MSK PROTOCOL COVER SHEET

Implementing Tobacco Treatment in Low Dose CT Lung Cancer Screening Sites

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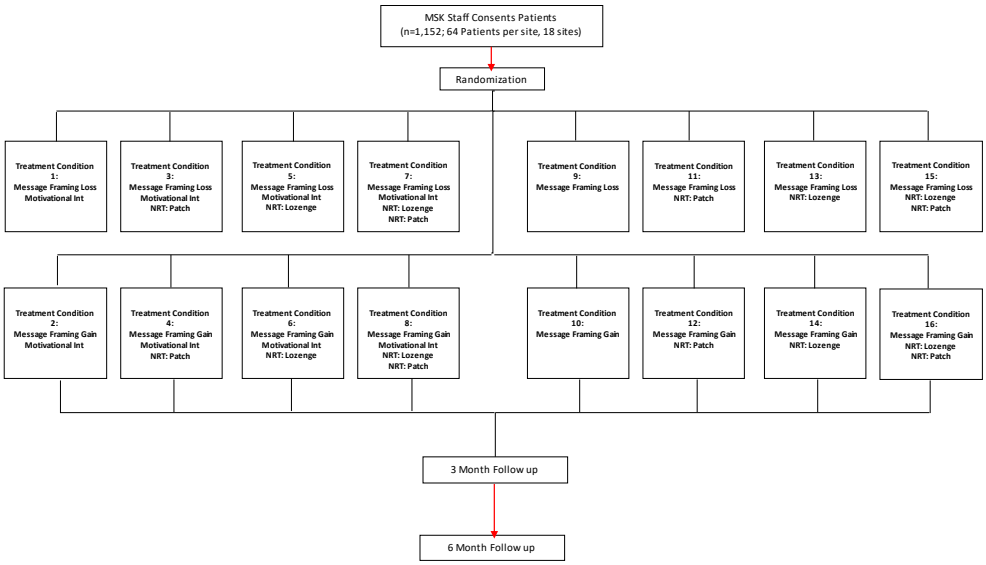
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This multi-site smoking cessation clinical trial protocol is supported by an R01 grant awarded in response to RFA #15-011 Smoking Cessation within the Context of Lung Cancer Screening. All 8 funded projects have formed the SCALE Grantee Collaboration being coordinated by the National Cancer Institute (NCI).

Our long-term goal is to maximize the public health benefits of lung cancer screening by providing a blueprint of best practices for integrating and sustaining tobacco treatment delivery in lung cancer screening settings. The current project will make a vital contribution by identifying superior tobacco treatment components with relevance for current smokers seeking screening that can be cost-effectively delivered with high implementation fidelity by heterogeneous lung cancer screening sites. The overall objective of the proposed research is to use an innovative methodological framework, the Multiphase Optimization Strategy (MOST), to design an optimized, scalable evidence-based tobacco treatment package that can be integrated within lung cancer screening sites. MOST involves highly efficient, randomized experimentation to precisely quantify the effects of individual treatment components and identify synergistic effects by combining them into an effective tobacco treatment package. This information then guides assembly of an optimized treatment package that achieves target outcomes with least resource consumption and staff burden. The rationale for the proposed research is that once an optimized tobacco treatment package is established, future comparative effectiveness trials can examine strategies for wider implementation and dissemination in LDCT-LCS settings. In partnership with the Lung Cancer Alliance and their National Framework for Excellence in Lung Cancer Screening, this NCI-funded R01 will engage 18 heterogeneous lung cancer screening sites across the United States that will serve as demonstration field sites. Sixty-four current smokers will be recruited from each of the 18 participating screening sites (n=1,152). Smokers will be randomly assigned to one of 16 experimental tobacco treatment conditions. The primary outcome is smoking abstinence at six months follow-up. The findings will guide assembly of an optimized smoking cessation treatment package that achieves superior cessation outcomes with attention to minimizing burden in lung cancer screening sites.



We received an NCI Diversity Supplement to support an ancillary investigation,

ed to throughout this protocol as the PACT (Participation of African-Americans in Cessation Trials) ancillary study, to develop a better understanding of recruitment and engagement of African-American smokers seeking lung cancer screening into tobacco cessation treatment. By having a better understanding of why patients refuse to enroll in CASTL, we can potentially improve recruitment strategies and education for CASTL as well as other future tobacco treatment trials. Dr. Chloé M. Martin, our Co-Chief Postdoctoral Research Fellow in the Department of Psychiatry and Behavioral Sciences will be examining reasons for refusal among African-American smokers who refuse participation in our CASTL Trial (n=30).

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Aim 1: To use a highly efficient MOST design to identify which of four evidence-based tobacco treatment components contribute to superior cessation endpoints among current smokers seeking lung cancer screening. The four tobacco treatment components to be tested are: (1) Motivational Interviewing (MI) (Yes vs. No); (2) Nicotine Replacement Therapy (NRT) Patch (Yes vs. No); 3) NRT Lozenge (Yes vs. No); and 4) Message Framing (Gain vs. Loss). We hypothesize that all four treatment component main effects will be statistically superior to Standard Care and that some synergistic treatment component effects will emerge. The primary cessation outcome will be biochemically verified smoking abstinence at 6 months following study enrollment. Secondary cessation outcomes will be self-reported 7-day point prevalence abstinence at 3 months, continuous abstinence (between date of randomization and date of completion of follow-up surveys) at 3 and 6 months, self-reported 24 hour quit attempt at 3 and 6 months.

Aim 2: To estimate the cost and incremental cost-effectiveness of evidence-based tobacco treatment components, delivered alone and in combination.

Aim 3: To conduct a robust, mixed methods evaluation of the implementation process and assess organizational factors that may influence referrals, dissemination and implementation of delivering effective models for smoking cessation treatment in lung cancer screening settings.

Aim 4 (PACT ancillary study): To gain a better understanding of factors impacting refusal among African-American smokers using a rigorous qualitative approach.

3.0 BACKGROUND AND RATIONALE

Heralded as a seminal breakthrough in cancer prevention and control (1), the United States Preventative Services Task Force (USPSTF) recommends annual low dose computed tomography (LDCT) for high-risk smokers and the Centers for Medicare and Medicaid Services (CMS) has determined that Medicare will cover LDCT for lung cancer screening (LDCT-LCS) at radiology imaging sites that provide high quality screening. Considering that there are an estimated 8.6 million Americans eligible for lung cancer screening and that approximately 50% are likely to be current smokers, LDCT-LCS provides an unprecedented opportunity to further reduce tobacco-related morbidity and mortality by delivering evidence-based smoking cessation treatment within the context of LDCT-LCS (2, 3).

Dr. Ostroff and colleagues were the first investigators to examine how the context of lung cancer screening may influence smoking beliefs, quitting motivation and behaviors (4). At baseline, we found that 85% of current smokers seeking LDCT-LCS were considering quitting within the next 6 months. We found that 23% of current smokers (n=134) reported smoking cessation 12 months following enrollment in a lung cancer screening program. Our group also published smoking relapse data from (5) former smokers at baseline and found very low 6-year cumulative rates of relapse (4%) at annual repeat follow-up suggesting that screening and the reassurance of a negative screen had little effect on relapse among long-term former smokers. We have also studied risk perceptions, utilization of evidence-based tobacco treatment following enrollment in LDCT-LCS (6) and adherence to repeat scans (7-10).

Most recently, our group published a paper summarizing the organizational priority, readiness and current tobacco treatment practices of a nationwide sample of LDCT-LCS sites (11). We partnered with the GO_2 Foundation to collect online surveys (n=93, 61% response) from a network of Site Coordinators at LDCT-LCS sites. Organizational priority for promoting smoking cessation was high. Most sites reported that patients are routinely asked about their current smoking status (99%) and current smokers are advised to quit (91%). Fewer (57%) sites routinely provide cessation counseling or refer smokers to a quitline (60%) and even fewer (37%) routinely recommend cessation medications. Perceived lack of patient motivation to quit, limited time and lack of staff training were the most frequently cited barriers for delivering smoking cessation treatment. Findings indicate that further attention to treatment implementation is needed in order to maximize the potential benefit of integrating smoking cessation into lung cancer screening protocols.

PACT Ancillary study: It is well established that recruiting African-Americans in tobacco cessation trials is often challenging (12). African-Americans have high lung cancer mortality rates (12-14) Smoking is a modifiable behavior that significantly contributes to the life expectancy gap between Black and White men in the U.S. (15) and results in excess health expenditures (16).

