Lung Cancer Screening and Smoking Cessation Clinical Trials

SCALE (Smoking Cessation within the Context of Lung Cancer Screening) Collaboration

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Abstract

National recommendations for lung cancer screening for former and current smokers aged 55–80 years with a 30–pack-year smoking history create demand to implement efficient and effective systems to offer smoking cessation on a large scale. These older, high-risk smokers differ from participants in past clinical trials of behavioral and pharmacologic interventions for tobacco dependence. There is a gap in knowledge about how best to design systems to extend reach and treatments to maximize smoking cessation in the context of lung cancer screening. Eight clinical trials, seven funded by the National Cancer Institute and one by the Veterans Health Administration, address this gap and form the SCALE (Smoking Cessation within the Context of Lung Cancer Screening) collaboration. This paper describes methodological issues related to the design of these clinical trials: clinical workflow, participant eligibility criteria, screening indication (baseline or annual repeat screen), assessment content, interest in stopping smoking, and treatment delivery method and dose, all of which will affect tobacco treatment outcomes. Tobacco interventions consider the "teachable moment" offered by lung cancer screening, how to incorporate positive and negative screening results, and coordination of smoking cessation treatment with clinical events associated with lung cancer screening. Unique data elements, such as perceived risk of lung cancer and costs of tobacco treatment, are of interest. Lung cancer screening presents a new and promising opportunity to reduce morbidity and mortality resulting from lung cancer that can be amplified by effective smoking cessation treatment. SCALE teamwork and collaboration promise to maximize knowledge gained from the clinical trials.

Keywords: tobacco use cessation; lung cancer screening; clinical trial design

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In 2010, the National Cancer Institute (NCI) completed the landmark National Lung Screening Trial (NLST) (1). This study randomized 53,454 current or former heavy smokers to three annual screens with either low-dose computed tomography (LDCT) or chest X-ray screening. Compared with chest X-ray screening, LDCT screening yielded a 20% reduction in the lung cancer mortality rate. Along with the American Association for Thoracic Surgery (2), American Cancer Society (3), American College of Chest Physicians (4, 5), American Lung Association (4, 6), American Society of Clinical Oncology (4), American Thoracic Society (7), and National Comprehensive Cancer Network (8), the U.S. Preventive Services Task Force (USPSTF) issued recommendations in favor of screening for persons at high risk based on age and smoking history (grade B) (9). The USPSTF defined *high risk* as adults aged 55–80 years who have a 30–pack-year smoking history and currently smoke or have quit within the past 15 years.

Clinical Priority

Studies suggest that at least 50% of individuals undergoing LDCT screening will be current smokers and that there are approximately 5 million current smokers eligible for screening in the United States (10, 11). The USPSTF recommendation to screen smokers at high risk for lung cancer creates a demand to implement efficient and effective systems to offer tobacco treatment on a large scale. Lung cancer screening (LCS) provides an additional interaction between a smoker and the healthcare system. Smokers seeking LCS may be more open to quitting than the general population of smokers (12). A recent study, however, describes low rates of providing assistance with quitting and arranging follow-up (two of the "5 As" recommended in the clinical practice guideline [13] for smoking cessation) by primary care providers for participants in the NLST, although assistance and arranging follow-up were significantly associated with increased odds of quitting (odds ratio, 1.40; 95% confidence interval, 1.21–1.63; and odds ratio, 1.46; 95% CI, 1.19–1.79, respectively) (14). The combination of LCS and smoking abstinence resulted in the maximum reduction in mortality in the NLST (15).

Although there are established clinical practice guidelines for treatment of tobacco dependence (13), smokers who undergo LCS may vary widely in their readiness to quit, interest in smoking cessation treatment, and prior experience with pharmacological and behavioral therapies. The Society for Research on Nicotine and Tobacco and the Association for the Treatment of Tobacco Use and Dependence have provided a clinical guideline regarding delivery of smoking cessation interventions in the context of LCS but acknowledge the paucity of data specific to this patient population as well as the need for research on how best to design and deliver cessation programs in this context (16).

Incentives and Barriers to Integration of Smoking Cessation into LCS

The Centers for Medicare and Medicaid Services (CMS) decision to cover LCS with LDCT on February 5, 2015 (17, 18), included strict criteria for LCS, such as the requirement that patients participate in a face-to-face shared decision-making visit with a credentialed provider and receive smoking cessation counseling before screening (19). Although reimbursement to the imaging facility is contingent on offering smoking cessation counseling, many LCS sites indicate that they face significant implementation barriers to the delivery of tobacco cessation care (20). These include lack of patient interest, lack of staff training, and complexities of reimbursement for smoking cessation services.

