Gain-framed messages and NRT for lung cancer screening patients (Pro00055397)
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SPECIFIC AIMS

Screening for lung cancer at earlier, more treatable stages has the potential to reduce mortality from the US's most deadly cancer.[1] The US Preventive Services Task Force (USPSTF) now recommends annual screening for lung cancer with low-dose computed tomography (LDCT) for high risk individuals based on age and smoking history.[2] The Center for Medicare and Medicaid Services (CMS) recently approved annual lung cancer screening for its beneficiaries when conducted in centers offering comprehensive programs that include advice on smoking cessation.[3] While it has been suggested that LC screening is a potential teachable moment, most current smokers seen for screening have variable motivation to quit, and many are unwilling to engage in a formal cessation program. Thus, there is a strong need to address smoking cessation across this continuum, catalyzing treatment engagement and cessation among all. The interventions in this study are broad and translational – effectively promoting quitting among all smokers and doing so in a way that is easily disseminable. In the context of 3 lung cancer screening programs (MUSC, VA and Yale) this project will evaluate a more intense yet still feasible intervention to enhance patient motivation to make and succeed in a quit attempt.

Our group has established effective tobacco interventions that demonstrate increased quit attempts and smoking cessation from: 1) gain-framed messaging, and 2) nicotine replacement therapy (NRT) sampling. Based on the tenets of Prospect Theory[4] and an accumulating body of evidence from our previous studies, messages emphasizing the benefits of smoking cessation (i.e., gain-framed) are more effective than messages emphasizing the risks of continued smoking (i.e., loss-framed) for increasing intentions to quit, quit attempts, and smoking cessation in general populations of smokers.[5-9] Our work also includes several studies showing that sampling of cessation medications leads smokers (both motivated and not) to increased cessation.[10-12] Together, gain framed messaging and NRT sampling offer a novel and compelling opportunity to engage smokers and catalyze cessation. Our methods, if shown to be successful, can be easily shared with lung cancer screening programs across the country. Thus, we plan to conduct a randomized trial of gain-framed intervention (yes vs. no) x NRT sampling (2-week supply of both nicotine patch and lozenge vs. not) within a high-risk group of smokers (N=367) across 3 study sites (MUSC, VA and Yale). This study is powered to examine main effects of our 2 interventions:

Primary Aim 1: *To determine if the rate of smoking cessation among lung screening patients is improved by delivering gain-framed smoking cessation messages and delivery of a free starter package of medication (gain-framed behavioral intervention + 2 weeks of nicotine patches and lozenges vs. unframed behavioral intervention + no medication).*

Hypothesis 1: Cessation rates will be significantly higher at 6-months after lung screening for the smoking cessation strategy involving a gain-framed intervention + 2 weeks of nicotine patches and lozenges compared to a strategy of an unframed behavioral intervention + no medication. We define cessation as 7-day point prevalence but will assess multiple definitions of success.

Exploratory Aim: *To examine mediators and moderators of treatment to determine mechanisms of treatment effects and which subgroups are most likely to respond to the gain-framed and medication interventions, and to explore differential effects of the study factors across treatment groups. Treatment interactions will also be explored secondarily.*

Hypothesis: Changes in self-efficacy, smoking cessation outcome expectancies, familiarization with NRT, motivation, and autonomy will act as mechanisms for the smoking cessation effects (i.e., will act as mediators of treatment). Lung screening findings (e.g., presence of a nodule, cancer, etc), nicotine dependence, and health disparities will modify treatment response (i.e., will act as baseline moderators of treatment).

Exploratory Aim: *To examine additional treatment endpoints: patient reach, intervention fidelity, patient acceptance and engagement, cost, and the ease of delivery and feasibility.*

Hypothesis: We hypothesize that this project will be a low-cost feasible intervention that will reach a majority of patients who are smokers, with high adherence to and acceptance of the critical intervention elements.