Fortunately, African-American smokers indicate that they want to quit smoking (17, 18) and when engaged in evidence-based tobacco treatment, African-Americans have been able to successfully quit smoking (19, 20) resulting in reduced lung cancer mortality (13, 14, 21). These findings underscore the need to identify effective recruitment strategies targeting African-American smokers (22).

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

Overview. The overarching study goal is to apply the MOST approach to determine which of four tobacco treatment components or combinations of components contribute to the highest point prevalence abstinence. The four treatment components are: 1) Motivational Interviewing (yes vs. no); 2) Nicotine Replacement Therapy (NRT) Lozenge (yes vs. no); 3) NRT Patch (yes vs. no) and 4) Message Framing (gain vs. loss). The selection of these treatment components was guided by consideration of potential counseling and cessation medication options with demonstrated safety, efficacy and broad relevance to smokers (23). Our final selection of treatment components also reflects the LDCT-LCS site preferences and resource limitations identified in our prior work (11). Based on random assignment, participants may receive one or more of the tobacco treatment enhancements.

Study Design. We have chosen to conduct a full factorial experimental design (16 experimental conditions shown in Table 1) for two reasons. First, factorial experiments separate component effects. Our design enables estimation of the main effect contribution of each of the four treatment components and all interactions between components. Second, a factorial experiment is a highly economical way to obtain this information compared to alternative parallel-arm design (24, 25). A total sample of up to 36 site coordinators and 1,152 smokers seen at 18 U.S. lung cancer screening sites (estimated accrual of 64 current smokers per site) will be randomized into the full factorial design of 16 intervention conditions. With 20% expected attrition, we anticipate a final sample size of 922.

Table 1: Summary of Experimental Conditions/Treatment Components

Components / Conditions	Enhanced Standard Care	Motivational Interviewing	NRT Lozenge	NRT Patch	Message Framing
1	Yes	Yes	None	None	Loss
2	Yes	Yes	None	None	Gain
3	Yes	Yes	None	Patch	Loss
4	Yes	Yes	None	Patch	Gain
5	Yes	Yes	Lozenge	None	Loss
6	Yes	Yes	Lozenge	None	Gain
7	Yes	Yes	Lozenge	Patch	Loss
8	Yes	Yes	Lozenge	Patch	Gain
9	Yes	No	None	None	Loss
10	Yes	No	None	None	Gain
11	Yes	No	None	Patch	Loss
12	Yes	No	None	Patch	Gain
13	Yes	No	Lozenge	None	Loss
14	Yes	No	Lozenge	None	Gain
15	Yes	No	Lozenge	Patch	Loss

16	Yes	No	Lozenge	Patch	Gain

It is important to understand that this design should not be considered a 16-arm RCT. This factorial design is powered very differently from a parallel-arm RCT design (26). All of the estimated main effects and interactions will be based on all experimental subjects. For example, the main effect of Motivational Interviewing will be estimated by comparing the average abstinence rates of Experimental Conditions 1 through 8 versus the mean of Experimental Conditions 9 through 16. Similarly, the main effect of NRT Lozenge will be estimated by comparing the average abstinence rates of Experimental Conditions 5-8 and 13-16 vs. the average abstinence rates of Experimental Conditions 1-4 and 9-12. We opted for a full factorial design rather than a fractional factorial design because: 1) synergistic effects may occur when behavioral interventions are combined; 2) smokers may respond to a unique combination of several intervention components; and 3) cost-effectiveness of higher-level interactions (e.g., non-linear, multiplicative effects) provide information on the feasibility of intervention bundles.

The GO_2 Foundation will be responsible for the recruitment of 18 US lung cancer screening sites (community-based and academically-affiliated sites). Participating sites will be selected from a large and growing network (n=450+) of screening sites that have pledged adherence to the GO_2 Foundation's Guiding Principles for Lung Cancer Screening Excellence and have been designated as an American College of Radiology (ACR) Lung Cancer Screening Center (27). Our pilot data (11) indicates strong site enthusiasm (85% agreement) for participation in research testing various models for integrating tobacco dependence treatment. MSK will be the lead site for this study. For practical (research staffing capacity) reasons, we will recruit and engage LDCT-LCS sites in staggered waves to efficiently manage the resources that we have available (total n = 18). We will recruit up to 36 site coordinators from the LDCT screening sites (approximately 2 site coordinators/site) and each LDCT-LCS site will recruit 64 participants (Total n=1,152). We will work with each site to tailor the implementation of CASTL project recruitment, data collection and tobacco treatment delivery in a manner consistent with their existing workflow.

Once an eligible screening site cedes regulatory oversight to MSK and signs the Memorandum of Agreement (MOA) and Data Transfer Agreement , we will verbally consent the LDCT-LCS Site Coordinators (SCs) as participants in this study. The NRT medication supplies, patches and lozenges, will be ordered and sent to the site for distribution to consented smokers randomized to treatment conditions that call for NRT use on the day of their randomization, sent to the site by MSK pharmacy for dispensing on the day of the randomization, or sent by mail directly to participants from GlaxoSmithKline Consumer Healthcare via their distribution partner Arrowhead Promotion & Fulfillment once they have been randomized – medication orders will be placed through Arrowhead's website after the participant has completed their baseline survey and they have been randomized. Prior to recruitment of eligible smokers and delivery of tobacco treatment, SCs will complete a 30 minute baseline survey (Appendix A) administered via telephone by MSK study staff, the screening site coordinator or REDCap. SCs will receive training (described in section 4.2) regarding all study-related research and clinical procedures. To provide additional flexibility around clinical operations at each of the sites, sites may choose to identify clinical staff to be trained other than the site coordinator (e.g. residents) to deliver the intervention to patients, specifically the counseling and the medication use training. These "interventionists" will not be asked to complete any surveys and therefore will not be consented. The MSK PI or study staff will

also be able to deliver the counseling intervention to patients if needed. At each site, eligible smokers will be informed about the smoking cessation study when scheduling or discussing their LDCT scan (Appendix T). Eligible smokers who express preliminary interest will provide verbal and/or written permission (Appendix T) to be contacted by MSK research study staff to learn more about the study. Study posters and brochures will also be placed at screening sites allowing patients interested in participating to contact MSK directly to enroll in the study. Permission forms will not be provided for patients who self-refer to the study. MSK staff will contact all eligible smokers by telephone, and obtain verbal consent from interested and confirmed eligible participants. MSK research staff will also collect the baseline (Appendix B) survey either by phone, mail or via REDCap. The baseline survey is expected to take about 25 minutes to complete and must be completed within 1 month of the date of consent. Given the expected clinical volume, we anticipate that most sites will be able to recruit 64 eligible smokers within approximately 6-9 months. Follow-up surveys (Appendix C) will be collected from participating smokers at 3 months (expected to take about 35 minutes to complete) and 6 months (expected to take about 20 minutes to complete) post-randomization. These will be conducted either over the phone by MSK staff, via mail, REDCap or by the screening site coordinator. In order to biochemically verify self-reported abstinence at 6 months, we will collect saliva samples from those reporting abstinence and analyze samples (to be conducted by the Orlow MSK Molecular Epidemiology Lab) to measure cotinine, a metabolite of nicotine. Participants will be asked to submit a smoking abstinence verification form along with their sample (Appendix N). Other strategies for smoking status verification (e.g., carbon monoxide monitor, designated proxy) may be used when necessary.

For the ancillary PACT study, Site Coordinators will be contacted to schedule an approximately 45 minute semi-structured referral interview with Dr. Martin once they have approached at least 30 participants. These interviews (see draft in Append E) will be audio-recorded using an encrypted device (Olympus DS-3500) and transcribed for analysis of qualitative themes. Site coordinators will receive a $50 e-gift card incentive for their participation in this additional interview.

At the end of the site's participation (i.e. delivery of the study interventions to all of the site's 64 participants), Site Coordinators will complete a follow up survey via REDCap, which is expected to take approximately 15 minutes (Appendix D) and will be contacted by MSK research staff to complete an audio-recorded semi-structured interview (see draft attached - Appendix E) via WebEx, a secure, widely used, and HIPAA compliant communication platform, and will take an estimated 30 minutes to 1 hour. Site coordinators will receive a $500 incentive (money order, e-gift card or gift card) in appreciation for the services after completion of their semi-structured interview. For sites whose SCs cannot receive the incentive directly, the payment will be rolled into their final site honorarium.

