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IMPLEMENTATION OF SMOKING CESSATION SERVICES WITHIN NCI NCORP COMMUNITY SITES WITH ORGANIZED LUNG CANCER SCREENING PROGRAMS (OaSiS)

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Protocol History:

Initial	Version 12/15/2017	This version will be activated but patient participant enrollment will not be open. Activated 1/31/2018
Amendment 1	Version 01/19/2018	Activated and released on 3/19/2018
Amendment 2	Version 06/29/2018	Activated and released on 10/5/2018
Amendment 3	Version 12/03/2018	Activated and released on 04/29/2019
Amendment 4	Version 10/01/2019	Activated and released on 12/09/2019

<table>
<tr><th colspan="3">CONTACT INFORMATION</th></tr>
<tr><th>For regulatory requirements:</th><th>For patient enrollments:</th><th>For study data submission:</th></tr>
<tr><td>Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal.
Regulatory Submission Portal:
(Sign in at www.ctsu.org,
and select the Regulatory > Regulatory Submission.)

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support.

Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.</td><td>Refer to the patient enrollment section of the protocol for detailed instructions.</td><td>Data collection for this study will be done exclusively through REDCap. Refer to the data submission section of the protocol for further instructions.

For assistance, please contact the NCORP Research Base Data Management Center at:
(336) 713-3172
-or-
(336) 713-6507.

Address:
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Fax: (336) 713-6476
Email: NCORP@wakehealth.edu
Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.</td></tr>
<tr><td colspan="3">The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific page of the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log on with CTEP-IAM username and password.</td></tr>
<tr><td colspan="3">For study related questions (i.e. patient eligibility) please contact the WF NCORP Research Base site coordinator at NCORP@wakehealth.edu or (336) 716-0891 or OaSiS Project Manager Rebecca Stone at rjstone@wakehealth.edu or (336) 716-6201.</td></tr>
<tr><td colspan="3">For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</td></tr>
<tr><td colspan="3">The CTSU Website is located at https://www.ctsu.org.</td></tr>
</table>

Participation is limited to the following Wake Forest NCORP Research Base sites:

CTEP ID	NCORP Site Name
DE028	Helen F. Graham Cancer Center
GA020	Augusta University Medical Center
GA106	Lewis Cancer and Research Pavilion at Saint Joseph's/Candler
HI010	Tripler Army Medical Center
IA003	McFarland Clinic PC-William R Bliss Cancer Center
IA008	Mercy Medical Center - Des Moines
IL168	Carle Cancer Center
LA017	Louisiana State University Health Sciences Center Shreveport
MI005	William Beaumont Hospital-Royal Oak
MI013	Saint Joseph Mercy Hospital
MI132	Spectrum Health at Butterworth Campus
MN059	Ridgeview Medical Center
MO042	CoxHealth South Hospital
MO046	Missouri Baptist Medical Center
NC047	Novant Health Forsyth Medical Center
ND039	Sanford South University Medical Center
NV011	Saint Mary’s Regional Medical Center
NV017	University Medical Center of Southern Nevada
NY045	Montefiore Medical Center - Moses Campus
OH182	Adena Regional Medical Center
PA052	Geisinger Medical Center
SC060	Greenville Health System Cancer Institute-Faris
TN029	Baptist Memorial Hospital and Cancer Center-Memphis
VA010	Virginia Commonwealth University/Massey Cancer Center
VA205	Virginia Commonwealth University/Stony Point
WI011	Aurora Saint Luke's Medical Center
WI029	Gundersen Lutheran Medical Center

SCHEMA

IMPLEMENTATION OF SMOKING CESSATION SERVICES WITHIN NCI NCORP COMMUNITY SITES WITH ORGANZED LUNG CANCER SCREENING PROGRAMS (OaSiS)

Study Population*: Lung Cancer Screening Patients presenting to 26 Lung Cancer Screening Clinics*

↓

Randomization *at the Clinic Level (13 Intervention, 13 Usual Care), matched on organizational characteristics (e.g., volume, current cessation services, race/ethnicity composition of patients)*

↓

Intervention*: Training of Lung Cancer Screening Personnel on implementation of the US PHS Guidelines for Smoking Cessation and Performance Coaching during Implementation Phase of the Study*

↓

Data collection from Patients*: demographics, health status, smoking history, quitting behavior, perceptions of lung cancer risk and worry, impact of screening on tobacco use behavior, and exposure to the intervention. (baseline, ≤14 days, 3 months, and 6 months)*

↓

Data collection from Key Informants *(Lung Cancer Screening Site Personnel): Feasibility of Intervention, Appropriateness, Compatibility, Resources, Acceptability (Implementation Metrics)*

↓

Primary Endpoint*: 7-day smoking abstinence with cotinine validation at 6 months*

Study Sample*: n=minimum 1,114 to a maximum of 1,300 patients who have undergone LDCT lung cancer screening*

Study Duration*: 4.5 years*

Brief Eligibility Criteria:
Clinics*:* Screened ≥50 patients within the last 6 months; Agrees to have NCORP research personnel serve as the study liaison and another person to serve as the cessation program champion; Agrees to participate in all aspects of the intervention, randomization, and evaluation

Patients*:* Age 55-77; Current smoker; Not using medications to quit (use of Bupropion for depression only is acceptable); Willing to participate.

TABLE OF CONTENTS

Informed Consent

Appendices:

1. OBJECTIVES

1.1 Primary Objectives

1.1.1. **Evaluate a multi-faceted training program to improve immediate (≤14 days after the screening visit), short-term (3 months after the screening visit) and sustained abstinence (6 months after the screening visit) among 1,114-1,300 enrolled smokers who present for LDCT lung cancer screening in 26 community-based practices. The primary endpoint is sustained abstinence.** We will use a cluster, randomized control trial to achieve this aim. Thirteen intervention sites will receive the multi-faceted training program (n=557-650 patients), and 13 sites will receive "usual care" (n=557-650 patients). We expect at least 836 participants to complete the 6-month follow-up survey. **Deliverable:** A rigorous test of the effectiveness of the multi-faceted intervention to promote quitting among high risk patients who present for LDCT lung cancer screening in community-based practices.

1.1.2. **Characterize the adoption and adaptation of evidence-based tobacco cessation strategies in 26 diverse, community-based LDCT lung cancer screening imaging facilities within NCORP components/subcomponents**. Community-based practices offering lung cancer screening are rapidly evolving; therefore it is unknown how these practices adopt and adapt evidence-based cessation strategies. We will use extensive qualitative data collection methodologies to inform this aim, including an analysis of strategic planning SWOT data, analysis of a team blog and performance coaching notes, key informant interviews, and observational data in the intervention arm. We will also evaluate the implementation of evidence-based cessation strategies in usual care clinics. **Deliverable:** These data will yield critical information on how diverse, community-based LDCT lung cancer screening practices implement the evidence-based strategies for tobacco cessation (with and without the intervention) to inform the development of an implementation toolkit for dissemination and scale-up.

1.1.3. **Develop and evaluate an implementation toolkit for integrating evidence-based tobacco cessation strategies in community-based LDCT lung cancer screening imaging facilities.** The majority of lung cancer screening will occur in non-academic, community-based settings with diverse patient populations. Therefore, it is critical for community-based (non-academic) settings to have a resource for implementation that can be used in absence of a research team. We will develop an implementation toolkit for LDCT screening sites and invite an external advisory board and national stakeholders to evaluate its potential for dissemination and scale-up (e.g., External Advisory Board members, Legacy Foundation, Partnership for Prevention, American Cancer Society, Lung Cancer Alliance, American Society of Clinical Oncology). **Deliverable:** An implementation toolkit for community-based LDCT lung cancer screening sites that describes how to implement evidence-based tobacco cessation strategies in absence of the research team, thereby promoting scale-up and sustainability.

1.2 Secondary Objectives – N/A

2. BACKGROUND

2.1 Study Disease

Evidence and Opportunity: An estimated 8.7 million US adults may be eligible for low-dose computed tomography (LDCT) lung cancer screening, and up to half of patients presenting for lung cancer screening are smokers[1]. Effective, evidence-based strategies exist to encourage smoking cessation in clinical settings. We will determine how to best implement these strategies in lung cancer screening

components/subcomponents, leading to increased tobacco cessation rates and decreased tobacco-related mortality.

Tobacco is a leading cause of death: Implementing effective smoking cessation within LDCT chest screening is needed, as quitting, even later in life, increases life expectancy,[2] decreases risk of competing causes of death,[3,4] improves survival among lung cancer patients, [5] and maximizes the cost-effectiveness of lung cancer screening.[6,7] Cessation services can also be used to correct misconceptions about lung cancer screening that may inadvertently lower the likelihood of quitting.[8]

New Support for Lung Cancer Screening: In 2011, the National Lung Screening Trial (NLST) reported that three, annual LDCT lung cancer screens provided a 20% reduction in lung–cancer specific mortality in a high risk cohort relative to screening with single view chest radiograph.[1,9] Medical societies and the United States Preventive Services Task Force have endorsed annual LDCT screening in asymptomatic adults who have a 30 pack-year smoking history and currently smoke or have quit smoking within the past 15 years.[9] It wasn't until 2014, however, that The Centers for Medicare and Medicaid Services (CMS) added annual LDCT lung cancer screening as a covered service benefit for persons at high risk for lung cancer and who meet the eligibility criteria (age 55 – 77 years; asymptomatic for lung cancer; tobacco smoking history of at least 30 pack-years; current smoker or a former smoker who quit within the last 15 years).[10] Today, community-based LDCT screening is rapidly evolving, making this an optimal time to understand how to implement evidence-based tobacco cessation services during screening.

Lung Cancer Screening Targets High Risk Smokers: CMS requires that the LDCT imaging center "make available smoking cessation interventions for current smokers." What is not specified in the mandate is what qualifies as "available". Services could be as limited as ask, advise, and refer or as resource intensive as multi-session individual counseling. Health care delivery system factors that affect the level and intensity of cessation services may include: the referral and follow-up procedures for screening; provider willingness and capacity to offer cessation support; reinforcement for cessation by the primary care provider before and/or after the screening visit; availability of centralized cessation services within a hospital and/or community-based services, etc. [11] Patient factors may also affect uptake of these services and quitting, such as receptivity to counseling and pharmacotherapy, willingness to access recommended services and therapies (e.g., Quitline, nicotine replacement), self-efficacy to quit, prior quit attempts, and familial support for quitting.

Effective Guidelines for Treating Tobacco Use Exist: The PHS Guidelines detail clinic, provider, and patient strategies for tobacco cessation which are cost-effective and can impact a large number of smokers. [12] Strategies include: 1) implement a tobacco user identification system for all patients; 2) educate all clinic staff about strategies to promote cessation; 3) dedicate specific personnel responsible for organizing each clinic's efforts to promote cessation; and 4) use effective, evidence-based treatments for tobacco cessation including counseling and pharmacologic treatments. Combining systems- and provider-level services is more effective in promoting cessation than either approach alone .[12]

2.2 Study Intervention

Effective strategies for implementing cessation services during LDCT screening are unknown: Primary care settings have traditionally been the locale for PHS Guidelines implementation,[13] including many clinics that meet the needs of health disparate populations.[14–16] However, the LDCT screening environment is new and distinct from primary care practices. Accordingly, prior research "cannot be applied without consideration of the setting" (RFA-CA-15-011). While organizational priority of integrating smoking cessation within LDCT screening is high, implementation of the strategies that "assist" patients with quitting and ensure follow-up care are limited.[11] Greater attention is needed to understand the barriers to and opportunities for implementing evidence-based smoking cessation into

LDCT lung cancer screening imaging facilities.