Observations of Smoking Cessation Derived from LCS Programs

Findings derived from observational studies of smokers in LCS programs indicate substantial interest in quitting (67–95%) (12, 21–24), although there is variability by screening result and by study. For example, of current smokers in the NLST, 70% considered quitting, 17% were preparing to quit, and only 13% had no intention to quit (25). In the New York Early Lung Cancer Action Project, 32% were seriously thinking of quitting within 30 days, and 47% were seriously thinking of quitting within 6 months (26).

Self-reported smoking cessation rates among those undergoing LCS are fairly high (16–42%), but reports are inconsistent (22, 23, 26–31). Selection factors may limit the generalizability of extant smoking cessation outcome data derived from these observational studies. For instance, the NLST population likely differs from the true population of smokers undergoing LCS because they are early screening adopters as well as research participants. Early screening adopters may be more likely to quit smoking than those who elect screening in later years or not at all. Other limitations include that most smoking cessation interventions in the LCS setting have relied on low-intensity treatment strategies such as the provision of self-help materials and referral to a quitline (32). There could be additional benefit to enhancing the intensity of smoking cessation treatment provided to smokers who participate in LCS. Also, important confounders, such as heaviness of smoking and mental health diagnoses, often were not considered in earlier studies (33).

Knowledge Gap

There is a critical gap in knowledge about how best to deliver cost-effective smoking cessation treatment in the context of LCS. Patients participating in LCS are unlikely to be representative of the general population of smokers or even of the population of smokers eligible for screening. For example, those electing LCS are older than the general population of smokers; are more likely to have medical comorbidities; and are more likely to be heavy, long-standing smokers. Although smoking at older ages may suggest resistance to smoking intervention ("hard-core smokers") (34, 35), some data suggest that older smokers, including those undergoing LCS, are interested in quitting (36), and treatment trials with older patients suggest effectiveness (37–40). Compared with younger smokers, older smokers are known to hold unique beliefs regarding the harms of smoking, their personal ability to quit successfully, and the benefits of quitting, all of which may affect their engagement with and response to a cessation intervention embedded in this setting (41).

Eligible patients who undergo LCS may differ from those who do not in ways other than age. For example, they may interact more frequently with the healthcare system and be more proactive about their health care than average smokers. On one hand, participation in screening may indicate recognition of the adverse consequences of smoking and interest in behavior change, and screening results may improve the impact of a smoking cessation intervention. On the other hand, it is possible that they have been offered smoking cessation treatment but are more refractory. These differences raise important questions about the application of results of smoking cessation trials that have been conducted in other settings to the population of patients currently undergoing LCS and create a compelling research opportunity. This knowledge gap can be addressed by conducting randomized clinical trials (RCTs) to test specific smoking cessation interventions.

The need for randomized trials conducted in the setting of LCS is made more pressing by the broad range of LCS facilities, including stand-alone programs, primary care, academic sites, or referral-based programs. Staff training and lack of reimbursement have been identified as important barriers to implementing smoking cessation treatment (20). Research on systems designed to improve program reach is needed.

SCALE Collaboration

The NCI announced a funding opportunity, SCALE (Smoking Cessation within the Context of Lung Cancer Screening) (R01; RFA-CA-15-011), in June 2015. The goal of the funding opportunity announcement was to support projects testing smoking interventions for patients undergoing LDCT for LCS and to build an evidence base for effective interventions delivered in this setting. Requirements include comparative designs, capacity to determine effective intervention components, common endpoints, measurement of patient acceptance and reach, and cost. NCI is interested in intervention design as well as dissemination and implementation strategies that would be effective in the context of LCS programs. NCI has funded six clinical trials under the funding opportunity announcement as well as an additional trial, and another SCALE trial is funded by the Veterans Health Administration.