Smokers (eligible screening enrollees) will receive financial incentives (money order, e-gift card or gift card) for completion of baseline and follow-up surveys (Baseline: $25 incentive; 3 Month Follow-Up: $25 incentive; 6 Month Follow-up: $25 incentive). If participants respond to the study surveys within 2 days of receipt, they will receive an additional $10. Participants reporting 6 month smoking abstinence will also receive $25 incentive for return of saliva sample collection and an additional $10 incentive if the sample is returned within 1 week of the kit being delivered to the participant.

PACT Ancillary study

Self-identified African-American smokers (n=30) who are site eligible for participation in the CASTL trial but have declined participation to CASTL either actively (i.e. stated s/he is not interested) or passively (i.e. did not respond to invitation) will be invited to participate in this PACT sub-study. Maine Medical Center Cancer Institute will be exempt due to low screening rate of African-American smokers at Maine. Participation consists of a semi-structured interview (Appendix AA) conducted via the MSK telephone conferencing system, Cisco WebEx, by Dr. Martin. The semi-structured interview will last about 30 minutes and will be audio-recorded via the WebEx recording function. These interviews will be transcribed by Ubiqus for subsequent coding of qualitative themes.

In appreciation for their time and attention, a $50.00 gift card (or e-gift card) will be mailed or emailed to all participants (African American smokers) who participate in the PACT interviews.

Cost and Cost-Effectiveness Endpoints

The economic impact of the tobacco treatment components will be assessed by performing (1) a cost analysis and (2) a cost-effectiveness analysis. The goal of the cost analysis is to estimate the incremental costs associated with delivering tobacco treatment components in the context of LDCT-LCS. The primary endpoint of this analysis is the cost of each treatment component and the cost of each permutation of components. The base-case cost analysis will take a societal perspective, including the costs of all resources consumed for the implementation and delivery of smoking cessation treatments. In separate analyses, we will examine costs and potential payment sources (e.g., health insurance benefits) from the provider (i.e., LDCT-LCS site) perspective, in order to estimate the net cost to screening sites that want to adopt the optimized treatment combination or individual components of it. While analysis from the societal perspective includes all costs regardless of the parties to whom they accrue, analysis from the LDCT-LCS perspective can inform the very practical decision making and budgeting that are essential to sustainable dissemination of smoking cessation interventions.

Information to estimate tobacco treatment costs will be captured from several sources. Treatment logs documenting the delivery of treatment components will be used to ascertain average time spent (see Appendix P) will be compiled by MSK research staff, based upon the intervention checklists submitted for each participant by their SC (Appendix L). The cost of personnel time will be based on site-specific salaries. In sensitivity analysis, we will substitute site-specific salary information with national average wage rates for the relevant occupational categories from the Bureau of Labor Statistics. Administrative and overhead costs will be estimated by each study site. The cost of NRT lozenges and NRT patches will be based on the acquisition costs. In sensitivity analysis, we will examine a range of unit cost values for these items, reflecting the range of values reported in the medical literature and on pharmacy websites. Intervention cost estimates will include only the resources used in implementing and delivering the study interventions. They will not include the cost of resources used solely for research purposes.

Cost-effectiveness will be estimated as the incremental cost per quit achieved, where effectiveness is defined by the primary endpoint of biochemically verified, 7-day point prevalence abstinence at 6 months. In addition to intervention costs, described above, the numerator of the cost-effectiveness ratio must also reflect relevant downstream costs within the 6-month follow-up

period. This includes the costs of smoking cessation supplies consumed after the study treatment period and other non-study tobacco treatment services received, and the patient time and travel costs associated with these services. Utilization of additional tobacco treatment will be reported by patients as part of the 3- and 6-month follow-up surveys. Unit cost values will obtained from the Medicare Physician Fee schedule and Resource-Based Relative Value Scale (RBRVS). Even though not all study participants will be Medicare beneficiaries, Medicare's reimbursement methodology, based on the RBRVS, was developed to reflect true resource costs (28). In sensitivity analysis we will evaluate a range of unit cost estimates, both lower and higher than the average Medicare reimbursement level. Patient time and travel costs will be based on participant self-report in the tobacco treatment utilization survey.

Consultant Roles and Expertise: This proposal brings together an outstanding group of investigators co-led by Drs. Jamie Ostroff at Memorial Sloan Kettering Cancer Center (MSKCC) and Donna Shelley at New York University Medical Center (NYUMC). Dr. Shelley will assist in the development of the evaluation plan and finalization of the data collection tools. She will also assist in the training and supervision of the Site Coordinators Dr. Shelley will contribute to the data analysis and dissemination of research project findings through oral presentations and manuscript preparation. She will not receive any identifiable patient data. Collectively, the investigative team has relevant expertise in tobacco treatment (Ostroff, Shelley), training providers to deliver tobacco treatment and facilitating tobacco treatment delivery in health care settings (Shelley, Ostroff), implementation science (Shelley, Ostroff, Weiner), cost analysis (Elkin), trial methodology/statistics (Li, Collins), cancer risk communication and message framing (Banerjee), and radiology and lung cancer screening. A major strength of this proposal is the collaboration with Dr. Linda Collins, who has applied design ideas from engineering (29-31) to develop the Multiphase Optimization Strategy to meet the unique needs of behavioral scientists wanting to design and evaluate optimized behavioral interventions. In addition, the feasibility and sustainability of the work is enhanced by the well-established partnership with the G02 Foundation for Lung Cancer (formerly the Lung Cancer Alliance), a leading lung cancer patient advocacy group that has been at the forefront of driving lung cancer screening from research-to-policy-to-practice. The GO_2 Foundation has developed collaborative relationships with a large network of lung cancer screening sites (n=450+) throughout the United States that have pledged adherence to the guiding principles for high quality lung cancer screening.

4.2 Intervention

Training of LDCT-LCS Site Coordinators: To enhance the real-world generalizability, the Site Coordinators (SCs) employed by LDCT-LCS sites or another site designated clinical "interventionist" will deliver the tobacco treatment to consented patients. Recognizing that our prior work (11) identified a strong need for staff training, participating SCs/interventionists will receive training via webinar presentations from Drs. Shelley and/or Ostroff. The training will be divided into sections as outlined below. Drafts of the training materials that will be used are included in the Appendix items (see Appendices F, H & J). At least one booster training session targeted to address problem areas identified during the collaboratory calls will be conducted during the aforementioned calls following the start of recruitment at each site.

Standard Care: SCs/interventionists will receive 1 hour of training on distribution of self-help cessation materials and referral to the Quitline.

MI Training: SCs/interventionists will receive 1 hour of didactic training in brief MI (Appendix F). In addition to the training, each SC/interventionists will receive an MI/cessation counseling resource manual (see Appendix J) that will provide a detailed overview of the MI session contents and complete an MI self-assessment for each participant assigned to the MI treatment arms (Appendix L). They will also receive a copy of the MI Treatment Integrity Coding Manual (Appendix H) (32).

NRT (Lozenge and Patch) Training: SCs/interventionists will receive 1 hour of training about use of NRT (lozenge and patch for management of nicotine cravings and other symptoms of nicotine withdrawal).

During each site's period of active engagement and tobacco treatment delivery, participating SCs will meet about weekly by conference calls (i.e. collaboratory calls), conducted via WebEx (will be recorded), with members of the CASTL team, including Drs. Ostroff and/or Shelley for group supervision intended to promote adherence to the study protocol.

Treatment Components

Enhanced Standard Care: Once trained, all SCs will deliver a minimum standard of tobacco treatment including distribution of self-help cessation materials and enactment of a seamless workflow for referring all current smokers from their LDCT-LCS site to the Quitline; currently available in all 50 states and the District of Columbia, and accessed by calling the 1-800-QUIT NOW portal that transfers callers to their respective state Quitline. LDCT-LCS sites will distribute an educational brochure developed by the GO_2 Foundation that targets smokers seeking lung cancer screening, *Why Quit Now? A Resource for Those at Risk for Lung Cancer* (see Appendix I).