Implementation of cessation services in the context of a lung cancer screening encounter may present unique challenges. Patients come to the clinic for screening and may not be primed for quitting smoking, leading to lower motivation to accept cessation support. Patient motivation may be further weakened if a negative LDCT screen creates a false sense of security about personal risk of lung cancer.[8,17] Additionally, providers may perceive cessation as secondary to screening and satisfy the CMS mandate through an "ask, advise, and refer" mechanism. This "fulfillment" of the mandate may be no more than checking a box, and patients might not follow up with referrals.[11,18] Finally, lung cancer screening is evolving rapidly in varied clinical contexts (e.g., radiology, pulmonology, free standing clinics vs. hospital systems). Different clinical contexts may have unique cultures and clinical operations systems making a 'one size fits all' approach to implementing tobacco cessation services unlikely.

Implementation Science and Practice Change Models Guide our Scientific Approach:
Implementation science focuses on the translation of scientific discovery into "real world" clinical and community-based settings.[19] Translating research findings into practice is challenging, taking ~17 years for only 14% of research to benefit patient care, discrediting the assumption that efficacious interventions are easily implemented in practice-based settings.[20] Implementation research is intended to close the gap between efficacious interventions (such as the PHS Guidelines) and real-world health care (such as community-based LDCT lung cancer screening imaging facilities).[21] Importantly, implementation science emphasizes adaptation to the "local context" to embed evidence-based interventions in clinical settings.[22] Our proposed study uses implementation science principles as an organizing framework to embed the PHS Guidelines into lung cancer screening imaging facilities within NCORP components/subcomponents.

2.3 Rationale

Focus on Cancer Care Delivered in the Community: This proposal is innovative because it will leverage NCI's NCORP community sites, an existing resource for conducting large-scale community-based trials. Concerns have been expressed that rapid expansion of lung cancer screening may affect quality of care in community settings.[23,24] Our proposal capitalizes on the NCORP research network to support cancer care delivery research.[25] We will collect data from 26 community-based lung cancer screening facilities nationwide, providing excellent geographic and socio-demographic diversity of enrolled patients. The NCORP is a practice-based research network consisting of 34 NCORP community sites and 12 Minority-Based NCORP sites, representing approximately 900 practices nationwide. The goal of the NCORP program is to expand access to cancer research to patients without easy access to tertiary-care centers, including ethnic minority survivors and those in rural communities. [26] Use of NCORP also allows our team to take advantage of NCI-funded data collection infrastructure provided through the Wake Forest NCORP Research Base and the NCORP community sites. This is not only innovative, but critical to ensure our findings our generalizable to diverse patients treated in community settings.

Ensuring Participant Diversity Through Inclusion of Community Screening Facilities: Smoking prevalence and lung cancer incidence are higher among economically disadvantaged, rural, and racially/ethnically diverse communities, patient groups who may be less likely to be treated at academic medical centers.[9] The vast majority of NCORP component/subcomponents are not academic medical centers. Because our project includes 26 NCORP imaging facilities, including those affiliated with Minority-Underserved NCORP community sites, we expect to recruit a geographically, socioeconomically, and racial/ethnically diverse patient population who present for LDCT lung cancer screening. Since 1999, the Wake Forest NCORP Research Base has recruited 3,345 patients to clinical studies: 29% racial/ethnic minorities and 21% rural, as defined by Rural Urban Commuting Area codes.

Emphasis on Sustainability & Dissemination: Our research team places high value on disseminating research findings to non-academic, community-based settings that will ensure rapid translation of cessation services in clinical practice. We will develop an implementation toolkit with community-based LDCT lung cancer screening sites as the "end user" to ensure dissemination of evidence-based smoking cessation services to clinics and patients outside of research.

Preliminary Data: Our team has extensive, collaborative experience in conducting randomized, clinic-based trials for smoking cessation interventions,[15,28,29], lung cancer screening;[30] training on the clinical integration of evidence-based tobacco cessation strategies;[31–33] and NCORP studies on smoking cessation.

- In a randomized, clinic-based study to implement the PHS Guidelines in free clinics (R21DA024631-01, Foley, PI; Spangler, Sutfin, Co-Is), we demonstrated the need for cessation services in free clinics serving low-income, diverse patients and the ability of our research team to successfully implement the PHS Guidelines in low-resource settings.[15,16,28,34] Our study was highlighted as a model program in *An Implementation Guide for Community Health Centers*, a partnership between Legacy Foundation and Partnership for Prevention (Sept 2013).
- In an implementation study to integrate evidence-based tobacco cessation strategies on college campuses, we conducted regional, accredited training with student health personnel (R21CA161664, Sutfin, PI, Foley, Spangler, Co-Is). We demonstrated an increase in patient reports of exposure to tobacco cessation signs/brochures and being screened for tobacco use among intervention clinics. Interventions among tobacco users, however, did not significantly increase after intervention.
- In our collaboration "Development of a Web-Based Tobacco Cessation Curriculum" (R25 CA96562-01A1, Spangler, PI: Foley, Miller Co-Is), we developed interactive, Web-based curricula to integrate tobacco cessation into undergraduate medical education to address a major gap in medical education training.[31–33]
- Our research team has led two NCORP studies focused on smoking cessation: (a) Feasibility of Delivering a Quitline Based Smoking Cessation Intervention in Cancer Patients Receiving Outpatient Treatment (CCCWFU 99211, PI: Weaver; 5U10 CA081851); and (b) Randomized Placebo-Controlled Phase 2 Pilot Study of Memantine (Namenda) for Smoking Cessation among Cancer Survivors (CCCWFU 99311, Spangler, 5U10 CA081851). An enhanced quitline smoking cessation intervention appears to be acceptable to participants and to result in a trend towards slightly higher cessation at 12 weeks.

Preliminary data from NCORP. Data from the 2017 NCORP CCDR Landscape assessment, indicate that 68% of responding practice groups (224 of 301) had low dose CT screening for lung cancer available on site. Management/co-management of LDCT lung cancer screening services took place in a variety of departments: radiology (69%), pulmonology 52%), surgery (19%), oncology (36%), and general internal or family medicine (18%).

To specifically prepare for this study, we conducted an online survey of NCORP components/subcomponents who are and are not current members of the Wake Forest NCORP Research Base to ascertain their interest and preliminary eligibility for the study. Ninety percent (n=111) of responding components/subcomponents (N= 122) reported having LDCT lung cancer screening available onsite. Of these 111 sites, 69 reported screening volume consistent with inclusion in this study (at least 50 screens in the past 6 months). Most (75%) reported having a central coordinator/navigator to facilitate patient scheduling, follow-up, and data entry. A variety of smoking cessation services were being offered at components/subcomponent LDCT screening programs: 59% had a designated person to counsel patients, 67% routinely advised patients to use nicotine replacement therapy, 21% provided free or low-

cost nicotine replacement therapy, 22% routinely prescribed pharmacotherapy, 24% enrolled patients in online resources, 66% referred patients to telephone quitlines, 29% provided telephone follow-up, 84% documented cessation support in the medical record, 64% offered cessation support when sharing screening results, and 73% provided cessation educational materials to all current smokers. We counted the number of services offered to calculate a current services score from 0-10. Among the 69 clinics that had sufficient screening volume, six offered 9-10 services. We contacted these clinics by telephone and they reported that the services are not routinely offered to all smoking patients, they are not evaluated, and many of the services are fulfilled by referral only (i.e., not offered onsite within the imaging facility). All believed that their programs would benefit from participation in the study.

Onsite LDCT lung cancer screening is available onsite at a majority of NCORP components/subcomponents surveyed through the 2017 NCORP CCDR Landscape Assessment. As we hypothesized, community-based lung cancer screening imaging facilities are emerging in varied clinical departments, and health care systems are implementing the CMS mandate to offer smoking cessation in diverse way. Yet, we do not know: (1) if the cessation services embedded within LDCT are effective at promoting quitting (demonstrating the need for an randomized, control trial design); (2) if there are certain strategies for cessation that work well in some lung cancer screening programs, but not others (demonstrating the need for implementation science); and (3) how to scale-up implementation of evidence-based guidelines in the rapidly emerging landscape of diverse LDCT lung cancer programs (demonstrating need for dissemination science).

3. SUMMARY OF STUDY PLAN

We utilize an **effectiveness-implementation hybrid design**, employing a cluster, randomized control trial of community-based NCORP sites to study the effectiveness of a multi-faceted intervention to improve smoking cessation among lung cancer screening patients, as well as dissemination and implementation (D&I) science to optimize and accelerate translation of findings into clinical practice.[35,36] We will: (1) Evaluate a multi-faceted training program to improve short-term smoking cessation rates (1-week post-visit) and sustained abstinence (3 and 6 months) among 1,114-1300 enrolled smokers (557-650in each trial arm) who present for LDCT lung cancer screening in community-based lung cancer screening practices; (2) Characterize the adoption and adaptation of the evidence-based tobacco cessation strategies in 26 community-based LDCT lung cancer screening imaging facilities with NCORP components/subcomponents; and (3) Develop and evaluate an implementation toolkit for integrating evidence-based tobacco cessation strategies in community-based LDCT lung cancer screening imaging facilities. The Wake Forest Study Team will collect qualitative data from key informants at participating components/subcomponents during and after intervention implementation. Quantitative survey data (baseline, ≤14 days after screening, 3 months after screening, and 6 months after screening) and saliva specimens (6 months only) will be collected by participating NCORP sites from smoking patients receiving screening within these imaging facilities.

4. STUDY SITE AND PARTICIPANT SELECTION

4.1 NCORP Clinical Site Inclusion Criteria

NCORP clinical site eligibility was determined by an online screener in Spring 2017 and a follow-up phone call to NCORP personnel when necessary. The unit of randomization is the lung cancer screening imaging facility/facilities within NCORP components/subcomponents.

4.1.1 Initial eligibility was collected electronically via a RedCap survey distributed to NCORP components/subcomponents. The survey included organizational characteristics: availability of CT

screening, # of new lung cancer screenings conducted within the past 6 months, presence of a lung cancer screening navigator, and types of smoking cessation services currently offered.

Selection will occur at the level of the NCORP community/ minority underserved community site. Once an NCORP site is selected to participate, they will be asked to rank order their eligible components/subcomponents in preference of participation. The study investigators will select a component/subcomponent from each NCORP sites to participate. The Research Base will randomize the lung cancer screening imaging facility/facilities within the NCORP. If less than 26 NCORP sites express interest in participating, we will select an additional component/subcomponent from interested NCORP sites. Selected components/subcomponents may not share personnel across multiple lung cancer screening imaging facilities. Up to two components/subcomponents per NCORP community/minority community site may be eligible.

Screening programs must meet all of the following eligibility criteria:

4.1.2 Lung cancer screening imaging facility/facilities within an NCORP components/subcomponents screened >= 50 patients for lung cancer within the past six months.

4.1.3 Agrees to have NCORP research personnel serve as the study liaison and another person to serve as the cessation program champion. The major qualifications of the champion are: availability of the champion at the time of the screening visit, a commitment to smoking cessation, communication skills, and the capacity to affect change within the imaging facility. Examples of appropriate champions include, but are not limited to, the lung cancer screening coordinator or navigator, nurse/NP/PA on site who provides cessation services, or physician leader of screening program. We will also ask the "program champion" to help identify an assistant who can assume this role in the absence of the designated program champion – either for time away, transfer, or change in job description**.**

4.1.4 Agrees to participate in all aspects of the intervention, randomization, and evaluation.

4.1.5 The lung cancer screening location at the participating components/subcomponents must be rostered with a current CTEP code and have a rostered investigator available to enroll patients.