Our rigorously designed study will be the first to demonstrate the individual and combined effects of gain-framed messaging and NRT sampling in a lung cancer screening population, which is a high-risk, difficult to

treat group of smokers in need of feasible, easily administered interventions, thus offering strong potential for clinical and population impact.

RESEARCH STRATEGY

A. Significance:

Cigarette smoking leads to more than 480,000 deaths annually in the United States.[13] Smoking causes 30% of all cancer deaths and nearly 90% of all lung cancer deaths.[14] While many of these deaths occur in former smokers, continued smoking remains an ongoing public health challenge, despite the remarkable progress that has been made in development of effective smoking cessation treatments.[15] Lung cancer is now the leading cause of cancer death in both men and women in the US.[16] In addition to primary prevention (tobacco control), secondary prevention through early detection is another strategy to reduce lung cancer death rates. More specifically, lung cancer screening with low-dose CT scans (LDCT) identifies lung cancer at an earlier, more treatable stage in high-risk patients. Evidence from the National Lung Screening Trial (NLST), for which MUSC was a study site, showed that screening with LDCT for high risk individuals (>30 pack years of smoking, <15 yr quit-time, and 55-74 yrs of age) conferred a 20% reduction in mortality for those patients who received 3 annual low dose CT scans.[17] These findings led the USPSTF to recommend annual screening with LDCT for lung cancer in persons at high risk based on age and smoking history (grade B),[18] with CMS and many private insurers now covering screening for this population. With an emphasis on the components necessary for a high-quality lung screening program[3] which includes smoking cessation efforts, comprehensive screening centers are opening across the nation. Tobacco treatment options offer limited success,[19] thereby increasing the importance of smoking cessation for this population. Much is known about cessation within the general population, but less is known for lung screening patients. *The proposed study is the first study of a smoking cessation intervention specifically for patients enrolled in a clinical lung cancer screening program.*

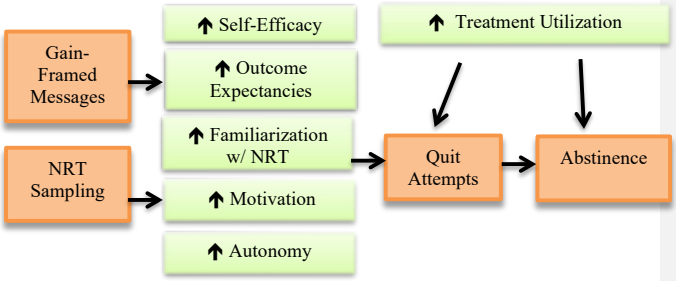
While one might hypothesize that simply having a CT scan may promote cessation, evidence suggests that having a scan increases quit rates only slightly, if there is any increase at all.[20,21] In a recent study, CT scanning prompted smoking cessation *shortly following the scan, especially when the results were abnormal*. However, long-term abstinence rates were similar for those with and without abnormal lung findings.[22] Likewise, referral to a physician for an abnormal scan result may increase initial quit attempts but this is not always sustained.[23,24] A recent evaluation of qualitative interviews from current smokers offered lung cancer screening showed that 49% of participants suggested that screening lowered their motivation for cessation.[25] Misperceptions include the belief that negative screening offers protection from lung cancer; or the perception that screening can save lives by catching cancer early when indeterminate findings are identified that can be monitored; or a belief that a cancer-free screening test result indicates that they are among “the lucky ones” who will avoid the harms of smoking. There is of course no safe level of smoking, even among those who screen negative, and the need to effectively address cessation in the context of screening is profound. There is limited direction from the CMS memo regarding how to implement smoking cessation, with the option to provide very limited advice, which only has small effects.[15] The present study is thus timely and novel – we will investigate whether we can achieve higher rates of short- and long-term cessation in a high risk population.