1. Motivational Interviewing (MI) (33): was selected to engage smokers with varying levels of quitting motivation. There is substantial evidence that even brief MI can increase adherence to tobacco treatment and quit rates. Smokers assigned to the MI component will receive two MI-informed cessation counseling sessions (Appendix N); the first session delivered face to face or via telephone by the SC within 1 month of randomization and the second, a booster session, delivered via telephone by the SC approximately 1 month (- 2 weeks /+ 1 month) after the first MI counseling session (see Appendix J for MI Training Manual). Reminders for scheduling MI II sessions will be made via phone and/or email.

2. Nicotine Lozenge (34, 35): Participants randomized to receive the nicotine lozenge (over the counter) will receive 6 packs of NRT 2mg lozenge and written instructions (Appendix K) to use the lozenge PRN to help manage acute nicotine withdrawal. Participants will be instructed to use the NRT lozenges no more than every 1-2 hours as needed. Participants will receive their study medications from their site coordinator or via mail from Arrowhead Promotion & Fulfillment after randomization.

3. Nicotine Patch: Participants randomized to receive the nicotine patch (over the counter) will receive 6 weeks of NRT patch with dosing dependent upon reported baseline cigarettes per day and written instructions (Appendix K) to use the patch daily starting on the date they mutually agreed upon with their site coordinator(34). Participants who smoke fewer than 10 cigarettes per day will receive 4-weeks of the 14mg patch (2 boxes), and 2-weeks of the 7mg patch (1 box). Those who smoke 10 or more cigarettes per day will receive 2-weeks of the 21mg patch (1 boxes), 2-weeks of the 14mg patch (1 box) and 2-weeks of the 7mg patch (1box). Participants will receive their study medications from their site coordinator or via mail from Arrowhead Promotion & Fulfillment after randomization.
4. Message Framing: Overall, a robust body of health communication literature demonstrates that gain-framed messages may be more effective than loss-framed or non-framed (neutral) messages for encouraging smoking cessation (36). In other words, quitting messages that promote smoking cessation are more persuasive if they emphasize the benefits of quitting (gain-framed) rather than the risks (loss-framed) of persistent smoking (36, 37). Within 1 month of randomization, participants will receive a printed individualized quitting message that emphasizes either the benefits of quitting (gain-framed) or the risks of continuing to smoke (loss-framed) and/or a link to a video or audio recorded version of the message via REDCap (Appendix G). A manipulation check will be conducted at the end of the video (Appendix G) and will also be included in the 3-month patient survey (Appendix C1).

Treatment Fidelity. We will use several approaches to enhance and measure fidelity to implementing Standard Care and the four treatment components following recommendations of the Treatment Fidelity Workgroup of the NIH Behavior Change Consortium (38, 39).

1. Training: Standardized didactic presentations will be used for all webinar training sessions. We will also confirm MI competency using role play of simulated cases.
2. Treatment condition: After patient registration and randomization, a designated MSK CRC will send each SC a secure email containing the patient's treatment assignment.
3. Treatment implementation: The study team will be responsible for collection and documentation of all implementation fidelity data. To assess referrals to the Quitline, we will obtain referral data from the SCs (e.g., review of fax referral forms). MSK research staff will obtain a monthly customizable, detailed utilization report from Arrowhead. This will include all basic information such as which patient received NRT, when it was ordered, when it was delivered, who placed the order, the exact package contents, delivery address, and other usable data points. SCs will complete a treatment manual for each participant and self-assessments for those receiving MI (see Appendix L) (32). The signed treatment manuals will be scanned and returned to MSK staff via email within 2 business days of the intervention delivery or SCs may directly update the REDCap database with this information. Study staff will request quitline utilization data from the NCI quitline intermittently throughout the project. Finally, study staff will document distribution of the message framing letter and scripted video/audio (Appendix G). Patient participants will be asked to submit a medication log (Appendix W) that we will use to determine adherence.

5.0 CRITERIA FOR SUBJECT ELIGIBILITY

5.1 Subject Inclusion Criteria

Site Eligibility (as per SC self-report)

- Must be designated as an American College of Radiology (ACR) designated lung cancer screening site
- Reports at least one year of lung cancer screening experience
- Reports conducting at least 20 new initial screenings per month

Site Coordinator (SC) Eligibility (as per SC self-report)

- Employed at a participating lung cancer screening site

Patient Eligibility (as per site/self-report)

- Between the ages of 50-80 years old (at the time of their scheduled or completed LDCT scan)
- Has a scheduled baseline or annual follow-up LDCT lung cancer screening within 60 business days **OR** has had a baseline or annual follow-up LDCT lung cancer screening within the last 60 business days and received the result for that scan **OR** has had a baseline or annual follow-up LDCT lung cancer screening but has not received the result for that scan
- Have at least a 20 pack-year history of smoking (per site report)
- Currently a smoker, defined as self-reported cigarette smoking (some days, every day) within the past 30 days.
- Must be reachable by telephone
- Must be English or Spanish speaking due to the study materials being available only these languages and limited available resources for translation.

PACT Ancillary study Patient Eligibility

- Listed as eligible for CASTL by the site as per the site weekly log
- Self-Identifies as African-American on the site weekly log
- Refused participation to CASTL either actively (communicated they are not interested) or passively (did not respond to an invitation to CASTL)
- Must be reachable by telephone
- Must be English speaking due to the study materials being available in English only and limited available resources for translation.

5.2 Subject Exclusion Criteria

Patient (as per self-report)

- NRT is medically contraindicated (e.g., recent heart attack within the last 2 weeks or unstable/worsening angina).
- Smokers who are receiving other tobacco treatment services or have used cessation medications (NRT, bupropion, varenicline) within the past month with the intent to quit smoking (used NRT 15+ days in the past month).
- Patients with complications that may prevent them from participating in the study (per the discretion of the screening site coordinator or study PI)

6.0 RECRUITMENT PLAN

Recruitment of Sites and Site Coordinators: Staff from the GO_2 Foundation will coordinate recruitment and retention of participating LDCT sites for this study. Eligible sites will have at least one year of lung cancer screening experience, will have a full-time SC and will report conducting at least 20 initial screenings per month so as to have an adequate patient volume for feasible recruitment of current smokers during the allotted study timeframe. As stated earlier, this study will recruit and engage LDCT-LCS sites in staggered waves for a total of 18 sites. MSK staff will verbally consent the SCs at each of the sites.

Recruitment of Smokers Seeking Lung Cancer Screening: We plan to recruit up to 36 site coordinators and 64 smokers from each site to achieve target enrollment of 1,152 smokers. Smoking status will be ascertained by screening sites at the time of scheduling from all screening participants as required to confirm screening eligibility. All eligible current smokers will be identified by the SCs (or designee) who will introduce the study to all current smokers scheduled for or who have recently completed an LDCT scan. Patients will provide their verbal permission to be contacted by MSK staff (Appendix T) and SCs will provide current smokers' names and contact information to the MSK study staff member (Appendix Q) at the end of each workday. Patients will also be able to self-refer to the study by calling the numbers on flyers and brochures posted at the screening sites. Permission forms will not be provided for patients who self-refer to the study. The SCs will also maintain a log of all patients who schedule a screening appointment noting the number of former and current smokers who are screened by them for study participation, if it is a baseline or follow-up screening appointment, the number of smokers who are ineligible and reasons for ineligibility, the number of refusers and their reasons for refusal, and demographic information (age, gender, race & ethnicity) of all current smokers (Appendix Q) which will be shared with MSK staff weekly and may also be shared with the NCI as part of our agreement for analysis and use in related collaborative projects (see section 13.0.1) that will be disseminated. This will include information de-identified demographics (age, gender, race & ethnicity), reasons for ineligibility and reasons for refusal. This method of recruitment has been shown to be successful for recruiting a large number of smokers in primary care clinics (40) participating in an cessation treatment effectiveness trial. An MSK CRC will contact all smokers who agree to hear more about the study. Interested patients will be screened to confirm their eligibility (Appendix V), and if eligible, will provide verbal consent. They will complete the baseline survey within 1 month of the consent date. In the final months of recruitment, the remaining active sites will receive additional incentives based on the number of participants they enroll.

PACT Ancillary study Recruitment:

The Site Coordinators of the CASTL study will be asked to give a PACT brochure (Appendix Z) either in person or via email or mail to patients who actively refuse to participate in MSK's CASTL trial (patients who do not give permission to be contacted by MSK's CASTL trial). The brochure will provide descriptive information about the PACT study. Interested patients will contact Dr. Martin directly by email or telephone (contact information is provided on the PACT brochure).