Randomization of Lung Cancer Screening Imaging Facilities within Components/Subcomponents: Three general characteristics will be considered as stratification factors prior to randomizing sites. These include: 1) lung screening volume, 2) current cessation services offered, and 3) race/ethnicity distribution of patients screened at the imagining facility. These three characteristics are included because we believe that each should be balanced between the treated and usual care sites to avoid possible confounding that could exist if they were imbalanced after randomization.

Prior to randomization, each site will complete the Pre-Randomization Site Checklist (Appendix 18). We will assess the distribution of lung cancer screening volume and % white, non-Hispanic in the population of patients seen for lung cancer screening at the imaging facility and decide on approprite cutpoints for strata. For current cessation services offered, we performed a short survey that assessed 10 possible cessation support services (e.g., medication, counseling, QuitLine) that could be offered, and determined that a threshold of 0-5 versus 6+ should be used to stratify sites. For the 6 clinics that offered 9-10 services, we contacted these clinics. These clinics reported that the services are not routinely offered to all smoking patients, they are not evaluated, and many of the services are fulfilled by referral only (aka: not offered onsite within the imaging facility). Therefore, we will not exclude clinics based on a high 'self-reported' rate of cessation services, but will stratify to ensure balance in cessation services in the intervention and usual care arms of the study. The actual values (volume, cessation services score, and % white, non-Hispanic) will be available as site level covariates that can be included in final analytical

models when assessing the intervention effect. In addition, individual level variables (race/ethnicity) can also be adjusted for in the final models if needed.

Rationale for Randomization: To reduce the likelihood that participants over- or under-state receipt of cessation services (e.g., advised to quit, provided with a text-to-quit number) patients will not be informed to which type of clinic (intervention vs. usual care) they are randomized. This is especially important to ensure that our implementation outcome, fidelity to the intervention, is not influenced by knowing the study arm whereby reducing the likelihood of response bias. The patient consent form explains, as follows:

"You are being invited to participate in a research study. This study has public funding from the National Cancer Institute (NCI), part of the National Institutes of Health (NIH) in the United States Department of Health and Human Services. The clinic you are visiting is part of a randomized trial designed to test whether or not training lung cancer screening staff improves their ability to help patients quit smoking. We are working with 26 clinics across the United States; half of the clinics receive training and half of the clinics do not receive training. We are inviting you to participate in this study to help us evaluate the effectiveness of our training."

If patients ask clinic staff if they are in an intervention vs. usual care clinic, staff may inform patients. There are two groups of study participants: patients and key informants.

4.2 Patient Inclusion Criteria

4.2.1 Age 55-77, reflecting the age criteria for the USPSTF guideline-approved referral for lung screening.

4.2.2 Patient participants must also be a current smoker, defined as anyone who responds "every day" or "some days" to the question: "Do you smoke cigarettes every day, some days, or not at all?" (BRFSS).

4.2.3 Patients with a history of lung and/or other cancer(s) (who do not have current signs or symptoms of lung cancer) will be eligible.

4.3 Patient Exclusion Criteria

4.3.1 Current use (previous 30 days) of a tobacco dependence treatment including bupropion, varenicline, and nicotine replacement because the person is trying to quit. Use of bupropion for depression does not exclude the patient from participating. The occasional use of tobacco dependence treatment (e.g., NRT) to avoid using tobacco in public spaces is not considered to be an exclusion criteria.

4.3.2 Individuals who use e-cigarettes and who are not smoking cigarettes. Dual users (those who use both e-cigarettes and cigarettes) will be included in the trial.

4.3.3 The presence of a physical or cognitive impairment that would prevent a person from engaging in survey research (such as blindness, deafness, or dementia).

4.3.4 Individual has already completed the intended LDCT lung cancer screening for this study.

4.3.5 Non-English speaking

4.4 Patient Recruitment and Retention Strategy

The lung cancer screening clinic will provide the site coordinator with information on when patients are scheduled to be screened for lung cancer. The site coordinator will come to the clinic on the day when patients are scheduled, invite them to participate, and if interested, screen them for eligibility. A waiver of documentation of written consent is appropriate for eligibility screening because the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. Among patients who are eligible, the site coordinator will invite patients to participate in the research study, administer a written informed consent, and conduct the baseline survey (~10-15 minutes). By conducting the interview in-person at baseline, we reduce the likelihood of having enrolled patients to the study who may otherwise "no show" to their appointment and would therefore be enrolled, but never exposed to the intervention.

We will track numbers of individuals approached and screened, and reasons for nonparticipation. All written materials will be at an 8th grade reading level. We will seek participant permission at baseline to follow-up with participants via telephone ≤ 14 days of the baseline interview (to assess receipt of the intervention and immediate cessation) and at 3-months (short-term cessation) and 6-months (sustained abstinence). Participants will be given the opportunity to drop out of the study at any time. A Participant Recruitment Flow Chart and sample recruitment script is provided in Appendix 1.

4.5. Patients: Inclusion of Racial/Ethnic Minorities

We will encourage participating components/subcomponents to approach all smoking patients, regardless of race/ethnicity and ensure an even distribution of NCORP components/subcomponents with a high versus low percentage of racial/ethnic minority patients in our study by including proportion minority/white as a stratification factor prior to randomization. All Minority-Underserved NCORPs affiliated with the WF NCORP RB have been informed of the study and will be invited to participate. We will emphasize the importance of robust minority accrual at our study kickoff meetings and provide specific education and discussion about strategies to overcome barriers that underserved patients may experience to study participation. Leaders of the Wake Forest Baptist Comprehensive Cancer Center Office of Cancer Health Equity will facilitate this aspect of training and have provided feedback on our recruitment strategy. We will also ask participating Minority-Underserved NCORPs to provide suggestions about strategies for approaching and consenting racial/ethnic minority patients. We will monitor minority recruitment rates at our monthly WF NCORP RB executive steering committee meetings and provide feedback to the NCORP sites via bi-monthly study teleconference calls. Specifically, we will monitor the minority recruitment rate in conjunction with available data about the population of patients receiving lung cancer screening at the site to identify sites that are potentially under and over performing with regards to minority accrual. Sites with strong minority recruitment will be asked to share their experiences with other sites during these calls.

Both men and women (as applicable) and members of all races and ethnic groups are eligible for this trial. The table reflects the number of patient participants enrolled at baseline assuming 1114 total enrolled. If we recruit up to 1300 to account for attrition and balance across recruitment sites, we anticipate maintaining the same cell percentages as described below.

	Females	Males	Total
Ethnic			
Hispanic	5	13	18
Not Hispanic	463	633	1096
ETHNIC TOTAL	468	646	1114

	Females	Males	Total
Racial			
Am Indian	5	7	12
Asian	0	0	0
Native Hawaiian	0	0	0
Black	47	64	111
White	416	575	991
RACIAL TOTAL	468	646	1114

4.6 Key Informant Inclusion Criteria

4.6.1 Age ≥18 years

4.6.2 Member of the lung cancer screening team who is (or would be) responsible for implementation and/or supporting smoking cessation support for patients receiving lung cancer screening. This will include the program champion (Intervention Clinic only) and is likely to include: imaging facility program directors, health care providers (e.g., physicians, radiological technicians), and other staff (e.g., receptionist). Coordinators of centralized services for tobacco cessation at the component/subcomponent would also be eligible.

4.6.3 Agrees to participate in a confidential 1-on-1 semi-structured interview with the research team.

4.6.4 Agrees to have the interview taped, transcribed and qualitatively analyzed.

4.7 Key Informant Exclusion Criteria

4.7.1 <18 years of age

4.7.2 Unwilling to participate

4.8 Key Informant Recruitment and Retention Strategy

The NCORP Site Coordinator and the Cessation Program Champion will work with the Wake Forest Study Team to identify 3 key informants within each LDCT imaging facility. Key informants should be individuals who are (or would be) responsible for implementation and/or supporting cessation support. Key informants will include the program champion (Intervention Clinic only) and are likely to include: imaging facility program directors, health care providers (e.g., physicians, radiological technicians), and other staff (e.g., receptionist). Coordinators of centralized services for tobacco cessation will also be invited to interview, if applicable. Once key informants are identified, the Wake Forest Study Team project manager will electronically send the NCI CIRB approved Key Informant informed consent form to each identified key informant and conduct consent to the study by phone. The Key Informant informed consent form will be signed by the key informant and returned electronically to the Wake Forest Study Team project manager prior to initiating the interview. A copy of the complete, signed consent form will be provided to the Key Informant. The Wake Forest Study Team will be responsible for consenting Key Informants and maintaining records of the signed Key Informant informed consent forms. The structured survey and interview guide are found in Appendices 5, 6, 21 and 22.

Intervention Sites: The key informant baseline interviews (which include both structured and open-ended

questions) will be conducted by telephone prior to the first onsite visit to the imaging facility. The key informant follow-up interviews will be conducted approximately 8 months after baseline (following full implementation) and will also be conducted by telephone.

Usual Care Sites: The baseline interview will be conducted during the same time period as the baseline interviews in the intervention sites and will be conducted by telephone. The follow-up key informant interviews will occur approximately 8 months later by telephone, and will coincide with the implementation training for those clinics that choose to participate in the delayed intervention.

Total number of key informant interviews:
Intervention Sites: 39 baseline, 39 follow-up (assumes an average of 3 interviews for each of 13 sites)
Usual Care Sites: 39 baseline, 39 follow-up (assumes an average of 3 interviews for each of 13 sites)

The baseline structured survey (Appendix 5) focuses on the feasibility and appropriateness of the clinic offering several different cessation services while the follow-up structured survey (Appendix 21) focuses on implementation of smoking cessation strategies and sustainability of those cessation strategies. The baseline semi-structured interview (Appendix 6) focuses on: (a) cessation services offered; (b) perceived need for integrating cessation strategies within lung screening; (c) compatibility/appropriateness of these services within lung screening; (d) relative advantage of offering cessation support as it relates to other needs of the patients; (e) resources needed to implement and administer services. The follow-up semi-structured interview (Appendix 22) focuses on new strategies implemented, sustainability, leadership support for cessation services, perceived need for change, and access to necessary resources to ensure the cessation services could be implemented and sustained. Key informants in the intervention group will likely be in regular contact with members of the study team as part of the intervention, encouraging their retention. Usual care sites are encouraged to maintain regular communication with key informants regarding study progress.

Our goal is to maintain the same key informants at baseline and follow-up, although we recognize that staff may change (e.g., new critical hire, promotions) during the course of the study. For key staffing positions (both new and replacement positions, such as a clinical nurse navigator), we will include these individuals in the study at follow-up only and identify these individuals as someone new to the study.

4.9 Key Informants: Inclusion of Women and Minorities

All nominated key informants, regardless of gender or race/ethnicity will be invited to participate.
Of 78 total key informants, we expect 70% (n=55) to be women, 5% (n=4) to be Hispanic, and 10% to be racial minority (n=8).