Gain-Framed Messages: Prospect Theory[4] provides the foundation to assert the influence of health message framing for smoking cessation. Prospect Theory suggests that decision makers organize or “frame” information relevant to a health decision in terms of potential gains or potential losses, as compared to a present reference point (e.g., one’s current level of health). Factually equivalent material can be presented differentially to individuals such that they encode it as either a gain or a loss from this reference point.[4] Prospect Theory summarizes these decision strategies by noting that individuals are, in general, *risk-seeking* in the domain of losses but *risk-averse* in the domain of gains. When behavioral choices involve risk, individuals will be more likely to take these risks when information is framed in terms of the relative disadvantages (losses or costs), and they will be more likely to avoid these risks when the information is framed in terms of the relative advantages (gains or benefits).[26] The *type* of health behavior also influences the effects of message framing.[26] Gain-framed messages are more effective in promoting physical exercise, sunscreen utilization, and smoking cessation, all prevention behaviors (e.g., McCall & Martin Ginis[27]). In a secondary data analysis of the NLST, we demonstrated that former smokers in the control arm abstinent for 7 years had a 20% reduction in lung cancer specific mortality compared that of those screened with LDCT. Further, the combination of smoking abstinence and LDCT screening resulted in a 38% reduction in lung cancer mortality.[28] This novel research will be an essential piece of the gain-framed messages specific to lung cancer risk reduction that we use in the proposed project. We emphasize, in line with Prospect Theory, that it is the *match* between a message frame (gain or loss) and the required health behavior (prevention or detection) that especially motivates behavior change. Gain-framed messages have been shown to be more effective than loss-framed messages for

increasing intentions to quit, quit attempts, and smoking cessation in general populations of smokers.[5-9] Thus, the primary hypothesis for our message framing intervention is that *gain-framed messages are especially persuasive when promoting cancer prevention behaviors like smoking cessation, and thus can be utilized to further improve standard tobacco cessation counseling in the context of lung cancer screening.* We also believe that gain-framed messaging will have a particularly salient effect when presented in conjunction with a concrete, behaviorally-based cue to action as is offered through NRT sampling.

Nicotine Replacement Therapy (NRT) Sampling NRT sampling merely refers to providing short, starter packets of NRT, which can be easily added to existing counseling (message framing) protocols. Sampling is distinct from a full course of NRT treatment, in that the intent is to engage smokers in the process of quitting, but without any requirement or expectation to quit immediately and/or abruptly. It is a softer, gradual exposure to the quitting process that is conceptually designed to heighten smoker acceptance and enhance motivation and self-confidence. It is also rooted in marketing research (businesses have been doing this for years), which shows that brief exposure to a product, when provided for free, increases positive opinion and more importantly increases further use of that product.[29]