The eight ongoing projects are testing various permutations of smoking cessation intervention strategies of different intensities (e.g., quitlines, cessation medications and medication sampling, integrated care, training toolkits, digital resources such as web-based programs and text messaging, gain vs. loss message framing) (Table 1). Study designs include traditional RCTs; cluster randomized control designs; sequential multiple assignment randomized trials; factorial experimental designs (multiphase optimization strategy;); and modeling of LCS outcomes, including potential health benefits of smoking cessation treatment. The trials range in size ($N = 616–1,650$); the number of sites and sample sizes are described in Table 2. All trials include cost-effectiveness analyses, and many examine strategies for dissemination and implementation. With leadership from the NCI's Tobacco Control Research Branch, investigators in the eight projects have formed the SCALE collaboration to facilitate data sharing and peer feedback and to maximize the knowledge gained from the clinical trials. The purpose of this paper is to describe common methodological issues related to design and implementation of smoking cessation clinical trials in the setting of LCS, given unique aspects of the study population and clinical setting.

Clinical Context of LCS

The current LCS guideline presents several opportunities and challenges to coordination of screening and smoking cessation treatment, and raises practical questions regarding how and where in the healthcare system smoking cessation treatment should occur. CMS requires a shared decision-making visit and mandates the offer of smoking cessation treatment; however, further research is needed to determine effective, scalable clinical workflow regarding where, when, how, and by whom smoking cessation treatment should be delivered.

Staffing of LCS Sites

The American Thoracic Society and the American College of Chest Physicians have published recommendations for best strategies to develop comprehensive LCS programs (7), but sites vary in their personnel and organizational readiness for smoking cessation treatment delivery (20). Some sites have clinical staff on-site, and others have radiologists read remotely. Some sites, particularly those in hospital settings, are affiliated with tobacco treatment clinics. Who should provide cessation treatment? Should the primary care provider be responsible, or should the treatment be delivered by a specialty service such as a tobacco treatment clinic or quitline? On-site staff may vary in their level of training and comfort in delivery of smoking cessation treatment. Similarly, who should prescribe pharmacotherapy for smoking cessation, and who can provide behavioral counseling? Should it be dispensed on-site by tobacco treatment specialists? Although the clinical practice guidelines stipulate that a broad range of healthcare clinicians can treat tobacco dependence, it is clear that one-size-fits-all staffing plans are not realistic. The SCALE projects have selected various staffing plans (e.g., primary care provider, pharmacists, nurse practitioners, quitlines, tobacco treatment specialists) for smoking cessation treatment delivery and will generate materials and protocols that can be shared with the LCS community.

Study Recruitment

The main eligibility criteria for LCS are age and smoking history; therefore, there is potential to identify patients who are eligible for screening based on electronic health record (EHR) data. The EHR identifies current smoking status with good accuracy (42) and has proved useful for recruitment of patients to prior smoking cessation intervention treatment trials (43, 44). The EHR can facilitate evaluation of population-based intervention and quit rates. Using the EHR for recruitment may also be effective at overcoming provider bias in offering LCS and/or smoking interventions to a variety of patient populations, including racial and ethnic minorities, low-income patients, or patients with mental health disorders. Pragmatic clinical trial designs are especially promising in that recruitment emphasizes broad participant inclusion with few exclusion criteria; interventions are delivered by practitioners; primary outcomes are clinically meaningful; and analysis includes all participants (43, 45, 46). The researchers in the SCALE trials