	Females	Males	Total
Ethnic			
Hispanic	3	1	4
Not Hispanic	52	22	74
ETHNIC TOTAL	55	23	78
Racial			
Am Indian	0	0	0
Asian	1	0	1
Native Hawaiian	0	0	0
Black	6	1	7

	Females	Males	Total
White	48	22	70
RACIAL TOTAL	55	23	78

4.10 Cancer Therapy Evaluation Program Investigator Registration Procedures

4.10.1 **All sites must register through the CTSU.**

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.
RCR utilizes five person registration types:

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

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

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

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

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance). Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.10.2 Cancer Trials Support Unit Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).Protocol Documents are found on the CTSU website, but supplemental documents may be available on the Wake Forest NCORP Research Base website.

IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the site-protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and

- Holds an appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

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

Protocol Specific Requirements for WF-20817CD Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- Multi-faceted training program to include: (1) in-person, didactic and case-based training on evidence-based strategies to assist patients with quitting and strategies that can be used to arrange follow-up services; (2) site-specific SWOT analysis to guide implementation of the PHS Guidelines; and (3) performance coaching for eight months during the implementation phase.

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log on to the CTSU members' website → Regulatory → Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:
You can verify your site registration status on the members' side of the CTSU website.

- Log on to the CTSU members' website;
- Click on *Regulatory* at the top of your screen;
- Click on *Site Registration;*
- Enter your 5-character CTEP Institution Code and click on Go.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.11 Research Base Online Patient Enrollment

4.11.1 The Wake Forest NCORP Research Base will randomize at the level of the lung cancer screening imaging facility/facilities within NCORP components/subcomponents. The intervention program targets the providers and clinic within the intervention arm of the trial. All patients who present for lung cancer screening and are seen in an intervention clinic may be exposed to provider and/or clinic level changes that result from intervention. Intervention strategies focus on training and performance coaching to support clinics and providers as they implement the PHS Guidelines for smoking cessation. Patients in both arms of the trial who meet eligibility for the study will be invited and consented to participate.

4.11.2 Online Patient Enrollment

NCORP site staff will electronically enroll their study participants in the WF CCC REDCap website, https://redcap.wakehealth.edu/redcapccc. Step-by-step instructions will be provided by the WF NCORP Research Base Data Management Center (DMC).

If you have questions related to the electronic subject enrollment process or require assistance with electronic enrollment, please contact the WF NCORP Research Base DMC between 8:00am and 5:00pm EST, Monday through Friday at (336) 716-0891; or contact Rebecca Stone at (336) 716-6201. REDCap is a secure, web-based and HIPAA compliant forms and research database platform utilized by the WF NCORP for many research projects. This study will be using REDCap as the electronic data collection platform with electronic Case Report Form (eCRF) for multi-site studies. Site users must have current Human Subject Protection (HSP) and Good Clinical Practice (GCP) training certification in order to be granted access to the WF CCC REDCap system. Sites may submit user information including user name, email, CTEP ID, and training records to NCORP@wakehealth.edu.

5. AGENT ADMINISTRATION - NA

6. PHARMACEUTICAL INFORMATION - NA

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Patient Schedule of Events

Evaluation of the intervention depends on administration of surveys at baseline, within 14 days after the lung cancer screening visit, 3-months after baseline, and 6-months after baseline. At 6 months cotinine salivary sample will be collected on participants who self-report ***not*** smoking within the last 7 days. The patient schedule of events is as follows:

Prior to Enrollment:

- Eligibility Assessment
- Informed Consent

In-Person, Interviewer-Administered Baseline Survey:

- Complete the baseline questionnaire at the time the patient presents for screening, prior to their scan.

Survey Between 1-14 Days After the Lung Cancer Screening Appointment:

- ≤14 Day Telephone Patient Survey

3-Months after the Lung Cancer Screening Appointment:

- Complete the 3-Month Telephone Patient Survey
- CRA completes Lung Cancer Screening Imaging Report

6-Months after the Lung Cancer Screening Appointment:

- Complete the 6-Month Telephone Patient Survey
- Saliva collection only for patients who self-report not smoking within the last 7 days

Evaluation of the intervention depends on surveys (Baseline, ≤14 days of the lung cancer screening visit, 3-months after baseline, and 6-months after baseline). At 6 months, a cotinine salivary sample will be collected on participants who self-report ***not*** smoking within the last 7 days.

Study Patient Assessments	Screen In-person	Baseline In-person	≤14 days Telephone	3-months Telephone (7 days prior and up to 21 days after)	6-months Telephone (7 days prior and up to 21 days after)
Eligibility Checklist	X				
Reason for Refusal (Baseline)		X			
Patient Survey Baseline		X			
Reason for Refusal (Follow-up)			X	X	X
Patient Survey ≤ 14 Days			X		
Patient Survey 3 Months				X	
Lung Cancer Screening Imaging Report				Appended at time of 3-month survey	
Patient Survey 6 Months					X
Cotinine validation of smoking status, for those who self-report not smoking					X

7.2 Patient Baseline Testing/Pre-study Evaluation

All individuals who visit a participating lung cancer screening program will receive a single page document that informs him/her that the site clinic is participating in the study, regardless of his/her eligibility or interest. This will be an information-only sheet provided at check-in which describes the purpose of the study. Trained NCORP clinical site personnel will screen individuals for eligibility during a regularly scheduled lung cancer screening visit. If the individual meets all eligibility criteria and agrees to participate, trained NCORP site staff at each NCORP clinic site will seek interest and written informed consent for participating in the study.

Participants taking nicotine replacement therapy or other pharmacotherapy to promote smoking cessation (e.g., bupropion) will be excluded if taking these medications at baseline—See exclusion criteria. The NCORP clinical site staff will measure whether the participant begins taking these over-the-counter and prescribed medications at the ≤14 day, 3-month and 6-month follow-up surveys in order to measure

intervention effectiveness. It is not necessary to obtain concomitant medications for these participants as the collection of this information would pose an unnecessary burden to participants and is not needed to answer the questions in this research study.

Individuals who decline participation will be asked to complete the brief decline form which includes basic demographic information and primary reason for declining study participation.

Patient surveys (baseline, ≤14 days, 3 months, and 6 months) are found in Appendices 9-12. Core measures include: demographics, health status, smoking history, quitting behavior, perceptions of lung cancer risk and worry, impact of screening on tobacco use behavior, and exposure to the intervention. The baseline assessment will be administered by an interviewer and completed in-person. All responses will be hand recorded by NCORP site staff on paper forms and/or entered directly into the online database. If data are collected on paper forms, NCORP site staff will be responsible for entering the data into REDCap. We will also collect contact information from a secondary contact person (Appendix 9) that will be stored in a separate de-identified data entry screen.

Participants will receive a $10 gift card at the time the Baseline survey is completed. Gift cards will be supplied directly to the NCORP site coordinator at each participating clinic for the baseline data collection and given out by the site coordinator/data collector. They will be distributed at the completion of the survey.

7.3 Patient Evaluation During Study Intervention

NCORP site coordinator will call each participant to administer a 5-minute telephone survey within 14 days of the lung cancer screening clinic visit. Participants will receive a $10 gift card following completion of the 14 day telephone survey, distributed by Wake Forest Study Team as described in Section 7.4. This assessment focuses on exposure to the intervention and subsequent quit attempts.

7.4 Patient Follow-up Period

Short- and long-term abstinence will be measured by telephone survey at 3 months and by telephone survey with cotinine validation for non-smokers 6 months after baseline. These surveys should take <5 minutes and will assess quit attempts, smoking cessation, and strategies used to try quitting. Patients will be offered a $10 gift card for participation at each wave of the survey and $20 for returning the saliva sample. Gift Cards will be mailed to participants by the Wake Forest Study Team.

To minimize attrition, NCORP study staff will mail pre-printed/pre-postage paid sealed postcards to participants 1-2 weeks prior to the 3- and 6-month follow-up surveys. At least three attempts will be made to reach each participant by phone. As a final step, the team will consider a mailed survey to non-respondents with an enclosed incentive.

Rationale and Strategies for Minimizing Attrition:
In a study led by PI Kristie Foley, we trained safety net clinic staff how to integrate the PHS Guidelines and support cessation during routine clinical visits. Ninety-nine percent of patients who were approached during their clinical visit agreed to participate in the baseline survey.[16]

In Strecher et al.,[49] of the potential 3256 patients who visited an HMO, 2651 were screened for eligibility (81%). Of those, approximately 60% were eligible to participate (with the main reason for ineligibility was too limited smoking or contraindications of NRT usage). We proposed that we would need to screen 2500 at baseline to identify 1,114 eligible smokers (45%). At six month follow-up, 76% were retained in the cohort and were contacted by telephone to complete the survey.[49] We proposed that 75% of the

original cohort would be retained at 6-months, consistent with the Strecher et al. study.

In Bock et al.,[50] low-income smokers were recruited and assessed at baseline, 1 month, 2 months, 6 months, and 12 months with biochemical verification of smoking status at each of the follow-up time points. In this study 16% of participants dropped out immediately after the baseline assessment.

If we find that we have a higher than expected drop out at our ≤14 day assessment (we expect 7%), we will be well-positioned to recruit additional participants to ensure that we sustain at least 75% of the original cohort at the 6-month time point (the primary endpoint). We will work closely with our statistical team to assess attrition at ≤14 days and 3 months.

The following strategies will be used to minimize attrition:

- Including secondary contact information as part of the baseline patients survey (maintained in a participant de-identified secondary data base)
- Sealed reminder post cards, 1-2 weeks prior to the telephone survey
- Pre-printed/pre-stamped sealed "thank you" post cards with enclosed gift card, after completing a survey
- Mailed survey with incentive included in the mailing (as a final resort)

This is a surveillance study and participants are only indirectly targeted by the intervention as a result of being screened in intervention clinics, whereby minimizing participant burden and maximizing follow-up. Participants will receive a $10 gift card at each wave of the survey and $20 for completing the salivary cotinine at 6-months.

We will carefully monitor accrual. Given that we have a ≤14 day follow-up survey, we will be able to assess any concerns with early drop out and be able to recruit additional patients to the study. We will work closely with our statisticians to ensure adequate accrual and maintenance of the cohort.

Self-reported smoking status will be validated at six months using salivary cotinine among patients who report successful quitting during the 6-month telephone survey. When a research participant self-identifies as a non-smoker at 6-months, this will be an electronically 'flagged' response, such that this will trigger the distribution of the cotinine assay from the Wake Forest NCORP Research Base Lab located in Winston-Salem, NC. The Wake Forest NCORP Research Base Lab will be responsible for shipping kits and receiving the cotinine samples.

Cotinine, a major metabolite of nicotine with a long half-life, is highly sensitive and specific for tobacco use, making it an excellent test for confirming tobacco cessation. [37] Patients will receive via mail a salivary collection kit (including a salivette—a plastic vial that contains a small cotton roll, like those used by dentists) along with written instructions on how to obtain the salivary sample. The written instructions will explain that participants should place the absorbent roll under their tongue for 1-2 minutes and then replace the roll in the storage tube. They should collect the sample in the morning before breakfast and coffee, or drinking, and before brushing their teeth. The completed test kit should be returned to Wake Forest NCORP Research Base Lab within one week. This is a validated procedure for collecting saliva via mail.[48]

Saliva samples will be collected from subjects using SalivaBio Oral Swab saliva collection kits available from Salimetrics, Inc. (Carlsbad, CA). Saliva specimens will be mailed to the NCORP Research Base Core Lab, centrifuged to collect the saliva from the swabs, the volume measured, and transferred to smaller freezer tubes for storage of the specimen at -80°C. Cotinine levels will be determined by ELISA

using the high sensitivity Salivary Cotinine quantitative Enzyme Immuno Assay kit provided by Salimetrics, Inc. This is a competitive immune assay kit with a determination range from 0.8 to 200 ng/mL. Saliva samples will be analyzed in duplicate. When the determined level of a sample is above the upper range of the ELISA (200 ng/mL), the assays will be repeated with a higher sample dilution to obtain cotinine levels within the standard range of the assay. Analysis will be conducted by the Wake Forest NCORP Core Lab located in Winston-Salem, NC.

