-60.

79. Levy DE, Thorndike AN, Biener L, Rigotti NA. Use of nicotine replacement therapy to reduce or delay smoking but not to quit: prevalence and association with subsequent cessation efforts. Tob Control. 2007;16(6):384-389.

80. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict. Sep 1991;86(9):1119-1127.

81. Perez-Rios M, Santiago-Perez MI, Alonso B, Malvar A, Hervada X, de Leon J. Fagerstrom test for nicotine dependence vs heavy smoking index in a general population survey. BMC public health. 2009;9:493.

82. Biener L, Abrams DB. The Contemplation Ladder: validation of a measure of readiness to consider smoking cessation. Health psychology : official journal of the Division of Health Psychology, American Psychological Association. 1991;10(5):360-365.

83. Bernstein SL, Boudreaux ED, Cabral L, et al. Nicotine dependence, motivation to quit, and diagnosis among adult emergency department patients who smoke: a national survey. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. Aug 2008;10(8):1277-1282.

84. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical care. Jun 1992;30(6):473-483.

85. Lerman C, Schwartz M. Adherence and psychological adjustment among women at high risk for breast cancer. Breast cancer research and treatment. Nov 1993;28(2):145-155.

86. PROMIS Measures. http://www.nihpromis.org/measures/instrumentoverview. Accessed September 26, 2015.

87. The Social Science Research Center, The National Social Climate of Tobacco Control, 2008. http://www.socialclimate.org/pdf/us_scs_08_Report.pdf (Accessed 20 June 2017).

88. West R, Ussher M. Is the ten-item Questionnaire of Smoking Urges (QSU-brief) more sensitive to abstinence than shorter craving measures? Psychopharmacology. Feb 2010;208(3):427-432.

89. Cella DF, Bonomi AE, Lloyd SR, Tulsky DS, Kaplan E, Bonomi P. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. Lung Cancer. Jun 1995;12(3):199-220.

90. Interventions for smoking cessation in hospitalised patients. Cochrane Database of Systematic Reviews; 2009.

91. Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley & Sons; 1987.

92. Collins LM, Dziak JJ, Li R. Design of experiments with multiple independent variables: a resource management perspective on complete and reduced factorial designs. *Psychol Methods.* 2009; 14:202-24.

93. Montgomery AA, Peters TJ, Little P. Design, analysis, and presentation of factorial randomised controlled trials. *BMC Med Res Methodol.* 2003; 3:26.

94. Cost-Effectiveness in Health and Medicine. New York: Oxford University Press; 1996.

95. Methods for the Economic Evaluation of Health Care Programmes. . Third ed. Oxford: Oxford University Press; 2005.

96. Thompson, T.G., n.d. Department of Health and Human Services 382.

97. Effectiveness of a nicotine patch in helping people stop smoking: results of a randomised trial in general practice. Imperial Cancer Research Fund General Practice Research Group, 1993. . BMJ 306, 1304–1308.

98. Gourlay, S.G., Forbes, A., Marriner, T., Pethica, D., McNeil, J.J., 1995. Double blind trial of repeated treatment with transdermal nicotine for relapsed smokers. BMJ 311, 363–366.