Figure 1: Conceptual Model for Gain-Frame Messages and NRT



There are several mechanisms by which gain-framed messages and NRT sampling, when offered in conjunction with lung cancer screening, could promote downstream changes in smoking behavior (quit attempts, abstinence; see **Figure 1**). We discuss these potential mediators for both interventions below. One is through improved self-efficacy. As smokers gain confidence in controlling smoking, they may be more likely to believe that total abstinence is possible.[9] Changes in outcome expectancies have been shown to act as a mediator in our previous gain-framed messaging research.[30] NRT sampling might also heighten motivation. Whereas abrupt quitting is often daunting, gradual exposure to cessation, particularly when that experience is made easier through NRT, might remove some of the perceived barriers to quitting (e.g., "this isn't so bad, I can do this"). A third mechanism is through increased familiarization with NRT. Many smokers continue to hold misperceptions about cessation pharmacotherapy, and particularly NRT. Misperceptions are broad, but typically pertain to concerns about 1) safety (e.g., addictive potential, adverse events), and 2) efficacy.[31-35] In our prior efficacy trial of NRT sampling (discussed below), sampling of NRT yielded direct improvements in each of these mechanisms; i.e., increases in motivation, confidence, and knowledge/attitudes of NRT,[10] which themselves are predictive of eventual cessation.[34,36-39] Finally, while not an explicit outgrowth of self-determination theory,[40,41] NRT sampling is wholly consistent with it; i.e., with the rationale that smokers will be more invested in the quitting process if they autonomously decide for themselves the goals and pace for changing tobacco use. Uptake of cessation treatment is higher when accessibility is increased,[42] as would be the case when NRT is proactively provided at the point of lung screening. One older study examined outcomes of smokers in a cessation program who either received NRT for free, or paid for it.[43] Use of NRT was higher when provided for free, as was long-term abstinence. Within tobacco control, the best example of NRT sampling is through quitlines. Evidence consistently shows that quitlines that offer free medication result in improved cessation rates as compared to quitlines that do not.[44-49] Some[45,50] but not all[46] research suggests that 2-week provision of NRT is as cost-effective for promotion of quitting as is extended supply. However, whereas quitlines typically exclusively draw smokers who want to quit,[47,51,52] we believe that NRT sampling is ideally suited to smokers across the motivational continuum, serving as a catalyst for treatment engagement among those who are not wanting to quit. *In the context of lung cancer screening, NRT sampling is particularly useful because it can be delivered on-the-spot (at the point of screening) and does not require specific training or skill. See below for prior and ongoing work within our group in support of NRT sampling. We believe that NRT sampling will have additional benefit when presented in concert with gain-framed messaging about quitting. This would be the first*

such test of this hypothesis, which, when presented in the context of a teachable moment, i.e., lung screening, offers additional clinical and public health significance.

In the proposed study, we integrate these 2 complementary approaches to test a gain-framed intervention specifically designed for lung screening patients (vs. unframed messaging), as well as evaluating NRT sampling (vs. no medication). These interventions are complementary in that the evidence shows they will both lead to higher quit rates. Yet they are functionally somewhat independent. The evidence shows that self-efficacy may be a mediator for both. However, the other mediators are independent – outcome expectancies is specific to gain-framed messaging and familiarization with NRT, motivation, and autonomy are specific to NRT sampling. The primary hypothesis is that gain-framed messages designed specifically for lung screening patients will be especially persuasive when promoting smoking cessation (a prevention behavior), and thus can be utilized to further improve standard counseling for lung screening patients. Further, we hypothesize that sampling NRT in the lung screening population of smokers will also promote smoking cessation in addition to the standard counseling and gain-framed intervention. While our study is based on a 2x2 design, we are appropriately focused on the effect of combined treatment (vs. neither) and main effects (of either treatment); interactions are explored but cannot drive our scope as such a study would be wholly infeasible (>5,000 participants). Our project is designed to be translational (in that it can be transferable from our controlled efficacy study to other lung screening programs).

Our proposed study will also evaluate important moderators of response to the intervention. Several framed message intervention studies from our group and other research groups have found that patient characteristics can moderate treatment efficacy (e.g., baseline characteristics such as tobacco dependence measured by the Fagerström scale, which may be very relevant in this patient population).[53-56] We will evaluate nicotine dependence as a moderator of treatment outcomes, and anticipate that participants with lower nicotine dependence scores will have higher quit rates overall regardless of condition assignment but there will be a differential benefit of gain-framed messaging and medication for those with higher nicotine dependence scores. Further, very large disparities in tobacco use remain across groups defined by race, ethnicity, educational level, and socioeconomic status.[13] These groups, plus those with mental illness who smoke, are at an increased risk for tobacco-related health disparities.[57] Given the disparities in tobacco use and health among these groups, we will evaluate these variables and determine if they moderate treatment outcomes. We also anticipate that smoking outcomes may be affected by the lung screening findings. That is, perhaps a scan that identifies emphysema would motivate a patient to quit smoking. Because research is lacking on how screening findings affect the efficacy of personalized, gain-framed messaging and NRT sampling, we will carefully evaluate these factors and determine if lung screening findings moderate our intervention.