Table 1. SCALE Trial Descriptions

Trial Name, Institution, and PI(s)	Main Study Aims
LUNA University of Texas MD Anderson Cancer Center P. M. Cinciripini	To evaluate the efficacy of three smoking cessation treatment strategies of increasing intensity and integration: integrated care (which offers on-site tailored and individual smoking cessation counseling plus choice of pharmacotherapy), quitline (which provides standard five-session protocol of quitline counseling), and quitline plus (which offers quitline counseling plus choice of pharmacotherapy) To evaluate the cost and cost effectiveness of the different treatments To assess the moderating influence of mental health conditions on treatment outcome
Implementation of Smoking Cessation Services within NCI NCORP Community Sites with Organized Lung Cancer Screening Programs Wake Forest Baptist Health K. Foley and C. Chiles	To evaluate a multifaceted training program to improve short-term smoking cessation rates and sustained abstinence among patients who present for LCS in 22 community-based practices To characterize the adoption and adaptation of evidence-based tobacco cessation strategies in LCS programs To develop and evaluate an implementation toolkit for integrating evidence-based tobacco cessation strategies into LCS
MATCH Mayo Clinic, Rochester, Minnesota J. T. Hays and D. E. Midthun	To examine the comparative effectiveness of a digital (Internet and SMS) cessation intervention, alone and in combination with smoking cessation treatment by a tobacco treatment specialist counselor, compared with an ask-advise-refer usual care control condition To determine whether proactive enrollment increases treatment use and the representativeness of the study sample relative to all smokers screened for LDCT eligibility (reach) To evaluate the potential for intervention implementation (adoption) at LDCT clinics
PLUTO University of Minnesota A. M. Joseph	To use a SMART design to compare telephone-based tobacco longitudinal care vs. tobacco longitudinal care plus pharmacist-administered medication therapy management (for nonresponders to initial treatment), as well as monthly tobacco longitudinal care contact vs. quarterly contact (for complete responders to initial treatment) To determine if timing of identifying initial response to treatment moderates treatment effects
CASTL Memorial Sloan Kettering Cancer Center, New York University Langone Medical Center J. S. Ostroff and D. Shelley	To use MOST design to identify which of four evidence-based tobacco treatment components contribute to superior cessation endpoints: *1*) motivational interviewing, *2*) NRT patch, *3*) NRT lozenge, and *4*) message framing (gain vs. loss) To estimate the incremental cost and cost effectiveness of these tobacco treatment components over and above usual care To conduct a mixed-methods evaluation of factors that may influence implementation and sustainability for delivering effective models of smoking cessation treatment in lung cancer screening settings
The Lung Screening, Tobacco, and Health Project Georgetown University Medical Center K. L. Taylor	To compare eight sessions of telephone counseling plus NRT patch with three sessions of telephone counseling plus NRT patch To assess whether the screening result moderates cessation outcomes To evaluate reach and engagement of the interventions To conduct a cost-effectiveness analysis and employ the University of Michigan CISNET model to predict the long-term population impacts of the interventions
LUNG Medical University of South Carolina B. A. Toll	To conduct a 2×2 randomized trial of a gain-framed intervention (yes vs. no) $\times$ NRT sampling (2-wk supply of both nicotine patch and lozenge vs. not) within a high-risk group of smokers presenting for lung cancer screening
PROACT Veterans Health Administration S. B. Zeliadt and J. L. Heffner	To conduct a pragmatic trial in two VA medical centers offering LCS in the primary care setting, comparing usual care with integration of standardized proactive opt-out cessation support, including starter packs of cessation medication mailed with screening results letters and proactive behavioral telephone support conducted by the VA Quitline

Definition of abbreviations: CASTL = Cessation and Screening Save Lives; CISNET = Cancer Intervention and Surveillance Modeling Network; LCS = lung cancer screening; LDCT = low-dose computed tomography; LUNA = Optimizing Effectiveness of Smoking Cessation Intervention during LDCT Screening for Lung Cancer; LUNG = Lung Cancer Screening Patients Utilizing NRT and Gain-framed Messages; MATCH = Mayo and Truth Collaboration for Health; MOST = multiphase optimization strategy; NCI = National Cancer Institute; NCORP = National Cancer Institute Community Oncology Research Program; NRT = nicotine replacement therapy; PI = principal investigator; PLUTO = Program in Lung Cancer Screening and Tobacco Cessation; PROACT = Promoting Smoking Cessation in Lung Cancer Screening through Proactive Treatment; SCALE = Smoking Cessation within the Context of Lung Cancer Screening; SMART = sequential multiple assignment randomized trials; VA = Department of Veterans Affairs.

Table 2. Description of SCALE Lung Cancer Screening Sites and Populations Served

Trial Name	Sites (*n*)	Sample Size	Type of LCS Facilities	Populations Served (%)						Staffing of Tobacco Treatment
				White	Black	Asian	Native American/ Alaskan Native	Native Hawaiian/ Pacific Islander	Hispanic	
LUNA	1	630	Academic, comprehensive cancer center	59	19	5	0.4	—	33	Physicians, master's-level counselors, trained telephone tobacco coaches
Implementation of Smoking Cessation Services within NCI NCORP Community Sites with Organized Lung Cancer Screening Programs	26	1,114	Imaging facilities within NCORP community sites	Varies by site						Variable; not manipulated in this study
MATCH	7	1,650	Academic, community-based	87	8	3	2	0.1	12	Certified tobacco treatment specialists
PLUTO	2	1,000	Academic, Veterans Health Administration	63	15	6	3	—	10	Trained telephone tobacco coaches
CASTL	18	1,152	Academic, community-based	75	17	2	—	—	4	Trained site coordinators
The Lung Screening, Tobacco, and Health Project	5	1,330	Academic and community-based hospitals	78	9	4	—	2	—	Trained tobacco treatment specialists
LUNG	2	616	Academic clinic/hospital	64–66*	14–29*	2–4*	—	—	5–16*	Psychologists, nurse practitioners, pharmacists, and tobacco treatment specialists
PROACT	Two regional medical centers including five primary care clinics	500	Veterans Health Administration	56	37	2	1	1	2	VA Quitline telephone counselors