Patients who give permission to the local SC to be contacted by MSK or self-referred to the study, but actively or passively refuse CASTL once contacted by MSK staff will be provided with a verbal description of the PACT study by telephone during the point of contact or emailed a description of this PACT study once all recruitment attempts have been made.

In most cases, the initial contact with prospective participants will be conducted by the screening site team, investigator, or the research staff working in consultation with the treatment team. The recruitment process outlined above presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of:

1. Reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process;
2. Conversing with patients regarding possible enrollment;
3. Handling of PHI contained within those records and provided by the potential subjects;
4. Maintaining information in a screening log of patients approached.

7.0 ASSESSMENT/EVALUATION PLAN

MSK study staff will collect all assessment data from SCs and patients but the site SCs will collect data on screening site characteristics and implementation of tobacco treatment.

Conceptual Framework and Evaluation Plan: Two complementary evaluation frameworks, RE-AIM and Proctor's Implementation Outcomes Framework (IOF) guide our assessment plan and selection of implementation outcomes (31, 41). RE-AIM emphasizes five dimensions essential for assessing an intervention's potential for dissemination and public health impact. These include the: 1) intervention's reach into the target population; 2) intervention effectiveness; 3) adoption, 4) implementation fidelity; and 5) maintenance of effects. IOF expands the RE-AIM framework to include additional implementation outcomes: acceptability (perception that treatment is agreeable or satisfactory), appropriateness (intervention fit/ workflow compatibility), sustainability (potential for sustained use/integration and barriers to achieving durability), and cost. Finally, we will explore additional organizational characteristics or "inner settings constructs "defined by the Consolidated Framework for Implementation Research (CFIR) (e.g., organizational priority, implementation climate, resources, leadership) that may influence the implementation of smoking cessation treatment in lung cancer settings (42). The assessments include core and opt-in items that were chosen with consensus by members of the SCALE Collaboration (43). In order to minimize attrition, participants will receive a combination of 6 reminder phone calls, and/or emails, based upon their preference, for follow-up data collection – we will leave a maximum of 3 voicemails, and send up to 3 emails to participants who provide an email address. Participants who are unreachable after these attempts will be mailed a hardcopy of the survey for completion. Collection of the baseline survey will occur at T^{P1}within 1 month of consent), collection of the 3-month patient follow-up assessment will occur at T^{P2} (three months after randomization -1/+2 months), and collection of the 6 month patient follow-up assessment will occur at T^{P3} (six months after randomization -1/+6 months). Site coordinator follow-up and semi structured interviews will occur at T^{S1} (end of recruitment at each site +3 months). Semi-structured interviews to discuss referrals will occur once each site has approached at least 30 patients for participation in the CASTL study (T^{S2}).

Study constructs and assessment time points			
	PACT	**Patient**	**Site Coordinator Assessment**

	Participants	Assessment					
Domains (Administration Time)	Baseline	Baseline (T^{P1})	3 Month FU (T^{P2})	6 Month FU (T^{P3})	Baseline	During Study (T^{S2})	Study Conclusion (T^{S1})
Background Characteristics (8mins)		X					
Smoking Health Beliefs (5mins)		X	X	X			
Psychological Variables (2mins)		X	X	X			
Tobacco Use (5 mins)		X	X	X			
Smoking Cessation Attitudes (5mins)		X	X	X			
Program Satisfaction (15mins)			X				
Site Coordinator Characteristics (5mins)					X		
Site Characteristics (10mins)					X		
Organizational Priority & Feasibility (15mins)					X		X
Semi-structured Interview – Referrals (45mins)						X	
Semi-structured Interview – Implementation Process (~30-60mins)							X
Biochemical Verification of Smoking				X			
PACT Ancillary study interview (30min)	X						
Total Approximate Administration Time	30 min	25 min	35 min	17 min	30 min	45mins	45-75 min

Background Characteristics: We will collect background sociodemographic and medical history data from smokers at baseline (Appendix B). This includes questions aimed at assessing their health literacy and health status. This is expected to take about 8 minutes to complete.

Smoking Health Beliefs: Smoking health beliefs will be assessed to determine participants' perception of absolute and comparative risks of developing cancer. These questions were adapted from the National Lung Screening Trial (NLST). These items will be administered at the patient baseline and follow up assessments and are expected to take about 5 minutes to complete.

Psychological Variables: We will collect data on depressed mood using standardized items from the SCALE Collaboration. These items will be administered at the patient baseline and follow up assessments and are expected to take about 2 minutes to complete.

Tobacco Use: Tobacco use will be assessed utilizing standard questions for smoking cessation trials. We will use standard items assessing lifetime and current smoking pattern, number of cigarettes smoked daily, years of regular smoking, number of prior quit attempts, and longest period of cessation in the past year. These measures consist of questions on the 2015 NHIS Questionnaire (44). Nicotine dependence will be assessed with the *Fagerstrom Test of Nicotine Dependence* (FTND), a six-item self-report scale that assesses smoking behavior to estimate physical dependence level (45). We have included 1 question that asks about changes in tobacco use since the COVID-19 pandemic started. These items will be administered at the patient baseline and follow up assessments and are expected to take about 5 minutes to complete.

Smoking Cessation Attitudes: We will assess participants' cessation quitting history, motivation and self-efficacy using the core and opt-in items developed by consensus by the Smoking Cessation at Lung Cancer Screening (SCALE) Collaboration (37, 43, 46). These items will be administered at the patient baseline and 3 months follow up assessments and are expected to take about 5 minutes to complete. We have also included 1 question that asks about motivation to quit tobacco use since the COVID-19 pandemic started. This question will be included in the baseline and 3 and 6 month follow ups.

Program Satisfaction: Patient satisfaction will be assessed to determine how instrumental the study was in helping participants quit smoking. This data will be conducted during the 3 month follow up and is expected to take about 15 minutes to complete. For those patients who do not complete the 3 month follow up, we will ask these items at the 6 month follow up.

Site Coordinator Characteristics: Data regarding site coordinator demographics, primary role at the lung cancer screening site and prior training as a tobacco treatment specialist, and smoking related beliefs will be collected at baseline. This is expected to about 5 minutes to complete.

Site Characteristics: Data regarding site characteristics (e.g., geographic region, patient volume, organizational priority for treating tobacco dependence, academic affiliation, etc.) will be collected from the SC to inform us of standard site practices, and barriers/facilitators of implementation. This information will be collected during the SC baseline and follow up assessments and is expected to take about 10 minutes to complete.

Organizational Priority & Feasibility: Organizational priority surrounding the treatment of tobacco use in the context of lung cancer screening and the feasibility of implementing such processes will be assessed at baseline and follow-up using the Site Coordinator survey. It is expected to take approximately 15 minutes to complete.

Referrals: The drafted semi-structured interview (Appendix E) will assess the attitudes and experiences of site coordinators related to participant recruitment and will cover topics such as barriers, challenges and facilitators of referring participants to the CASTL study. It is expected to take about 45 minutes to complete.

Implementation Process Outcomes: The drafted SC semi-structured interview (Appendix E) will assess implementation processes including barriers (e.g., staffing, other resources, policy alignments) and facilitators for sustaining tobacco treatment components as routine practice in the LDCT-LCS once their site has completed participation. It is expected to take about 30 minutes to 1 hour complete.

Biochemical Verification of Tobacco use: Patients who report smoking abstinence within the past 7 days will be sent a saliva sample collection kit with a smoking abstinence verification form, instructions for saliva sample collection and shipping to MSK study staff by mail (Appendix N). Patients will be asked to return the saliva kits within approximately 4 to 8 weeks following the collection of their 6-month follow-up survey. In order to minimize misreporting, we will inform patients prior to obtaining their self-reports that a saliva test will be performed to examine recent tobacco exposure. Saliva specimens will be tested for cotinine which is regarded as the gold

standard for biochemical verification of smoking exposure. Salivary cotinine values of ≥3ng/mL, 1-2.9 ng/mL, and <1ng/mL are consistent with active, passive, and no smoking exposure, respectively according to Moskos et al 2014 (47). Saliva specimens will be collected using mailing kits from study participants reporting smoking abstinence and sent back to our study staff who will, upon receipt, either hand deliver or have it sent to Dr. Irene Orlow's lab In the Department of Epidemiology and Biostatistics for cotinine concentrations using an established competitive Enzyme-Linked Immunosorbent Assay (ELISA) that is currently being used to measure cotinine levels in saliva and urine samples in other studies. Any remaining saliva will be discarded upon completion of the assays. In special circumstances (e.g., unable to produce saliva sample, long-term use of NRT), verification of smoking abstinence can be conducted with carbon monoxide breath sample and/or designated proxy.