B. Innovation:

This study has many important, innovative features:

1. This research is the ***first*** randomized smoking cessation trial conducted within and specifically personalized for lung cancer screening patients presenting to a lung screening clinic. Novel tobacco treatments for this population is critically needed, given the growing population of lung screening patients, which will grow dramatically now that lung screening is an approved CMS benefit.
2. This is the ***first*** study to test both gain-framed messages and delivery of a free starter package of NRT to promote smoking cessation among lung cancer screening patients with varying levels of motivation to quit smoking.
3. The model is highly translatable to other lung cancer screening settings. We are proposing translational behavioral (gain-framed messaging) and pharmacotherapy (NRT starter packages) interventions that would not need a specialized service. This could be easily integrated into other lung cancer screening programs.

C. Approach:

Preliminary Data

Message Framing:

Quitline Message Framing Study. As described above, previous studies from our group showed that the framing of messages for smoking cessation (e.g., gain-framed) can substantially affect efficacy.[7-9] For example, we investigated whether gain-framed messages (i.e., presenting benefits of quitting) would be a more persuasive method to encourage smoking cessation than standard-care messages for callers to a telephone quitline. Coaches from the New York State Smokers' Quitline were randomly assigned to provide gain-framed or standard-care counseling and print materials. Smokers (n=2032) who called the NY Quitline were exposed

to either gain-framed (n=810) or standard-care (n=1222) messages via 2 counseling phone calls and framed smoking cessation print materials. All medically eligible callers received NRT. Gain-framed counseling was associated with a 10.7% higher rate of abstinence at the 2-week follow-up (i.e., 23.3% gain-framed vs. 12.6% standard-care, p<.001). Three-month follow-up data favored the gain-framed group, but was no longer statistically significant. However, this study had only very brief messaging one or two times; whereas the present study will engage patients with an in depth longer video intervention to begin with, then personalized print materials. This study was published in the *JNCI*[6] with an editorial by the NCI's Director of the Division of Cancer Control and Population Sciences, Dr. Croyle.[58]

Message Framing with Bupropion Study. We also tested a framed message intervention in a primary care model using bupropion SR. This study was a randomized smoking cessation clinical trial comparing 2 framed messages (gain or loss) for smoking cessation in combination with 7 weeks of open label bupropion SR (300 mg/day).[5] Participants (N=258) were randomly assigned to receive factually equivalent video and print messages encouraging smoking cessation that emphasized either the benefits of quitting (gain-framed) or the costs of continued smoking (loss-framed). Participants saw 2 brief framed videos in 2 separate pre-quit smoking cessation sessions then received print messages at 3 post-quit sessions. The primary outcome measure was biologically verified abstinence 6 weeks after the targeted quit date. There was a significantly higher proportion of continuously abstinent participants in the gain-framed (47.6%) as compared to the loss-framed condition (35.2%; p<.05). At a 6-month follow-up, the 7.3% advantage of gain-framed messages (24.4% gain-framed vs. 17.1% loss-framed) was marginally but still clinically significant (p=.07). In the present study we will conduct an intervention similar to the gain-framed message intervention in this study, but it will involve a significantly higher amount of tailoring and print interventions. Thus, we expect to obtain a slightly higher quit rate at 6 months than in this preliminary study.