To maximize validation, NCORP site staff should encourage the return of the saliva kits at the completion of the 6 month survey. Participants that do not return the kit within three weeks of mailing will be contacted by site staff to determine if the participant did not receive the kit or chose not to complete the kit. If the participant indicates that they would still like to participate and complete the kit, an additional kit may be mailed to them. Participants will be given a $20 gift card for returning the saliva sample. Once the specimen is received, the WF project manager will be notified and the gift card will be mailed by the WF project manager. Results of the assay will be recorded by the Core Lab.

7.5 Methods for Patient Clinical Procedures- NA

7.6 Clinic Assessment

NCORP sites will be invited to participate in the study via email and participating components/subcomponents will be asked to confirm their agreement to participate. If a component/subcomponent chooses not to participate, another component/subcomponent will be selected from the remaining eligible components/subcomponents within that NCORP site and/or another NCORP site will be invited to participate.

Prior to randomization, each participating component/subcomponent will complete the Pre-Randomization Site Checklist (Appendix 18). We will assess the distribution of lung cancer screening volume and % white, non-Hispanic in the population of patients seen for lung cancer screening at the imaging facility and decide on approprite cutpoints for strata. For current cessation services offered, we performed a short survey that assessed 10 possible cessation support services (e.g., medication, counseling, QuitLine) that could be offered, and determined that a threshold of 0-5 versus 6+ should be used to stratify sites. The actual values (volume, cessation services score, and % white, non-Hispanic) will be available as site level covariates that can be included in final analytical models when assessing the intervention effect. In addition, individual level variables (race/ethnicity) can also be adjusted for in the final models if needed.

Both intervention and usual care clinics will complete the baseline organizational characteristics assessment (Appendix 8) and the follow-up organizational characteristics assessment (Appendix 23). Key informant interviews will be conducted by phone by a Wake Forest Study Team Member for both intervention and usual care clinics. The semi-structured surveys and interviews will be performed at baseline and at a follow-up time point, approximately 8 months later.

Study Site Assessments	Eligibility	Selection	Randomization	Baseline	~8 mo Follow-up
Preliminary Eligibility Checklist	X				
Site Invitation to Participate		X			
Pre-Randomization Site Checklist		X			
Baseline Organizational Characteristics			X		
Key Informant Interview & Guide (Used by Wake Forest Study Team Members when conducting the Key Informant Interviews)				X	
Follow-up Organizational Characteristics					X
Key Informant Follow-up Interview & Guide (Used by Wake Forest Study Team Members when conducting the Key Informant Interviews)					X

7.7 Core Elements and Guiding Assumptions of the Intervention

Our multi-faceted training program targets health care delivery system changes (e.g., providers, clinics); therefore, all patients seeking LDCT screening at a single site will be in either the intervention or usual care arm of the RCT. Usual care clinics will receive instruction in evaluation and invited to attend a regional training program during Fall 2019. Intervention clinics will begin the training program via webinars.

Our multi-faceted training program includes: (1) webinars on evidence-based strategies to assist patients with quitting and strategies that can be used to arrange follow-up services; (2) in-person site-specific SWOT analysis and logic model development to guide implementation of the PHS Guidelines; and (3) performance coaching for eight months during the implementation phase. The rationale for our approach is based on the following. First, we have evidence-based guidelines to promote cessation that have been tested in various clinical venues and have demonstrated success via meta-analyses. We cannot assume, however, that the Guidelines will be efficacious in the context of LDCT lung cancer screening. Second, the strategies that accompany these guidelines are likely to be adopted if they are easy to implement (e.g., they are time and cost neutral, they are well-received by the implementers, they fit within the mission of the organization) and with implementation support. Third, strategies may be adapted to simplify implementation and adaptation can happen without sacrificing the PHS Guidelines integrity. Adaptation is an important part of implementation that should be measured and accounted for.

Part 1: Webinar-Based Training

The webinar-based training protocol includes:

- Tobacco Cessation during Lung Cancer Screening
- Overview of the PHS Guidelines
- Brief Intervention for Behavior Change, Motivational Interviewing, Pharmacotherapy
- Using Logic Models for Implementing the PHS Guidelines

Each webinar will be offered "live" two times (to accommodate different time zones) and will also be recorded and stored on the team website so that they may be viewed by personnel who could not

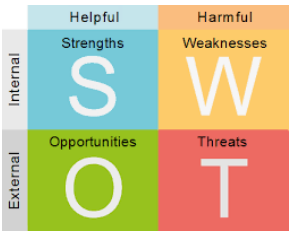
participate in the training.

Table 2: Training components of evidence-based smoking cessation strategies include:	
Provider Strategies • Setting, charting, and follow-up on a quit date • Motivational interviewing strategies to promote quitting. (The team will be introduced to common misperceptions and rationalizations for not quitting identified in the literature to incorporate counseling on how to address barriers.) • QuitLine referral • Pharmacotherapy options as outlined in the NCCN guidelines (e.g., varenicline, nicotine replacement therapy, bupropion) • Identify and refer patients to hospital-based or other community resources for quitting, including intensive counseling. • Webinars to share with the site clinicians strategies for assisting patients with quitting and ensuring follow-up.	Health Care Delivery System Strategies • How to embed electronic prompts for assist and arranging follow-up. If EHR prompts are not possible, identify an easy and low-cost "prompt" for providers (e.g., a tickler file) to ensure follow-up for cessation post-visit. • Enrolling patients in publically-available and free mobile health programs for smoking cessation such as iPhone/Android apps, text messaging, and web-based resources • Offering intensive counseling for patients who resist quitting or who fear relapse. • Fax and electronic referrals for the QuitLine
The Wake Forest study team will spend up to $300 per site to purchase environmental cues to promote cessation: e.g., "While you wait" videos to promote cessation during the screening encounter; low-cost brochures for patients in the waiting rooms; low-cost posters for waiting rooms and patient rooms; pre-printed prescription pads designed for pharmacotherapy. The research team has prior experience helping clinics select environmental cues for site-specific tobacco cessation materials using low-cost and publicly-available resources. We will also discuss strategies for maintaining a stock of environmental cues.	

Part 2: In-Person, Site-Specific SWOT Analysis and Logic Model Implementation: This training will be conducted onsite at each intervention clinic by at least one clinician and one behavioral scientist.

SWOT is a strategic planning technique to evaluate Strengths, Weaknesses, Opportunities, and Threats to assess the likelihood of adopting a new strategy within a health care delivery system. SWOT analysis has been used extensively in business contexts, when new programs or policies are introduced. The approach is highly applicable to health care delivery systems change, especially when introducing new strategies for cessation support within rapidly evolving lung cancer screening programs. This approach recognizes that, while the PHS Guidelines offers a common set of strategies for cessation (taught during the morning session), that implementation will be influenced by internal and external forces, such as organizational structure, screening processes, and culture of each clinic.

Stages of the SWOT Analysis: The trainers will explain the SWOT process, help clinics identify strengths within the organization (e.g., dedicated staff for smoking cessation), identification of weaknesses (e.g., lack of training of clinicians or other personnel), list opportunities that are external to the organization that may affect implementation (e.g., availability of free/low cost resources that promote cessation), identify the strategies that are immediately ready for implementation and others that may require support after training. Barriers we may hear include: provider lack of time to counsel and provide pharmacotherapy, fear that smoking cessation counseling during the screening encounter will reduce the likelihood of return for their annual LDCT screening, lack of knowledge/skill for counseling and pharmacotherapy prescribing; lack of available external resources; lack of support from hospital



administrators, lack of care coordination between primary care provider and screening providers; lack of follow-up with patients after screening is complete.

Logic Model Development & Implementation: Each clinic will identify strategies that can be implemented immediately with limited resources (short-term outcomes) and those that will require adaptation or post-training support (long-term outcomes). We will prioritize strategies that focus on "assisting" patients with cessation and "arranging" follow-up care for patients who want to quit. These strategies will be conceptually mapped using a logic model (including inputs, activities, short-term, and long-term outcomes) to clearly identify the "points of interventions" for implementing evidence based cessation strategies. We will guide each clinic through development of its own logic model, but we expect that a few logic model "templates" will emerge that will ultimately allow our team to characterize implementation of cessation services within LDCT screening programs (Aim 2).

We will provide a variety of evidence-based cessation strategies, some that require very limited resources and are very easily implemented with minimal interruptions to clinic flow. Other cessation strategies require more resources and may have a greater impact on work flow. As a result, we have designed the implementation process to be responsive to each clinic's existing resources and ability to implement change.

Our team has experience using SWOT, logic models, and performance coaching to improve the translation of science into practice and policy changes in consecutive tobacco control capacity building projects (Foley, PI; Spangler, Sutfin-Co-Is).

A Theory-Guided Intervention: The SWOT analysis and strategic planning session uses constructs from organizational change theories (e.g., Diffusion of Innovations). These constructs include organizational climate and culture (compatibility of the evidence-based tobacco cessation with the clinical mission of LDCT screening) .[22] We will also measure organizational readiness to implement the evidence-based strategies (self-efficacy of the providers and program leaders, as well as relative value of the PHS Guidelines services relative to other required services).[38] We expect implementation of cessation strategies to depend on simplicity of the services (e.g., pharmacotherapy prescribing versus intensive onsite counseling), trialability or allowing differing strategies to be used in different clinics (willingness to allow clinics to adapt services to the local needs), and observability of clinic, provider, and patient benefits (creating systems for feedback on success of cessation services in promoting quitting among screening patients).[39–42] Following SWOT analysis, the teams will come together for a small group meeting to share their logic models and then hear an overview of the performance coaching aspect of the training program.

Step 3: Performance Coaching: Coaching has predominantly been used in performance management as a strategy for offering ongoing support and feedback to employees.[43,44] Performance coaching is an adaptable methodology aligned with the unique needs of lung cancer screening sites. "Coaches" provide support and feedback that is timely and clear as a method to help clinics implement smoking cessation services.[43] There are four main dimensions to coaching in this context: (1) providing direction, which includes clear articulation of the goals and values of implementing tobacco cessation services during LDCT screening; (2) offering support during implementation (identifying gaps in implementation and helping identify improvements); (3) engaging personnel within the LDCT screening process in problem-solving; and (4) identification and removal of barriers to implementation. Papadakis et al (2015) have an ongoing trial to use performance coaching to enhance quit rates of cessation treatment delivered by primary care providers (PCPs).[45] This team is offering performance coaching for PCPs for 2-4 weeks following a training session on how to ask, advice, and assist patients with quitting.

We will use active and reactive performance coaching. Each site will have a coaching team: two members of our research team including an expert in tobacco cessation and an expert in lung cancer screening. Active coaching includes six, 1-1 ½ hour video exchanges among program sites and coaching teams, once every 4-6 weeks over an 8-month implementation phase. One week prior to the call, each site will be prompted with an email to inform the coaching team of any challenges associated with implementation. The coaching teams, in consultation with the EAB, will identify potential solutions to the identified problems during the call. Reactive coaching: Unsolicited successes and barriers during implementation may also be submitted to a team blog.