Definition of abbreviations: CASTL = Cessation and Screening Save Lives; LCS = lung cancer screening; LDCT = low-dose computed tomography; LUNA = Optimizing Effectiveness of Smoking Cessation Intervention during LDCT Screening for Lung Cancer; LUNG = Lung Cancer Screening Patients Utilizing NRT and Gain-framed Messages; MATCH = Mayo and Truth Collaboration for Health; NCI = National Cancer Institute; NCORP = National Cancer Institute Community Oncology Research Program; PLUTO = Program in Lung Cancer Screening and Tobacco Cessation; PROACT = Promoting Smoking Cessation in Lung Cancer Screening through Proactive Treatment; SCALE = Smoking Cessation within the Context of Lung Cancer Screening; VA = Department of Veterans Affairs.

*Varies by site.

will be collecting standardized data on participant recruitment rates (reach) and examining demographic characteristics of enrollees and study refusers.

Trial Eligibility Criteria

Every clinical trial must carefully define inclusion and exclusion criteria to enable full understanding of how potential treatment results apply to patient populations. There is good justification for matching eligibility criteria to the clinical population of interest as closely as possible. Trials of smoking cessation treatment in the setting of LCS face at least four unique issues relevant to patient selection, as described below.

Screen eligible versus screen completed. Some healthcare systems are putting considerable effort into recruiting patients for LCS. Some identify patients through the EHR and mail invitations to eligible current and former smokers. However, participation in LCS is voluntary, and many patients decline the screening invitation (47–49). Therefore, an interesting question is which groups of currently smoking screening-eligible persons should be included in smoking cessation intervention trials: only those who complete LDCT, or also those who decline screening, decline screening after a shared decision-making visit, or accept but do not complete the LDCT? The choice of eligibility criteria based on these patient characteristics has potential to affect trial recruitment and treatment outcomes. For example, it is plausible that those who accept and complete screening will be more responsive to interventions than those who do not. However, if intervention protocols include content that is specific to screening results, it may not be practical to include participants who do not complete screening. On one hand, including subjects who are screen eligible provides a larger number of patients from which to recruit and may more accurately represent the clinical population of interest. On the other hand, including only smokers who undergo LDCT enables more targeted evaluation of tobacco treatment in the specific context of LCS. There may be patients for whom LDCT is contraindicated but would still benefit from smoking cessation. Therefore, the decision about including screen-eligible or screen-completed patients has important implications.

Baseline screening versus annual repeat screening. LDCT LCS recommendations and insurance coverage for the procedure are relatively new; at the time the present authors were writing this paper, the majority of patients undergoing screening would be seeking baseline screens. Recommendations, however, include annual repeat screening. The annual repeat screen provides an opportunity for reengagement in smoking cessation treatment if the patient has not quit in the interim, and it may be a suitable framework for serial delivery of smoking cessation interventions. This opportunity raises many familiar issues concerning the "re-cycling" of smokers through treatment. Should treatments be repeated? Should they be revised? If revised, what is the best sequence of treatments? An important issue is whether smoking cessation treatment efficacy changes over time. For example, one might hypothesize that smoking treatment will be more effective at the time of the baseline screen than at annual repeat screens, or conversely that it might become more effective over time. A study cohort that includes both patients undergoing baseline screens and patients undergoing annual repeat screens would allow researchers to investigate these questions. However, inclusion of both types of patients introduces heterogeneity that may dilute the overall effect if treatment effects differ by this characteristic.

Interest in quitting smoking. Smoking cessation trials include smokers with a range of interest in quitting and willingness to set a quit date. Restricting eligibility to only smokers who are ready to set a quit date within 30 days, for example, will guide intervention content and may also be associated with higher quit rates than including all smokers eligible for LCS, regardless of motivation to quit. Some recent population-based studies including all smokers have shown that flexible, tailored treatment is effective even for those smokers who are precontemplators (50). Including "all comers," however, demands intervention components that range from increasing motivation to quit to pharmacotherapy; this may attenuate specific treatment effects. Also, cessation induction, smoking reduction, and aid-to-cessation trials require different outcome measures and timing of outcome measurements (51, 52).