We will also collect data on screening results (ACR LUNG-RADS, etc.) from the screening site (Appendix O) if this is applicable.

PACT sub-study interview: A semi-structured interview guide (Appendix AA) will be used to conduct the interviews. The interviews (~ 30 minutes in length) will cover topics such as barriers to tobacco treatment perceptions, attitudes, and experiences with research, and reasons for tobacco treatment trial refusal, with subsidiary probes to enable participants to elaborate on their prior tobacco treatment experiences (48).

8.0 TOXICITIES/SIDE EFFECTS

There should be minimal side effects or discomfort associated with participating in this research study for both SCs and smokers. The potential risk of participation for both SCs and smokers is loss of confidentiality. However, when we collect identifying data, unique code numbers will always replace patient names in the research database. Locked file cabinets will be used to store materials with identifying information (e.g., SC and smoker consent forms). Participants, both SCs and smokers, may refuse any part of study participation.

There are additional side effects considered to be minimal and far out-weighed by the potential benefits of participating in a cessation trial. Participating smokers may find it stressful to answer questions regarding their smoking history and behaviors especially in the context of lung cancer screening. If a smoker reports significant acute distress, the SC will assess and make an appropriate referral for clinical care if needed.

Additionally, for those smokers randomly assigned to receive NRT, the side effects are outlined below.

Nicotine Patch
The transdermal nicotine patch has been an FDA-approved treatment for nicotine dependence since 1991, and in 1996, the patch was approved for over-the-counter sale. Up to 50% of patients using the nicotine patch will have a local skin reaction. Skin reactions are usually mild and self-limiting but may worsen over the course of therapy. Local treatment with hydrocortisone cream

(1%) or triamcinolone cream (0.5%) and rotating patch sites may ameliorate such local reactions. In less than 5% of patients, such reactions require the discontinuation of nicotine patch treatment.

Nicotine is not an independent risk factor for acute myocardial events, but NRT should be used with caution among those in the immediate (within 2 weeks) post myocardial infarction period, those with serious arrhythmias, and those with serious or worsening angina pectoris. Mild sleep disturbances, such as vivid dreaming or insomnia, have been reported for approximately 12% of patients wearing the transdermal nicotine patch for 24 hours (49). Other less common side effects are nausea, dizziness, tachycardia, upset stomach, restlessness, and headaches. Nicotine patches are sold without prescription (over the counter, OTC) in the U.S.

Nicotine lozenge
The nicotine lozenge is FDA-approved treatment for nicotine dependence. The most common side effects are sore jaw, sores in the mouth, hiccups, dyspepsia, and nausea. In rare cases nausea, dizziness, or tachycardia can occur. Nicotine lozenges are sold without prescription (OTC) in the U.S. There are no significant safety concerns associated with using more than one OTC NRT at the same time, or using an OTC NRT at the same time as another nicotine-containing product—including a cigarette.

9.0 PRIMARY OUTCOMES

The primary outcome will be 7-day point-prevalence tobacco abstinence captured at the 6-month follow-up. Although misreporting of smoking status classification among lung cancer screening enrollees appears low (50), biochemical verification of smoking abstinence will be conducted. Consistent with Intent to Treat, unless self-reported smoking abstinence is biochemically verified, (<3 ng/ml for mailed salivary cotinine assay) for participants who fail to return the saliva sample, the cessation outcome will be considered non-abstinent. We chose 7-day point prevalence abstinence since it is biochemically verifiable and highly correlated with continuous and sustained abstinence (51, 52).

Secondary cessation outcomes will be self-reported 7-day point prevalence abstinence at 3 months, continuous abstinence(between date of randomization and date of completion of follow-up surveys) at 3 and 6 months, self-reported 24hr quit attempts reported at 3 and 6 months (53). To enhance interoperability and data pooling across LDCT smoking cessation studies funded by this NCI RFA, we will collect data on core and opt-in items developed by consensus by the SCALE Collaboration (43).

Cost endpoints include average treatment costs, for each treatment component and for permutations of components, assessed from both the societal and provider perspectives. We will also estimate the incremental cost-effectiveness at 6 months of treatment components and their permutations. Information about participants' use of health care services, and related time and travel costs in the 6 months following randomization will be collected using the Health Service Utilization Questionnaire which will be adapted for the current study of lung cancer screening patients receiving tobacco cessation treatment.

10.0 CRITERIA FOR REMOVAL FROM STUDY

We do not expect any serious adverse events to occur. In the unlikely event that a participant expresses distress, the research staff will refer to appropriate assistance at each site as needed, or to the study PIs if appropriate. It will be made clear to all study participants (SCs and smokers) that they are allowed to withdraw from the study at any time. If at any time the participant is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility, the participant will be removed from the study. We will also remove patients who do not complete the baseline assessment from the study.

11.0 BIOSTATISTICS

General Approach: This study follows a randomized, MOST design (Multiphase Optimization Strategy) to recruit a total of (up to) 36 site coordinators, and 1,152 smokers from 18 lung cancer screening sites (n=64 per site) and randomize them into one of the 16 combinations of intervention strategies (summarized in Table 1). The MOST design is essentially a factorial experimental design to simultaneously evaluate the efficacy of 4 intervention ingredients (1. Motivational Interviewing, 2. NRT Lozenge, 3. NRT Patch, and 4. Message Framing). In addition, all participants will receive an Enhanced Standard Care (cessation brochure and Quitline referral). Factorial designs are often used in the development of consumer products. For example, a company may wish to evaluate products that differ in cost, color, and size. In this study, we propose to estimate the extent to which different intervention features helps individual quit smoking and compare its effectiveness against that of other features in the factorial design.

Each intervention feature involves two levels (e.g., NRT patch ‘yes’ and ‘no’). For example, a participant randomized to treatment arm 1 will be offered standard care (self-help cessation brochure/Quitline referral) and motivational interviewing. They will *not* be offered NRT lozenge, *not* the NRT patch, and they will receive a printed individualized quitting message that emphasizes the risks of continuing to smoke (“loss-framed”). Randomization of individual patients will be conducted by MSK and stratified by site. Within each site, a sample of 64 patients will be recruited, resulting in a total N=1,152 individual participants nested within 18 sites. Consented and randomized individuals who are later found to be ineligible for the low dose CT lung cancer screening will be replaced. Recruited eligible individuals who are lost to follow-up or who did not receive an LDCT scan will not be replaced. Those who are lost to follow up will be considered cessation failures (consistent with intent-to-treat principles). The primary outcome is biochemically verified self-reported, 7-day point prevalence abstinence at 6 months.

<u>Analytic Strategies to Address Research Aims</u>

Aim 1: To use a highly efficient MOST to identify which of four evidence-based tobacco treatment components under consideration contribute to superior cessation endpoints among current smokers seeking lung cancer screening.

The primary analytic plan will involve a Generalized Hierarchical Linear Mixed Effects modeling approach with a logit link to address the binary outcome. A fully saturated model will include all four main effects, 6 two-way interactions, 4 three-way interactions, and 1 four-way interaction. The effects associated with screening sites will be generally entered as random effects.

The main analytic strategy will involve a model simplification process. In essence, we will fit the saturated model first. Next, model terms with a statistically reliable effect (by $p < 0.05$ in the type-3 ANOVA table) will be retained. It would not be pragmatic to prescribe all possible contingencies in this model reduction process. Rather, we offer a hypothetical example to make it more concrete. Suppose, for example, the model reduction yields this final model:

$$\Pr(\text{abstinence}) = \text{logit}^{-1}(\text{Motiv Interviewing} + \text{Message Framing} + \text{Motiv*Patch}),$$

where the main effects on Motivational Interviewing and Framing, as well as the Motiv*Patch interaction are deemed important by type-3 ANOVA. Then the MOST solution is an intervention with Motivational Interviewing and Message Framing. Also, NRT Patch should also be included because of the interaction between Motivational Interviewing and NRT Patch, despite that the NRT Patch main effect is not statistically reliable. NRT Lozenge will be excluded because it is not in the final model. We envisage that some synergistic effects (interactions) will emerge and deemed the optimized tobacco treatment package. Different final models may prescribe the same intervention components. Several treatment combinations may yield comparable effectiveness. If this happens, then the cost and cost-effectiveness analysis may be factored into this consideration. To control for false discovery, selection of model terms will generally be guided by the adjusted p-values by using the method of Benjamini and Yekateuli (2001) (54) for Dependent False Discovery Rate because there may exist plausible correlations in the p-values between the main effects and the interaction terms.