The Wake Forest project manager in consultation with the coaching team will identify potential solutions during the interim period between active coaching video calls. Using data from the active and reactive performance coaching notes, we will develop and continuously update a list of frequently asked questions (FAQs) and responses that were generated. The intent using a team blog is to share information with NCORP intervention sites is to create a co-learning experience during the implementation phase of the project. [46]

Who will participate in coaching? We encourage all Program Champions to participate in each active coaching session. Other personnel who would like to discuss 'best practices' for implementing the PHS Guidelines, brainstorm strategies to overcome implementation barriers, and discuss new strategies that are working well for their clinic are also invited and encouraged to participate, although this is not required.

7.8 Summary of Expectations for Participating in this Study

- **Webinars:** Cessation Program Champions and staff who are central to implementing the PHS Guidelines (expected to vary from site-to-site) are expected to watch the training webinars prior to the onsite visit. We encourage sites to watch the webinars live, but they will be recorded and available to maximize the opportunity for staff to watch the training videos. Total time commitment 3.5 hours over a period of 2-3 months, prior to the onsite visit. Intervention Sites only, initially. Available to Usual Care Sites later in the study, post-data collection.
- **SWOT Analysis and Logic Model Implementation:** Requires onsite visit with Program Champion and other key staff central to implementing the intervention. The intensity of the visit will depend on the clinics needs and readiness to engage in the logic model exercise. We anticipate the onsite 'training' will be ~ 2 hours. Intervention Sites only, initially. Available to Usual Care Sites later in the study, post-patient data collection.
- **Active Performance Coaching:** A video web conference will be held once every ~6 weeks and is expected to last approximately 1 hour. The Program Champion must participate. Others are welcome, but not required. Intervention Sites Only.
- **Reactive Performance Coaching:** This is on an as-needed basis, so the time commitment will depend on the needs of the clinic. Intervention Sites Only.
- **Coordination of Site Visit:** Our team will visit each intervention site twice and each usual care site once. We will need local support for managing the site visit and can work with NCORP personnel and the Program Champion to identify the best time, venue to minimize disruption to the clinic. Intervention and Usual Care Sites.

Team Blog: The team blog will be developed at Wake Forest with support from the biostatistics team and maintained by the Project Manager. We will use WordPress.org as the software platform. WordPress.org is an open source software platform allowing our team to build and maintain the blog. WordPress allows for the entire blog to be "private" and password protected. The Program Champion will be given the site password and asked to share with the imaging facility staff. We will explain the use of the blog as part of our onsite training.

7.9 Develop and Evaluate an Implementation Toolkit

The goal of the Implementation Toolkit is to support the successful implementation of evidence-based tobacco cessation strategies into clinical settings with LDCT lung cancer screening programs, in the absence of a research study. The Implementation Toolkit will be developed by the research team following implementation of the program into the 13 intervention sites in Aim 1 and using extensive, qualitative implementation data generated from Aim 2. NCORP components/subcomponents will not be required to participate in this aspect of the research study.

Using the SWOT analyses, the team blog and performance coaching notes, and key informant interviews, we will identify challenges faced during implementation and common strategies for overcoming these barriers. We will also explore what training tools were most useful and how those could be translated into a toolkit. We intend for the Implementation Toolkit to be comprehensive so that it can be used to guide the successful implementation of the PHS Guidelines in real-world settings after the research study. The research team will meet bi-weekly during a 6-8 month period to develop and refine each section of the comprehensive toolkit with monthly calls with EAB members. Sections will be brief and written in clear, simple language with step-by-step planning templates (where available). After each section is developed and refined, the document will be reviewed by the EAB and program champions from the early intervention clinics, as well as national stakeholders from professional medical societies (e.g., ASCO) and non-profit agencies committed to cancer prevention and smoking cessation (e.g., ACS, Legacy). This will be an iterative process with multiple opportunities for feedback. We have identified potential sections of the toolkit in Table 4, however, additional sections will be identified during the development phase. We have used a similar process on another study *Reducing HIV Disparities among Latinos: Disseminating an Effective Intervention* (R24MD002774, Rhodes, PI, Sutfin, Co-I).

Table 4. Toolkit for Implementing Evidence-Based Tobacco Cessation Strategies in LDCT Lung Cancer Screening Programs

Section Title	Description
How to use this toolkit	Explain how to use the Toolkit, its intended audience, and its organizational structure.
Why is smoking cessation important for LDCT patients?	Provide foundational knowledge about the importance of smoking cessation for patients being screened for LDCT
What are the PHS Guidelines for Tobacco Use and Dependence?	Provide an overview of the evidence-based strategies used in clinical setting to help tobacco-using patients quit.
Assessing our clinic's readiness to implement the evidence-based strategies using a SWOT analysis	Guide a clinic through the stages of SWOT analysis to determine if the clinic is ready for program implementation.
What if our clinic isn't "ready"	Describe strategies for increasing readiness to adopt.
What does it take to implement the PHS Guidelines?	Describe the personnel and budget resources required, as well as support from clinic administrators.
The role of the program champion	Describe the importance of selection of and role the program champion will play.
Roadblocks, detours, and delays	Help strategize when barriers to implementation arise.
How to adapt the PHS Guidelines to meet our clinics' needs	Discuss options for adapting systems-level approaches to meet the needs of individual clinics.
Sustainability	Describe approaches for sustainability.
Appendices: Assessing patients readiness to quit; Providing quit assistance; An introduction to	

quitlines; What you need to know about smoking-cessation pharmacotherapy

External Advisory Board: The EAB is charged with providing scientific and pragmatic support to the research team on the development of the intervention materials, facilitating and measuring implementation of smoking cessation into LDCT lung cancer screening sites, and developing an implementation toolkit. The EAB includes national and international experts in smoking cessation, lung cancer screening, and implementation science. We anticipate monthly EAB meetings with the research team and 8 additional "ad hoc" meeting hours per year. The EAB leader serves as the liaison to the research team and provides organizational oversight for the EAB. For his contribution, we anticipate 10 days per year of service.

Members of the EAB:

- Graham Warren, MD, PhD. EAB Leader. Med. Director for Tobacco Control at MUSC. Dr. Warren has led the development of cessation programs at Roswell Park Cancer Institute and MUSC, using opt-out strategies for cessation support and highly effective dissemination methods. He serves as Chair of member for tobacco committees for several leading caner organizations as well as the NIH, all devoted to effectively reducing the harms of tobacco through a variety of means including implementation of evidence-based support.
- Adam Goldstein, MD, Professor of Family Medicine, UNC. Dr. Goldstein has been extensively involved at the national, regional, state, and medical school levels in tobacco control research and evaluation for over 20 years. He has an exceptionally strong background in clinical tobacco cessation, and serves as the director of the UNC Tobacco Intervention Programs. In this position, he has implemented evidence-based tobacco cessation practices in the inpatient, outpatient and employee health settings.
- Judith Ockene, MD, University of Massachusetts, Barbara Helen Smith Chair in Preventive and Behavioral Medicine and Professor of Medicine and Chief. Dr. Ockene has developed tobacco cessation training programs for tobacco treatment specialists, medical schools, medical students and residents, as well as practicing physicians. These have been local, regional and national in scope. She was also part of NCI's Community Intervention Trial for Smoking Cessation (COMMIT) Study group, a very large and well recognized study, which also had a strong evaluation component.
- Phil Boiselle, MD, Beth Israel Deaconess Hospital. Dr. Boiselle's research focuses upon the application of advanced airway imaging methods to a variety of benign and malignant airway disorders. Dr. Boiselle served as the site principal investigator for the National Lung Screening Trial from 2002 through 2009. In May 2012, he was appointed Associate Dean for Academic and Clinical Affairs at Harvard Medical School. In January 2017, Dr. Boiselle became the Dean of the Charles E. Schmidt College of Medicine at Florida Atlantic University in Boca Raton, FL.
- Michael Gould, MD, MS is a Senior Scientist and Director for Health Services Research at Kaiser Permanente Southern California. He leads NCORP cancer care delivery efforts for Kaiser Permanente Southern California through the Kaiser NCORP community site. He will contribute expertise on health services research, lung cancer screening, and cancer care delivery research within NCORP to the EAB. *As a member of the EAB and with existing cessation services in the Kaiser system, Dr. Gould agreed that Kaiser will not participate in the study.
- Geoffrey Curran, PhD. Dr. Curran has expertise in implementation science with a particular emphasis on designing and testing implementation strategies to support the adoption and sustainability of evidence-based practices. Additional interests include: 1) formative evaluation methods to assist in developing and revising implementation strategies based on data derived from local contexts, and 2) "hybrid effectiveness-implementation" designs which combine elements of clinical/preventive effectiveness and implementation research to speed the translation of EBPs. He serves on the Editorial Board of Implementation Science.

- Alice Ammerman, PhD, University of North Carolina-Chapel Hill. Dr. Ammerman is an expert in dissemination and implementation research. With NIH colleagues, she hosted the first annual Training Institute on Dissemination and Implementation Research and recently completed a tenure on the NIH study section for dissemination and implementation research.

Stakeholders will be asked to evaluate the quality of each section of the toolkit, as well as quality of presentation (toolkit design, length, level of interest/engaging material, and perceived usability by LDCT screening practices) on a scale of 1 to 5 (1=poor, 3=average, 5=excellent) with an opportunity for comments for each rating. In addition, the stakeholders will identify potential dissemination outlets for scale-up of the toolkit. After receiving feedback, we will conduct a conference call with the evaluators to aid the research team and EAB to improve the toolkit for dissemination based on the evaluation. Using this information, the research team in partnership with the EAB will develop a dissemination plan for the Implementation Toolkit.

8. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

8.1 Summary Table of Endpoints, Measures, Measurement Strategies, and Time Points

	Measure	**Measurement Strategy**	**Time Point(s)**
Primary Endpoint (Effectiveness, Aim 1)	**7-day sustained smoking abstinence with cotinine validation**	Patient survey & mailed saliva sample for non-smokers	6 months
Secondary Endpoints (Effectiveness, Aim 1)	**Short-term smoking abstinence (self-reported)** **Quit Attempts**	Patient survey	3 months after baseline
Secondary Endpoints (Implementation, Aim 2	**Fidelity to the Intervention** Patients are asked if they received 18 cessation services during the screening visit—see Appendix 10, Questions 4a-4r.	Patient survey	≤14 days after baseline
Secondary Endpoints (Implementation Aim 2)	**Feasibility & Appropriateness** of offering services that promote cessation. See Appendix 5 & 21.	Key informant interview- including structured survey and semi-structured interviews (~3/clinic)	Baseline And Follow-Up (8 months after baseline)

8.2 Primary Endpoint, Aim 1 (Effectiveness)

Six months after the screening visit, the project manager will conduct a 5-minute telephone survey to measure long-term abstinence. Items will include current tobacco use, quit attempts in the past 6 months, and 7-day nicotine abstinence by asking when they last smoked a cigarette, and any changes in demographic characteristics. The validated question that measures 7-day smoking abstinence is below.

Have you smoked a cigarette (or other tobacco products), even a puff, in the last 7 days?