Inclusion of recent quitters. Some patients who are identified as eligible for LCS may stop smoking before the LDCT owing to fear arousal associated with the impending test. Careful consideration of the definition of "current smoker," therefore, is needed for eligibility criteria for a clinical trial conducted in this setting. The rationale for including recent quitters, such as those quitting within the last 30 days, is that these quits may be unaided by pharmacological intervention or behavioral counseling (the mainstays of evidence-based tobacco treatment), and the relapse rate for recent quitters is extremely high (53, 54). The rationale for excluding these potential subjects is that they may be more motivated and likely to quit, regardless of whether they receive the intervention, thereby mitigating differences between interventions that are being compared. A real-world matter is that patients may have started pharmacotherapy or behavioral counseling that is either inconsistent with or may contaminate the study protocol, and ethical concerns preclude stopping those therapies. The CMS requirement to provide smoking cessation treatment to current smokers undergoing LCS makes this scenario fairly common.

Issues Related to Smoking Cessation Intervention Content

Teachable moment hypothesis. One rationale for including a smoking cessation intervention with LCS is based on the teachable moment hypothesis (21, 55–57). This health behavior model suggests that certain health threats increase the likelihood of making behavioral changes and enhance the effectiveness of behavioral interventions. Examples that support this hypothesis are the high rate of smoking cessation after hospitalization for myocardial infarction (58), perioperatively (59), or after a cancer diagnosis (60–62). McBride and colleagues suggested that three conditions form the construct for a teachable moment: The event must *1*) increase perception of personal risk, *2*) create an emotional response, and *3*) change the patient's concept of themselves (55). The teachable moment model provides a conceptual framework for developing smoking interventions focused on these three parameters or at least for collection of data to document intervention effects on the three conditions, hopefully creating a therapeutic milieu during the LCS process. However, there is currently a

lack of evidence that undergoing LCS *per se* alters perceived lung cancer risk (63).

Positive and negative screening results. There are key questions about whether, how, and when to incorporate LDCT scan results with behavioral counseling for smoking cessation. In addition, the NLST and other screening studies suggest that approximately 25% of patients will have an abnormal finding that ranges from minor to severe (but the vast majority of abnormal scans are false positive results for lung cancer) (64). Recent data from the Veterans Health Administration suggest that the rate of abnormal findings may be as high as 60% (65). Furthermore, other smoking-related diseases may be detected, such as coronary artery calcification and emphysema, which might increase motivation to quit.

In general, observational studies suggest that scan abnormalities are associated with a higher smoking cessation rate (21–24, 27, 28, 30, 66, 67), supporting the premise that LCS may be an opportune time to promote cessation. In fact, the more serious the abnormality identified on LDCT, the more likely the patient will quit (11, 30, 27, 33). Robust trials are needed to test the tailoring of smoking intervention by LDCT results. For example, patients with a new diagnosis of emphysema by LDCT could receive tailored information about the relationship between smoking and emphysema. Although this approach may be effective, tobacco counselors are generally not trained in the clinical issues related to LDCT scan abnormalities and follow-up, so there are practical concerns about implementation.

However, up to 75% of screening results will be normal. Limited data do not support the common concern that a negative scan reduces interest in cessation (the "healthy certificate effect") (26, 30). Some qualitative data, however, support the possibility that patients with a "clean" LDCT screening scan may overestimate the benefits of screening and be falsely reassured, with potentially adverse effects on cessation behavior (68). It will be important for clinical trials to determine the most effective method to incorporate normal findings in smoking cessation intervention content and still maximize motivation to quit. It is also critical to measure whether normal findings have the unintended consequence of decreasing smoking cessation treatment efficacy. Careful attention to standardizing how LCS findings are described and incorporated into cessation trials is a critical methodological issue, and cessation outcomes should be analyzed by scan results.

Coordination of smoking cessation treatment with LCS clinical events. Positive scan results lead to clinical follow-up that ranges from repeat scanning at an interval of less than 1 year to bronchoscopy, needle biopsy, surgical lung biopsy, or resection. LCS involves a multidisciplinary clinical team, often including primary care, radiology, pulmonary, thoracic surgery, and oncology providers. Therefore, a subgroup of patients undergoing screening will have continued contact with the healthcare system, providing additional opportunities for smoking cessation treatment over time. Smoking cessation treatment efficacy may be amplified by the involvement of and coordination with this variety of clinicians providing follow-up care. Trial researchers may choose to engage the complete clinical team (or not).