Secondary cessation outcomes include: 1) self-reported 7-day point prevalence abstinence at 3 months; 2) continuous abstinence between date of randomization and date of completion of follow-up surveys at 3 and 6 months; and 3) self-reported 24 hour quit attempt at 3 and 6 months. These secondary outcomes will be fully summarized for each intervention component.

Statistical Power and Sample Size Considerations. Prior research using a similar MOST strategy and assessment time points reported a 20% attrition (40). Given that tobacco researchers often supplement the main analysis with a complete case analysis, with the possibility of as much as 20% attrition, we estimated statistical power based on a conservative analyzable sample of N=922 (a rounded 51 patients nested within 18 sites). Thus, each of the component main effect estimates will be based on 900 subjects, that is, 450 subjects in each of the two levels of the component. We base power calculations on our primary endpoint in identifying the treatment components that would allow the research team to reject the null hypothesis that those components have null effect on tobacco cessation. Using the statistical power calculation computer programs designed specifically for MOST studies (55) we found that a sample of N=900 will afford an 85% statistical power (Type-I error at two-sided 5%), at an estimated minimal effect size of 0.20 in standard deviation units, what Cohen would consider a ‘small’ effect in psychology research (56). For the purpose of explanation by illustration, a difference between 20% and 12% abstinence rates, when converted by an arcsine transformation, corresponds to a Cohen’s d=0.22. Overall, by powering the sample size to detect a d=0.20 or greater, our total sample size covers the anticipated main effects in the proposed intervention components. For Message Framing, a 2012 meta analysis (57) found that gain framing is significantly correlated with smoking abstinence ($r = 0.198$), which corresponds to a Cohen’s d=0.404, covered by the minimal d=0.20. For Motivational Interviewing, a 2015 Cochrane review of 28 studies published between 1997 and 2014 (58) reported that MI had a large effect when delivered by nurses (RR=1.24) and counselors (RR=1.25). Relative risks near 1.24 and 1.25, after conversion, are comparable to our

d=0.20. For NRT, a 2012 Cochrane review reported a RR=1.60 (59), again greater than our minimal anticipated effect size. Finally, the power estimation also incorporated an intra-class correlation of 0.10 among patients recruited at the same screening site; this 0.10 ICC is conservative, as typical correlations in community clusters are between 0.002-0.012 (60, 61).

Covariates (summarized in Section 7) will be used in exploratory analyses on how smoking cessation success is associated with Smoking Health Beliefs, Tobacco Use, Smoking Cessation Attitudes/Experiences, and Program Satisfaction. A series of exploratory correlations (point-biserial correlation coefficient between a continuous and a dichotomous variable) will be calculated to summarize the extent to which smoking cessation success is associated with, for example, beliefs in the benefits of quitting, lower tobacco dependence, past quit attempts, and higher satisfaction with the program.

Aim 2: To estimate the cost and incremental cost-effectiveness of evidence-based tobacco treatment components, delivered alone and in combination.

As previously described, the base-case cost analysis will take a societal perspective, estimating all costs associated with treatment components delivered separately and in combination. We will conduct a separate cost analysis from the provider perspective. We will use standard methods (62) of incremental cost-effectiveness analysis to estimate the additional cost per quit achieved, where cost includes both intervention costs and 6-month downstream costs of related health care tobacco cessation services, and the effectiveness measure is defined by 7-day point prevalence abstinence at 6 months.

Given the primary focus of the trial on non-economic endpoints, and sample size requirements associated with these endpoints, we will not conduct formal hypothesis tests on the economic outcomes. Resource utilization and cost data are typically skewed, and therefore the sample size of the trial may be insufficient to detect significant differences in costs between study arms (63). The economic impact of the intervention will be evaluated using standard incremental cost-effectiveness analysis methods, and we will conduct sensitivity analysis to assess the impact of assumptions and uncertainty on results and conclusions (62, 64). This analytic approach is appropriate in economic studies that “piggyback” randomized trials (65).

Aim 3: Guided by well-established evaluation and conceptual implementation science frameworks we will conduct a robust mixed-methods evaluation process and assess factors that may influence implementation and sustainability for delivering and disseminating smoking cessation treatment in LDCT settings.

We will use descriptive statistics to summarize key implementation outcomes (Reach, Adoption, Fidelity, Acceptability, Appropriateness) (66). To better understand implementation challenges and sustainability, semi-structured interviews will also be conducted with SCs following study participation via WebEx (will be recorded). Led by an experienced Qualitative Methods Specialist from the MSK PRO-CEL Core Facility, a team of trained and supervised coders will analyze the summaries prepared by the study team of the audio recordings of the semi-structured Site Coordinator interviews using ATLAS.ti, a qualitative data analysis management software program to facilitate iterative coding and thematic text analysis (67-69). Once all summaries have been coded, analytic domains will be identified and major and minor thematic areas will be described using rapid qualitative analysis techniques.

Transcripts of the audio-recorded semi-structured interviews of the SCs and PACT participants will be coded using open, axial, and selective coding phases- a process consistent with a grounded theory approach (70)- using NVivo Pro v. 12.0 to facilitate the analysis (71). Dr. Martin and an independent coder, will independently code each transcript with the goal of identifying and describing themes that persistently emerge as barriers to recruitment to CASTL, meeting regularly to reach consensus on code names, definition, and assignment to content. Each phase of analysis will iteratively generate a theory to inform reasons for tobacco treatment trial refusal among Blacks.

Site characteristics (summarized in Section 7) will also be used in exploratory analyses on variation in cessation and implementation outcomes to examine the extent to which site characteristics are associated with, for example, intervention effectiveness, fidelity; and acceptability.

12.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

12.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

12.2 Randomization

Individual study participants will be randomized to 1 of the 16 intervention combinations listed in Table 1. After eligibility is established and immediately after consent is obtained, participating smokers will be registered to the study in MSK's Clinical Trials Management System (CTMS), complete the baseline assessment, and then randomized using the Clinical Research Database (CRDB). Randomization will be accomplished by the method of random permuted block, and patients will be stratified by the participating lung cancer screening site.

13.0 DATA MANAGEMENT ISSUES

A Research Project Associate, Clinical Research Supervisor, and CRC(s) to be supported, trained and supervised by the Department of Psychiatry & Behavioral Sciences will be assigned to this study. The responsibilities of the MSK staff include project compliance, data collection, chart abstraction, data entry, data reporting, and coordinating of the activities of the protocol study team.

The data collected for this study will be managed through REDCap database. REDCap (Research Electronic Data Capture) is a data management software system supported by Memorial Sloan Kettering Cancer Center (MSKCC). REDCap is a tool for the creation of customized, secure data management systems including web-based data entry forms, reporting tools, and a full array of security features including user and group based privileges with a full audit trail of data manipulation and export procedures. REDCap is maintained on MSKCC-owned servers that are kept in a locked server room with appropriate environmental modifications (e.g. proper ventilation, power redundancy and fault tolerance arrangement) and backed up nightly with some back-up tapes stored off-site. The MSKCC Information Systems group is responsible for applying all operating system patches and security updates to the REDCap servers. All connections to REDCap utilize encrypted (SSL-based) connections. Nationally, the REDCap software is developed, enhanced, and supported through a multi-institutional consortium led by Vanderbilt University.

All survey hard copies will be stored in locked filing cabinets at 641 Lexington Ave. All surveys will be entered into REDCap. All these data will be presented in aggregate form. All audio-recordings will be stored in a restricted access folder on the MSKCC-secure shared drive.

The PACT audio-recorded interviews will be uploaded to our department's secure H: drive folder and deleted from WebEx immediately after the interview. The recorded interviews will be transcribed for analysis by study staff or Ubiqus with whom MSK has an existing master services agreement. Upon receipt of the transcription, the recordings will be deleted from the department's shared H: drive.