☐Yes
☐No
☐Refused

Biochemical Validation: We will validate self-reported smoking status at six months for self-reported non-smokers using salivary cotinine among patients who self-report successful quitting at 6-months. Cotinine, a major metabolite of nicotine with a long half-life, is highly sensitive and specific for tobacco use, making it an excellent test for confirming tobacco cessation.[37] Salivary cotinine levels less than 15ng/ml are consistent with no tobacco use for the prior 7 days. For biochemical verification of smoking cessation, we will overnight mail a saliva collection kit with a postage-paid return mailer to participants. This will be explained to participants during the 6-month telephone survey so that they will expect the saliva collection kit. We include information regarding salivary cotinine data collection in the patient informed consent document.

See Appendix 17 for the information that will be included in the salivary cotinine mailer to participants.

8.3 Secondary Endpoints, Aim 1 (Effectiveness)

Short-term smoking abstinence (self-reported) and quit attempts will be assessed via patient telephone survey 3 months after the lung cancer screening visits. See Appendix 11, Patient Survey 3 Months.

8.4 Secondary Endpoints, Aim 2 (Implementation)

Fidelity: Fidelity, in this study, is defined as the adoption of PHS Guidelines for cessation. We measure fidelity in two ways: from the perspective of the patient via telephone survey and from the perspective of lung cancer screening staff (aka "key informant" interviews).

For patients, fidelity is measured using the ≤14 days survey (see Appendix 10). The interviewer asks:

During your (lung cancer screening) visit, did any doctor, nurse or other health care provider offer the following support? Answer "yes" or "no".
There is a list of 18 cessation support items on the patient survey. See the following for examples:

- Advise you to quit
- Ask how important it is for you to change your tobacco use behavior
- Prescribe or recommend any kind of nicotine replacement therapy
- Suggest you enroll in a cell phone or tablet-based "Text to Quit" program

Fidelity is also measured from the lung screening staff perspective. We ask the staff (aka "key informants") to indicate how often they provide a list of cessation services. Response options are Never, Rarely, Sometimes, Most of the Time, Always (see Appendix 5 and 21).

Appropriateness and Feasibility: The secondary implementation endpoints, appropriateness and feasibility, are measured by asking lung cancer screening staff (aka "key informants") whether they strongly disagree, disagree, agree or strongly agree that cessation services are appropriate and feasible to implement in their clinic. We ask about 20 different smoking cessation services (see Appendix 5 and 21).

Feasibility: "Providing (insert cessation service) is feasible for our lung cancer screening clinic."

Appropriateness: "Providing (insert cessation services) is appropriate for our clinic."

We expect that clinics in the intervention arm will report a greater percentage of cessation services as feasible and appropriate at follow-up compared to baseline. We do not expect to observe a change in the control clinic.

8.5 Off-Study Criteria

Participants may go 'off-study' for the following reasons: the protocol intervention and any protocol-required follow-up period is completed, AE/SAE, lost to follow-up, non-compliance, concomitant medication, medical contraindication, withdraw consent, death, determination of ineligibility. For participants who go 'off-study' or are considered 'lost to follow-up' the Reason for Refusal Follow-up form (Appendix 4) should be completed.

8.6 Study Termination

NCI, DCP as the study sponsor has the right to discontinue the study at any time.

9. CORRELATIVE/SPECIAL STUDIES - NA

10. SPECIMEN MANAGEMENT

10.1 Laboratories

For biochemical verification of smoking cessation, we will overnight mail a saliva collection kit with a postage-paid, pre-labeled return mailer to participants from the Wake Forest NCORP RB Core Lab located in Winston-Salem, NC.

10.2 Collection and Handling Procedures

Patients will receive via mail a salivary collection kit (including a salivette—a plastic vial that contains a small cotton roll, like those used by dentists) along with written instructions on how to obtain the salivary sample. The salivary collection kit will be pre-labeled with a study identifier that can later be linked to the patient survey data.

The written instructions explain that participants should place the cotton roll under their tongue for 1-2 minutes and then replace it into the plastic vial. They should collect the sample at least 30 minutes after eating or drinking and before brushing their teeth. The initial informed consent explains the procedure, the risks and benefits of participation, the notice that there is no penalty for not participating, information on how to contact the IRB and the study team personnel. Individuals will return the salivary sample using a FedEx biospecimen approved mailer.

Saliva samples will be collected from subjects using SalivaBio Oral Swab saliva collection kits available from Salimetrics, Inc. (Carlsbad, CA). Saliva specimens will be received in the Research Base NCORP Core Laboratory, centrifuged to collect the saliva from the swabs, the volume measured, and transferred to smaller freezer tubes for storage at -80°C. Cotinine levels will be determined by ELISA using the high sensitivity Salivary Cotinine Quantitative Enzyme Immuno Assay kit provided by Salimetrics, Inc. This is a competitive immuneassay kit with a determination range of 0.8 to 200 ng/mL. Saliva samples will be analyzed in duplicate. In our experience with other studies, cotinine levels typically fall between two extremes with few intermediate values. Nonsmokers have no detectible cotinine whereas smokers often have levels above 200 ng/mL. When the determined level of a sample is above the upper range of the

ELISA (200 ng/mL), we will repeat the assays with a higher sample dilution to obtain cotinine levels within the standard range of the assay.

Analysis will be conducted by the WF NCORP RB Core Lab. Salivary cotinine levels less than 15ng/ml are consistent with no tobacco use for the prior 7 days. To maximize validation, participants will receive a $20 gift card for returning the saliva sample. Responses will be recorded by the Core Lab personnel conducting the analysis.

For the Research Team
Upon receipt of the salivary sample by the research team, the team will follow standard OSHA procedures for biospecimens, including wearing gloves while handling the salivettes and extracting the dental rolls via forceps. The Research Assistant will use gloves while handling the salivettes and forceps to collect the saliva samples. All materials used for collecting the saliva samples will be disposed of in accordance with OSHA regulations.

Labeling and Tracking
All salivary collection kits will be labeled with a unique study identifier allowing the data to be linked to survey data. A tracking log will be maintained, which will include the study identifier and the data shipped and received.

Temperature & Storage Requirements
Using the procedures outlined in Etter et al.[48], salivettes will be stored, upon reception, in a refrigerator at 4 degrees Celsius. Liquid contained in the salivettes will be extracted using centrifugation (500 g/2min) and cotton rolls removed. After centrifugation, saliva samples will be frozen at -20 degrees Celsius until ready for analysis by gas-liquid chromatography. Laboratory, centrifuged to collect the saliva from the swabs, the volume measured, and transferred to smaller freezer tubes for storage at -80°C.

10.3 Shipping Instructions

All biospecimens will be mailed in approved biospecimen mailers. Biologic specimens collected during the conduct of each clinical trial that are not used during the course of the study will be considered deliverables and the property of WF NCORP RB. At study completion, WF NCORP RB will discard any unused biological specimen unless otherwise specified in the protocol document.

11. REPORTING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS (AES AND SAES)

This is a group randomized controlled trial with minimal risks. NO routine Adverse Events or Serious Adverse Events are reported.

12. STUDY MONITORING

12.1 Data Management
The Eligibility checklist/Registration Form should be completed on-line. NCORP study site staff will enter data directly into the study website within the timeframe given in the table below.

Patient Forms	Submission Schedule	Responsible for Data Entry
Eligibility Form	within 14 days of registration	Site Staff
Patient Informed Consent	within 14 days of registration	Site Staff
Baseline Measures	within 14 days of completion of baseline survey	Site Staff
Exposure to the Intervention ≤14 days)	within 14 days of completion of baseline survey	Site Staff
Intermediate Outcomes (3-month survey & Lung Cancer Screening Report)	within 14 days of completion of 3-month survey and Lung Cancer Screening Report	Site Staff
Primary Outcomes (6- month)	within 14 days of completion of 6-month survey	Site Staff
Site Forms	**Submission Schedule**	**Responsible for Data Entry**
Pre-Randomization Site Checklist	within 14 days of site selection	Site Staff
Site Invitation to Participate	within 14 days of site selection	N/A
Baseline Organizational Characteristics	within 21 days of site randomization	Site Staff
Follow-up Organizational Characteristics	within 30 days of completion of the follow-up key informant interviews	Site Staff

12.2 Case Report Forms

Participant data will be collected using protocol specific case report forms (CRFs).

12.3 Source Documents

The sources of research material will include information provided through participant surveys, intervention sessions, key informant audio-recorded transcripts, and self-report questionnaires specifically for this research study. We will also obtain the lung cancer imaging report, de-identify the report, and append the report to the survey data. The imaging report will be obtained to ensure that the Lung RADS score (reported by staff on the 3-month survey) is accurate and complete, which is a required element of the SCALE collaborative.

A number of steps will be taken to ensure the confidentiality of research data collected during the study. All forms will be stored in locked file cabinets. Names will be removed from all forms and records and replaced with participant numbers. Audio-recorded sessions will be erased upon completion of transcription and transcripts will be recorded without personal identifying information. Information stored in the computer will be password protected. Only members of the investigative team will have access to any participant information and data. The identities of participants will not be revealed in publications and presentations of any results from this project. Procedures specified in the consent form are consistent with HIPAA regulations.

An investigator and other designated staff are required to prepare and maintain adequate and accurate documentation that records all observations and other data pertinent to the investigation for each individual participating in the study. All data recorded in the research record (including data recorded on CRFs) must originate in the participant's medical record, study record, or other official document sources.

Source documents substantiate CRF information. All participant case records (e.g., flow sheets, clinical records, physicians' notes, and correspondence) must adhere to the following standards:

- Clearly labeled in accordance with HIPAA practices so that they can be associated with a particular participant or PID;
- Legibly written in ink;
- Signed and dated in a real time basis by health care practitioner evaluating or treating the participant; and
- Correction liquid or tape must not be used in source documents or on CRFs.
- Corrections are made by drawing a single line through the error. Do not obliterate the original entry. Insert the correct information, initial, and date the entry.

12.4 Data and Safety Monitoring Plan

The Data Safety Monitoring Board meets annually to review all phase II and phase III protocols. The Board includes members demonstrating experience and expertise in oncology, biological sciences and ethics. The DSMB report is generated by the organization statistician. Areas of review may include the following: Date study Opened; Study Objectives; Participant Accrual; Participant Status and Retention; Study Status; Last Contact Status; Participant Compliance; Participant Characteristics; Adverse Events; Date, Event briefly described, Relationship to Treatment, Arm assigned; Summary of Secondary Measures.

Wake Forest University has a university-wide Data Safety and Monitoring committee. Three members of this committee as well as the organization statistician will oversee the safety monitoring of the study to ensure that the privacy of all participants in the study is protected; ensure that participants' interests are primary, that is, above the interests of the scientific investigation; and to ensure that all data collection is scrutinized for accuracy, privacy and levels of protection. The committee will perform reviews of the data handling and confidentiality, communicate any breaches in data safety to the administration of Wake Forest University Health Sciences and comply with recommendations to resolve such problems, and maintain written communication of the deliberations and recommendations that arise from their meetings. By examining this information, the data and safety monitoring team will keep abreast of critical issues regarding recruitment and data integrity. Reports of all DSMB meetings and recommendations will be provided to the NCI, CIRB, WF NCORP RB, and participating sites, as requested.

12.5 Sponsor or FDA Monitoring

The NCI (or their designee) may monitor/audit various aspects of the study. These monitors will be given access to facilities, databases, supplies and records to review and verify data pertinent to the study.