It is reasonable to hypothesize that details regarding the coordination of LCS events with delivery of smoking cessation interventions might influence the efficacy of treatment. Each potential clinical encounter provides a different context for intervention delivery, and the intervention content may interact with the context, with variable results depending on the situation. For example, a prescription for pharmacotherapy initiated by the patient's primary care provider may be more (or less) effective than the identical prescription from a quitline.

The sequence and timing of starting smoking cessation treatment relative to diagnostic testing may also be important (29). Patients may have apprehension before the scan is completed or before they receive the result that contributes to motivation to quit. Therefore, tobacco treatment delivery before receipt of results might enhance efficacy. Conversely, excessive anxiety about the screening result may distract the participant from engaging in behavior change. It may be difficult for researchers in clinical trials to fully control the sequence and timing of clinical events associated with LCS, however. For example, some patients will receive an LDCT scan result on the same day as the scan is done via electronic communication (especially if it is normal), and the smoking intervention may or may not have started. Secondary analyses can be done to examine the influence of timing and sequence of tobacco intervention activities relative to screening activities, so documentation of event logistics is important.

Issues Related to Data Collection

Anchoring of data collection. A variety of short- and long-term outcomes are monitored in smoking cessation trials, including abstinence from smoking and quit attempts. For smoking cessation interventions conducted in the context of LCS, outcome assessments could be anchored to the LDCT, to the initiation of smoking treatment, or to the quit date, presuming one occurs. There are advantages of linking to the LDCT, particularly if scan results figure prominently in the intervention. Disadvantages of this approach are that smoking treatment and quit dates may vary and be delayed, so long-term outcome measurement (e.g., 6 or 12 mo) may end up occurring close to the end of treatment. In most, but not all, of the SCALE trials, investigators will be collecting a core set of data on participant characteristics, anchoring data collection variably to ordering LCS, conducting of LCS, trial enrollment, or beginning of treatment (Table 3). Core measures include follow-up up data collected 7 days, 3 months, and 6 months after enrollment, but some trials have additional data collection points.

Unique data elements. It is typical to collect baseline data regarding factors known to moderate the effectiveness of smoking interventions, such as heaviness of smoking and depression. Trials conducted in the context of LCS may benefit from data collection on additional potential moderators and mediators of treatment effects that are specific to LCS, including lung cancer risk perception and worry. A family history of lung cancer has been shown to increase perceived risk of lung cancer and may be an important variable to collect (69, 70).

For patients who receive abnormal results, subsequent medical workup events may facilitate or impede smoking cessation. Undergoing invasive procedures such as lung biopsy or surgical lung resection may be especially influential because some surgeons will delay lung resection surgery to encourage smoking cessation (71). The outcomes of additional testing (e.g.,

Table 3. SCALE Trial Solutions

Trial Name	LCS Eligible vs. Completed	Baseline Screen vs. Annual Screen	Inclusion of Recent Quitters	Interest in Quitting Requirement	Including LDCT Results in Smoking Intervention	Anchoring of Outcome Assessment to LDCT Enrollment	Cost-Effectiveness Analysis
LUNA	Both	Any screen	No	Willing to quit or change smoking behavior	Will analyze but not manipulate	Yes	Yes
Implementation of Smoking Cessation Services within NCI NCORP Community Sites with Organized Lung Cancer Screening Programs	Screen completed	Any screen	No	Yes	Will analyze but not manipulate	Yes	Yes
MATCH	Screen completed	Any screen	No	No	No	Yes	Yes
PLUTO	Screen completed	Any screen	Quit within 30 d	Willing to set quit date within 12 wk	Yes	No; smoking cessation outreach call	Yes
CASTL	Screen completed	First screen	No	No	Yes	Yes	Yes
The Lung Screening, Tobacco, and Health Project	Screen completed	Any screen	No	No	Yes	Yes	Yes
LUNG	Screen eligible	Any screen	No	Willing to engage in study smoking cessation intervention; motivation stratified on basis of Contemplation Ladder	Yes	Yes	Yes
PROACT	Screen completed	Any screen	No	Yes	Yes	Yes	Yes