De-identified data, including demographic data (age, race, gender & ethnicity) on refusers and ineligible participants and their reasons for refusal or ineligibility, will be periodically shared with NCI for related cross-project research within the SCALE study sites. Patient and clinic-level data will be shared from baseline through follow-up with the NCI for analysis and use in cross-project collaborations that will be disseminated within 30 working days of receipt of an NCI request.

Data will be shared through a secure online portal developed by Information Management Services, Inc. (IMS), in which each SCALE study site will only have access to the data uploaded by members of that site. IMS provides a firewall, VPN, and intrusion prevention system. Routine security checks of the IMS computer resources are made with security analysis software tools. The production network is housed in physically separate and secured computing facilities. Only authorized user ID and password protected access is allowed to the network. In addition, IMS has an NIH approved IT System Security Plan in place that meets the OMB Circular A-130 guidelines and the NIST guidelines for IT system security at the "moderate" level.

A data transfer agreement written by the NCI legal office will be sent to each study site for review by each site's legal offices. Research proposals will be sent to the soon-to-be formed Steering Committee (in which NCI is a non-voting member) and vetted. When approved, NCI will send data to the researchers who are leading a given analysis; NCI may also conduct analyses with the approval of the Steering Committee. NCI will only send data to non-SCALE members when approved by the Steering Committee, except in very specific, limited circumstances described in the data transfer agreement.

The consent indicates that individualized de-identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

Final data sets for publication are required to be locked and stored centrally for potential future access requests from outside entities.

13.1 Quality Assurance

At MSKCC, registration reports will be generated regularly to monitor participant accruals and completeness of registration data. Routine data quality reports will be generated to assess missing and inconsistent data. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

13.2 Data and Safety Monitoring

The Data and Safety Monitoring Plan utilized for this study must align with the MSK DSM Plan, where applicable.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."

There are several different mechanisms by which clinical studies are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Deputy Physician-in-Chief, Clinical Research.

The degree of monitoring required will be determined based on level of risk and documented.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant/or by the end of the year one if no accruals and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

13.3 Regulatory Documentation

Prior to implementing this protocol at MSK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSK Institutional Review Board/Privacy Board (IRB/PB). There will be one protocol document and each participating site will utilize that document.

Participating sites that are consulting or conducting data analysis should submit this protocol to their IRB according to local guidelines. Copies of any site IRB correspondence should be forwarded to MSK.

13.3.1 Amendments

MSK will serve as the IRB of record for each participating site; however, each participating site must provide all site Privacy Board (PB) approvals for site-initiated amendments/modifications of the HIPAA and/or Research Authorization and the most current approved version of the site HIPAA authorization/RA at the time of approval. Documents must be submitted to MSK on a continuing basis.

For open sites relying on the MSK IRB, a site specific face page, and any site specific documents must be submitted for each amendment along with the MSK documents. All protocol amendments will be immediately distributed to each relying site upon receipt of MSK IRB/PB approval.

14.0 PROTECTION OF HUMAN SUBJECTS

There are two potential risks for participants in this study: 1) distress from discussion of smoking status and history and 2) breaches of confidentiality.

All study personnel will be trained and supervised to implement study procedures. In the unlikely event of extreme psychological distress observed or expressed by participants, appropriate referrals will be made. All assessments will be conducted by research staff skilled and trained in interviewing tobacco smokers in a sensitive manner with the utmost respect for human subjects' issues. The research study staff will carefully monitor subjects' reactions, and offer reassurance or referral, as appropriate. There is no guarantee of benefits to the subjects based on study participation. However, results from the proposed study may help to identify effective tobacco cessation treatments to integrate in lung cancer screening clinics to assist smokers seeking lung cancer screening quit smoking.

Although participants may benefit from participating in a smoking cessation program, there is no guarantee of benefit to participants based on study participation. There are no financial costs to participants for participating in this study.

Participants will be informed that information collected during their participation in this study is considered confidential. To ensure confidentiality of data, all records will be identified by the participant's identification number, not by name, and will be stored in a locked secure area. Only the PI and other MSK research staff will have access to the REDCap records. Data shared with the consultants will be de-identified. All necessary precautions will be taken to ensure that there is no breach of confidentiality.

Participation in this study is voluntary. All participants will be required to provide verbal informed consent that adheres to MSKCC guidelines. Participants may decide not to participate in this study or to withdraw their consent to participate at any time during this study.

14.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized, de-identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information, which will not include protected health information such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with others at the time of study publication

14.2 Serious Adverse Event (SAE) Reporting

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

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any events that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

- The report should contain the following information:
- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
  - An explanation of how the AE was handled
  - A description of the participant's condition
  - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

14.2.1 Reportable SAEs

For multicenter trials where MSK is the data coordinating center, please refer to the MSK Multicenter Trial Addendum. All required SAE reporting to the funders and/or drug suppliers will be completed by MSK only. As this is a minimal risk study, we will only report SAEs that are believed to be at least *possibly* related to the protocol intervention.

15.0 INFORMED CONSENT PROCEDURES

Lung cancer screening SCs and the patient smokers referred by the SCs or those who self-refer to this study will be contacted by MSK staff by telephone. Screening site patients will provide their verbal permission (Appendix T) to be contacted by MSK research staff when referred by SCs, who will discuss the study and explain that participation is optional. Permission forms will not be provided for patients who self-refer to the study. Verbal informed consent will be obtained over the phone and research staff will obtain a mailing address to share an information sheet with all participants that provides the rationale for the study, why the participant was selected, the study procedures, risks, benefits and other pertinent information as a reference document (Appendix R-S). Voicemails, including a call-back number, will be left for participants. After the participant has been properly verbally consented by phone, the consenting professional will sign the verbal consent form. We do not expect particular risks or benefits from participation, and this will be conveyed to the participant. The consenting professional will ask participants if they have any questions about the consent process, the study, or their participation.

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must verbally agree using an IRB/PB-approved verbal consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies).
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.
6. How the participants' data will be protected, who will have access to their PHI, and what data will be disclosed for research purposes.

Prior to inclusion in the study and before any protocol-specific procedures can be carried out, the consenting professional will explain the details of the protocol to participants/LARs. Participants/LARs will also be informed that they are free to withdraw from the study at any time. aspects of patient privacy concerning research specific information. The consent discussion may occur in person or remotely via teleconference, telephone, or videoconference.

The consenting professional must sign an IRB/PB-approved consent /research authorization script to document the consent discussion and the participant's agreement.
A note will be placed in the participant's medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

In following the Code of Federal Regulations Title 45, Part 46, Subpart A, the IRB is waiving the requirement for an investigator to obtain a signed consent form from the participant as the research:

- presents no more than minimal risk of harm to participants, and
- involves no procedures for which written consent is normally required outside of the research context.

In following the Code of Federal Regulations Title 45, Part 164, Subpart E, IRB/PB is waiving the requirement for the investigator to obtain signed research authorization from the participant as:

- the use or disclosure of the PHI involves no more than minimal risk to the privacy of the individuals, based on the following elements:
    - An adequate plan to protect identifiers from improper use and disclosure;

  - An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research (unless there is a health or research justification for retaining the identifiers, or such retention is otherwise required by law); and
  - Adequate written assurances that the PHI will not be reused or re-disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use of disclosure of PHI would be permitted by HIPAA.

- The research could not be practicably conducted without access to and use of the PHI
- The research could not practicably be conducted without the waiver

Aim 4: PACT Ancillary study

PACT ancillary study participants will be verbally consented by MSK study staff. As noted in the Recruitment section, those who refuse to be contacted by MSK staff will be provided a PACT brochure by the SC. If, upon receiving the brochure, the potential PACT participant contacts Dr. Martin, she will explain the study and verbally consent the participant. For those patients who agree to be contacted by MSK but refuse CASTL, the MSK staff will introduce the PACT sub-study and verbally consent them if the patient agrees. For past CASTL refusers (those who agreed to be contacted by MSK), Dr. Martin will call potential participants to introduce PACT, and will leave a voicemail, including her number, for patients. For those who the MSK staff is unable to reach after multiple attempts, a brochure will be sent (via mail or email). If these patients contact the MSK team about the PACT study, they will be verbally consented.

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17.0 APPENDICES

Appendix A: SC Baseline
Appendix B: Patient Baseline
Appendix B1: Patient Baseline (Spanish)
Appendix C1: Patient 3 month follow up
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