12.6 Record Retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, *etc*.), as well as IRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with Health Insurance Portability and Accountability Act (HIPAA), Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) regulations and guidances,

and NCI/DCP requirements, unless the standard at the site is more stringent. Records for this study will be retained for at least three years after the completion of the research.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Description

We anticipate screening approximately 2,500 participants from 26 clinics in order to enroll a total of 557-650 participants in the intervention and 557-650 participants in the usual care arms at baseline. We expect ineligible participants to be due to non-smoker status (52%) and lack of interest (5%), and anticipate these rates being similar in both arms of the study. Following enrollment, we expect 90% of baseline participants to participate ≤14 day telephone survey, which will ascertain exposure to the intervention, and 75% of baseline participants to participate in the 6-month, telephone survey.[49,50]

13.2 Randomization/Stratification

The pre-randomization eligibility checklist will include organizational characteristics that may influence the adoption and adaptation smoking cessation services. We will cluster sites according to these organizational characteristics (e.g., volume of the screening site, current cessation services, and racial/ethnic composition of the screening population) and then randomly select sites from within each cluster to receive the intervention (n=13) or usual care (n=13) to maximize balance in the study arms. Our multi-faceted training program targets health care delivery system changes (e.g., providers, clinics); therefore, all patients seeking LDCT screening at a single site will be in either the intervention or usual care arm of the RCT. If clinics opt out post-randomization, another clinic will be selected from the remaining eligible clinics within the NCORP site or another NCORP site will be added.

13.3 Accrual and Feasibility

With over 800 components/subcomponents within the NCORP network, we do not anticipate having any challenges with accruing 26 components/subcomponents to participate in this study. On the 2017 CCDR Landscape Assessment, 68% of responding practice groups (224 of 301) had low dose CT screening for lung cancer available on site.

We anticipate screening approximately 2,500 participants from 26 clinics in order to enroll a total of 557-650 participants in the intervention and 557-650 participants in the usual care arms at baseline and expect to retain 75% of baseline participants to participate in the 6-month telephone survey.[49,50] Any participants who complete baseline assessments after their LDCT screening or sign consent and do not complete any study specific assessments will be replaced.

Challenges with recruitment and attrition of participants could limit our ability to adequately test the effectiveness of the intervention. We will attempt to minimize attrition by sending postcard reminders of the upcoming surveys. We anticipate a capacity to enroll at least 50 smokers per clinic, but at present only require an average of 43 per clinic at baseline in order to retain 32 at 6-months (75% of the original cohort). We will allow clinics to enroll up to 50 smokers total for a maximum of 1300 (although we do not anticipate all clinics will enroll the maximum allowed). Because we anticipate some high volume clinics, we expect that we could oversample some participants in some clinics if needed. We could also increase the desired sample size per clinics should a clinic (post randomization and training) elect to drop out of the study. Alternatively, we can extend data collection longer than the 16-month accrual window. Our team has experience in conducting randomized clinical trials and can adjust both methodologically and/or analytically to address challenges that could affect statistical power.

13.4 Primary Objectives, Endpoint(s), Analysis Plan

13.4.1 Analysis Plan

In order to compare groups, a multi-level logistic regression model approach will be used.[51] This model allows for both fixed and random effects to be included. [51] This model allows for both fixed and random effects to be included. In these models, clinics will be random effects and both clinic and participant level characteristics can be included as fixed effects. The initial model for the primary analysis will include two fixed effects: cluster (used in the randomization) and intervention and one random effect, clinic. The model can be written as $Y_{ijk} = \mu + \gamma_k + \alpha_j + \beta_{k(j)} + \varepsilon_{i(jk)}$, where Y_{ijk} is the outcome (i.e. 6-month smoking abstinence) measured on the i^{th} participant, under the j^{th} intervention in the k^{th} clinic; μ is the grand mean; γ_k is the cluster (stratum) for clinic k; α_j is the fixed treatment effect for group j; $\beta_{k(j)}$ is the random effect of the k^{th} clinic nested within the exposure group; and $\varepsilon_{i(jk)}$ is the error term for the i^{th} participant nested within the treatment group and clinic. Other fixed effects can be added at the patient level (e.g. age, gender, race). The random clinic effect allows the possibility of correlated observations (participants) within clinics. Of primary interest is the treatment effect (α_j), which indicates difference in the dependent variable (7-day smoking abstinence) between groups. Additional longitudinal modeling can be explored using a Generalized Estimating Equations (GEE) approach that accounts for the participants being nested within clinic and also allows the early (1 week) endpoint to be included with the 6-month endpoint in the analyses. We can also explore if there are particular patterns of abstinence behavior (i.e., examine the 4 possible patterns between 7 days and 6 months: abstain/abstain, not abstain/abstain, etc.) to see whether there are any specific participant level risk factor profiles that may differentiate the response patterns.

13.4.2 Statistical Power

Sample size estimates are based on the following data. Approximately 48% of patients who present for lung cancer screening are current smokers, the percentage of persons who successfully quit smoking in the previous year ranges from 4.9% (among 45-65 year olds) to 7.4% (among persons 65 and older). [52] Receipt of counseling to promote cessation (vs. no counseling) increases abstinence 1.3 to 2.3 fold (low versus high intensity counseling), while pharmacotherapy (vs. placebo) increases the odds of abstinence 2.3-3.1 fold (patch vs. varenicline).[27]. Weanticipate that final sample sizes of 418 in the intervention and 418 in the usual care group will be obtained by enrolling 13 clinics with an average of 32 participants who will complete the 6-month survey. With this sample size, we have 80% power to detect a difference in the primary outcome (7-day abstinence) between groups. This calculation assumes that the control group abstinence rate will be 10% and the intervention group rate will be 20% using a 2-sided Z-test for comparing proportions with alpha=0.05 (2-sided). For this calculation, in order to account for the cluster randomized design we used an intra-class correlation value of 0.03.[53]. This calculation should be conservative since the control group abstinence rate may be lower than 10% which would mean that the intervention effect could also be less and still lead to statistical (and clinical) significance. To allow for flexibility in clinic accruals and loss to follow-up rates and maintain an analyzable minimum size of 418 in each group, we plan to enroll at least 1114 up to a maximum of 1300 patients (or approximately 42-50 per site) to conservatively allow for 25% to 35.5% loss to follow-up at 6 months respectively.

13.5 Secondary Objectives, Endpoints, Analysis Plans – N/A

13.6 Analysis Plan for Key Informant Interviews and Other Qualitative Data Elements

The qualitative data from key informants will be digitally audio-recorded and transcribed. Data will be cleaned by comparing transcripts to original audio-recordings and notes.

The qualitative data from the Team Blog and Performance Coaching Notes will be abstracted in text format using Microsoft Word.

All qualitative data will be imported into Atlas.ti software for data management and coding purposes. Codebook will be developed collaboratively, and data will be coded in Atlas.ti. Transcripts and coded text will be iteratively reviewed. Themes regarding care coordination will be reported using supporting quotations. Analysis will include an integrative synthesis of data (identification of key points, potential themes, areas of further exploration).

Evidence Integration: Using an evidence integration triangle (EIT), which combines multiple sources of qualitative data (team blog, performance coaching notes, and key informant interviews), we will determine the concrete attributes and cessation approaches used by LDCT lung cancer screening programs.[46] EIT is a methodology intended to synthesize data crossing multiple levels and requires information about the intervention, implementation process, and measures of progress using data generated from key stakeholders. This will be a process that will engage the entire research team and EAB members as we assign relative importance and feasibility to each cessation strategy (and under which conditions). EIT analysis will be supported by the EAB members, Drs. Curran and Ammerman who have extensive experience with qualitative data analysis and synthesis of multiple sources of qualitative data. Please refer to Section 7.9 for more information on the EAB members, their expertise and their level of commitment to support this process.

Data generated from Aim 2 will allow our team to characterize implementation of tobacco cessation strategies within LDCT screening sites, according to: (1) extent of training and coaching needed for adoption and adaptation and in response to the specific RFA requirements of fidelity, feasibility, and appropriateness; (2) organizational characteristics that promote or hinder implementation of the PHS strategies; and (3) characteristics of the evidence-based tobacco cessation strategies that make them more or less adoptable and adaptable in different types of community-based screening programs. These data will lead to an implementation toolkit that will be evaluated for disseminated and scale-up by national stakeholders (Aim 3). The toolkit will be developed with support from the EAB and will not require NCORP personnel participation.

13.7 Additional Data Elements Required by the SCALE Collaborative

- **Fidelity:** The degree to which an intervention was implemented as it was prescribed in the original protocol or as it was intended.
    - We will use self-reported data from patients (≤14 days of their screening visit) and ask if they experienced various cessation strategies.
    - Each clinic will have agreed to offer certain cessation strategies (based on the training and implementation planning).
    - We can create a measure of fidelity based on what clinics agreed to offer with what patients say was offered.
- **Patient Acceptance of the Intervention.** We agreed to use the following question, which we include on the ≤14 day patient survey.
    - "Did you receive smoking cessation support during your visit?" (CORE Item)
    - "If yes, how satisfied were you with the smoking cessation support you received?" (Optional Item from the SCALE collaborative)

- **Patient Reach**
  - As expected by the SCALE Collaborative, we will:
    - Calculate the percentage of current smokers enrolled
    - Representativeness of participating patients (compared to non-enrolled participants), by age, sex, race, ethnicity.
    - These data are included in the patient baseline survey (for those who are enrolled) and are also included in the "Reason for Refusal" information at baseline and follow-up assessments (see Appendix 3 and 4)
- **Feasibility/Appropriateness/Workflow Fit**
  - We will measure feasibility and appropriateness using the Key Informant Interviews for intervention and usual care clinics. These will be measured at baseline and at follow-up (8 months after baseline) for all clinics regardless of treatment arm.
  - The measure is a structured survey, consistent with the expectation of the SCALE collaborative and can be found in Appendix 5 and 21.
- **Cost**
  - Cost was not an original measure in our protocol. Therefore, we have agreed to partner with the Georgetown University team leading a CISNET modeling approach (Investigators: Rafael Meza, PhD, Jeanne Mandelblatt, MD, MPH, David Levy, PhD, Jinani Jayasekera, PhD, and Kathryn Taylor, PhD-PI). Data provided to the CISNET team include fixed costs (e.g., overhead, phone, interventionists, etc.) and variable costs (e.g., time spent in intervention, interventionists). Participation in the CISNET group will require addition time from the research team, but will require no additional data collection, support, or time from the NCORP personnel, the cessation program champion, or the lung cancer imaging personnel.
- **Lung RADS**
  - Lung RADS will be obtained from the lung cancer imaging report. We request the complete, de-identified imaging report for data quality purposes (the consent form includes this language). For example, a patient with a Lung RADS category 2S means that there is a significant finding. The type of significant finding (e.g., coronary arterial calcification) will be unknown without obtaining the full imaging report (a score alone may have limited utility for a more in-depth analysis of the influence of Lung RADS on smoking cessation).

13.8 Reporting and Exclusions

Missing Data Considerations: Our primary models use a mixed, multi-level models approach, which provides a valid approach for handling missing data if they are considered to be missing at random (MAR). If the missing data mechanism is not MAR, we may consider using a propensity score-weighted approach to compare groups. Each patient will have an estimated conditional probability of dropping out (propensity score) based on his/her characteristics pre-randomization; the propensity scores can be used as weights when making group comparisons. This analysis will be used to determine what impact missing data may have on the inferences made. Dr. D'Agostino's expertise in propensity score and missing data methods will be useful if needed. [54–56]

All of the participants who met the eligibility criteria will be included in the main analysis. All conclusions regarding effectiveness will be based on all eligible participants.

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