Definition of abbreviations: CASTL = Cessation and Screening Save Lives; LCS = lung cancer screening; LDCT = low-dose computed tomography; LUNA = Optimizing Effectiveness of Smoking Cessation Intervention during LDCT Screening for Lung Cancer; LUNG = Lung Cancer Screening Patients Utilizing NRT and Gain-framed Messages; MATCH = Mayo and Truth Collaboration for Health; NCI = National Cancer Institute; NCORP = National Cancer Institute Community Oncology Research Program; PLUTO = Program in Lung Cancer Screening and Tobacco Cessation; PROACT = Promoting Smoking Cessation in Lung Cancer Screening through Proactive Treatment; SCALE = Smoking Cessation within the Context of Lung Cancer Screening.

diagnosis of lung cancer or identification of nonmalignant etiology of findings) may also influence cessation outcomes. Researchers in cessation trials conducted in the context of LCS will need access to this information to evaluate the potential moderation of study outcomes. CMS requires participation in a registry for all centers conducting LCS. Currently, the only approved U.S. registry is that of the American College of Radiology (72). The registry may facilitate recovery of scan results to include in analysis.

Cost-Effectiveness Analyses

Clinical trials in this setting should consider including cost-effectiveness analyses, especially given the number of current smokers who will undergo LCS if recommendations are fully implemented. A broad range of smoking interventions have been shown to be very cost effective (73), from low-intensity electronic aids (74) to pharmacotherapy guided by pharmacogenetic testing (75). Smoking cessation intervention for lung cancer patients has also been shown to be cost effective (76). Data suggest that the cost effectiveness of LCS would be improved by between 20% and 45% if smoking cessation were added (77). However, even small differences in the cost of smoking cessation treatment will become important if programs are fully scaled up. Increased costs, however, may be mitigated at least in part by increased quit rates. Researchers in clinical trials can contribute to addressing this knowledge gap by collecting data about the fixed costs (e.g., overhead, training) and variable costs (e.g., participants, interventionists, medications). The Cancer Intervention and Surveillance Modeling Network models the effectiveness and cost effectiveness of cancer control initiatives, and it is planning to quantify the impact of smoking cessation integrated with LCS on mortality and cost effectiveness (78). The majority of SCALE trials will contribute data to this effort.

SCALE Trial Solutions

Investigators in the eight trials participating in the SCALE collaboration have considered these issues. A summary of strategies to address some of the key questions is shown in Table 3. Similar to all clinical trials, choices are governed by a combination of choosing the best design to address the scientific questions at hand and feasibility considerations.

Conclusions

There is a strong rationale for providing smoking cessation interventions for patients who smoke and are undergoing LCS. Effective smoking interventions could augment the benefits of LCS by reducing mortality and morbidity resulting from lung cancer, as well as from cardiovascular disease, cerebrovascular disease, and chronic obstructive pulmonary disease, among others.

Fortunately, a new set of RCTs will contribute information to the design and implementation of smoking cessation interventions in the context of LCS. All SCALE collaboration trials will use a common core and optional dataset (79). Coordination of measures will provide the capacity to merge and pool data across studies, as well as an opportunity to examine subpopulations of patients who are inadequately represented in single studies. The collaboration will also facilitate testing exploratory hypotheses regarding, for example, intensity of smoking intervention and the effectiveness of specific pharmacotherapies.

There are limitations not only to each of the trials in the SCALE collaboration but also to the group of studies as a whole. For example, some racial and ethnic groups will not be fully represented in the participant pool; head-to-head comparisons among medications are limited; and most participants will be having baseline screens, owing to the fact that LCS recommendations are only starting to be implemented. The efficacy of smoking cessation treatment may vary over the course of a patient's experience with screening. Also, the potential impact of incidental findings that are related to tobacco use, such as coronary calcification, on smoking cessation is important. There is still a considerable need for additional investigation of these questions and others.

Those designing clinical trials of smoking cessation in LCS should consider various methodological and practical issues presented in this paper. Examples include eligibility criteria, coordination of smoking intervention with LCS events, timing of assessments, and whether and how to incorporate screening results in smoking intervention. Feasibility may guide some of the many choices that are required, and some of the choices harbor important research questions. Regardless of design decisions, we recommend, whenever practical, that investigators collect data to describe these parameters so that the hypotheses can be explored in secondary analyses.

The advent of LCS affords a transformative opportunity to reduce morbidity and mortality of lung cancer. Innovative, methodologically rigorous trials focused on the dissemination and implementation of smoking cessation programs in the context of LCS will help achieve the full benefits of LCS. ■

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