Yale Lung SPORE. The newly funded Yale SPORE will investigate short and long term smoking cessation in a high risk population of lung nodule patients. In the SPORE study that just started in late August 2015, we will test gain-framed messaging and biofeedback for smoking cessation in a set of interventions specifically designed for lung nodule patients. We will investigate whether smoking quit rates among lung nodule patients can be improved by augmenting standard care treatment (counseling + pharmacotherapy) with a novel gain-framed video and print media intervention that is personalized based on an individual's lung nodule diagnosis and presented in a gain-framed manner emphasizing the benefits of quitting for someone with this diagnosis. Messages will also be personalized to other characteristics including name, gender, preferred brand of cigarettes, and amount smoked to maximize effectiveness. While there is a body of literature that messages personalized to smokers' characteristics seem to be effective and gain-framed messages are effective, no study to date has combined these two approaches and investigated a messaging intervention specifically personalized and gain-framed for lung nodule patients. We believe this study will be complementary and not competitive with the proposed study for two reasons. First, the primary method of recruitment for this study will be searches of patients' medical records to find smokers who have a nodule. Although some patients enrolled in this study will have had their nodule detected through lung screening, this will be a relatively small portion of the patients enrolled. Two, this study will allow our research team to be an integrated part of the Yale Screening and Nodule Program, which will facilitate subject recruitment and follow-up for the proposed study.

NRT Sampling: We have completed two and have a third ongoing trial of NRT sampling, each in support of our rationale that this approach is a particularly useful clinical strategy to promote treatment engagement and abstinence among smokers seen in real world medical settings.

NRT Sampling Study 1: Efficacy Trial among Unmotivated Smokers. We recently completed a randomized clinical trial (N=849) testing the concept of NRT sampling to induce cessation behavior among smokers unmotivated to quit.[10,59] Smokers were recruited nationally via online channels, recruited into a phone-based intervention trial, and were assessed for six months. Phone-based treatment consisted either of 1) NRT sampling, within the context of a practice quit attempt (PQA), or PQA alone. The PQA intervention was a behavioral exercise, within which smokers could (or could not) sample nicotine replacement. The PQA was

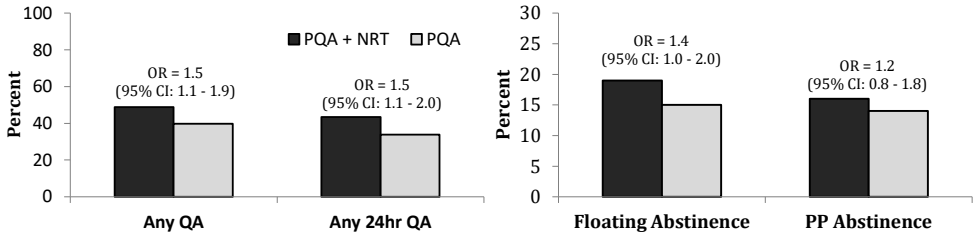


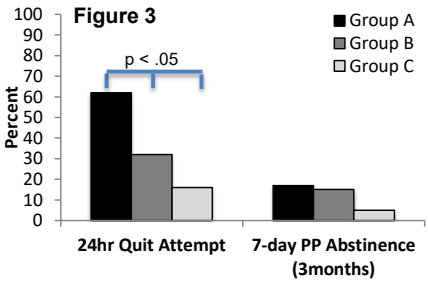
Figure 2: Rates of any quit attempt (QA), 24hr quit attempt, floating abstinence (seven days, no smoking, at any point in study), and point prevalence (PP) abstinence at Week 26

designed to increase motivation, confidence, and coping skills. The added value of NRT samples (nicotine lozenges) was hypothesized to familiarize smokers with NRT, promote wider acceptance of it, and ultimately to enhance motivation and confidence even further. Uptake of NRT during the sampling period was strong: 73% of smokers used the product, for an average of 9 days. Cessation outcomes were very promising, with significant increases in quit attempts and some measures of abstinence (**Figure 2**).[10]

Important observations from our previous work. First, our efficacy study was based only on unmotivated smokers, and was powered on quit attempts (abstinence was secondary). Within the current trial, smokers across the motivational continuum are included, and our primary outcome is abstinence. Second, participants in the NRT+PQA group displayed significant changes in a) motivation, b) confidence, c) knowledge of NRT, and d) both positive and negative attitudes towards NRT (**Table 1**), all of which are mechanisms by which NRT sampling works. Third, while the effect size for abstinence was modest (OR=1.2), we believe this is because the control group (PQA) had independent effects on quitting. We have since stripped NRT sampling down to its barest elements, most easily translated into clinical service. When implemented within the context of lung screening, sampling could have significant public health impact. Fourth, our trial embeds NRT sampling with message framing, which we believe will both a) significantly increase reach, and b) offer added weight and impact over NRT sampling in the absence of counseling (increased credibility vs. mailed NRT samples in prior study). Finally, outcomes from our prior trial were equal to or greater than those from established but time- and verbally-intensive options for cessation induction such as motivational interviewing[60-62] and provider-delivered brief advice.[63] We believe that NRT sampling in conjunction with grain-framed messaging as proposed herein is more conducive to producing abstinence-based outcomes.

Table 1: Benefits of NRT sampling	**Baseline**			**End of Treatment**		
	PQA+ NRT	**PQA**	**p**	**PQA+NRT**	**PQA**	**p**
Motivation to Quit: Next Month (0-10)	2.4 (2.8)	2.7 (2.9)	0.1	4.0 (3.4)	3.2 (3.1)	0.001
Confidence to Quit (0-10)	4.0 (3.0)	3.9 (3.0)	0.6	4.8 (3.2)	4.0 (3.1)	0.001
Positive Attitudes towards NRT (1-4)	3.0 (0.4)	3.0 (0.4)	0.6	3.2 (0.4)	2.9 (0.5)	<0.001
Negative Attitudes towards NRT (1-4)	2.6 (0.7)	2.6 (0.7)	0.8	2.1 (0.7)	2.7 (0.8)	<0.001
Knowledge of NRT (0-10)	4.5 (2.5)	4.4 (2.5)	0.6	6.5 (2.0)	4.6 (2.3)	<0.001

NRT Sampling Study 2: Evaluation of Motivation to Quit. The trial above was based on unmotivated smokers only. We next completed a separate pilot trial (N=157), of three groups, testing A) smokers motivated to quit, given 2-week samples of both nicotine patch and lozenge, vs. B) unmotivated smokers, given same treatment, vs. C) unmotivated smokers, no treatment.[12] Over 85% of participants in Groups A and B used medication. Results after three months of follow-up (**Figure 3**) provide even further evidence for the sampling intervention. While initial motivation to quit enhances outcomes (A vs. B), it is not a necessary precursor to success (B vs. C). Note that abstinence outcomes were comparable between smokers



who received NRT samples but who were or were not motivated to quit (Groups A vs B), thus suggesting that sampling medication is a valuable option for all smokers.

NRT Sampling Study 3: Real-World Comparative Effectiveness within Primary Care. We have ongoing a large (N=1160) cluster randomized pragmatic clinical trial of NRT Sampling within 20 primary clinics across South Carolina. This study is powered on abstinence, tracked through six months of follow-up. Outcomes will focus on the individual smoker (additional use of medication, quit attempts, abstinence), provider (satisfaction, confidence with cessation counseling) and aggregated across clinics (rates of tobacco screening, counseling). Everything (screening, consenting, baseline assessment, and treatment delivery) is done within the clinic, by clinic staff; only follow-up assessment is conducted centrally by research staff. Thus, we focus on real world implementation throughout. Seven clinics have completed enrollment to date (current N=426), and 3 more clinics are currently active. Clinician buy-in has been strong in large part because the "intervention" takes mere minutes to deliver. For the current proposal, we add the extra benefits of gain-framed messaging in conjunction with NRT sampling, further enhancing benefit but without any sacrifice of feasibility.

Attitudes toward Pharmacotherapy (2 studies). In addition to Dr. Cummings' prior work on attitudes and perceptions of NRT,[32,33,64] Dr. Carpenter locally conducted two complementary studies that document attitudes and misperceptions of cessation medication. The first was a qualitative study of perceptions of NRT specifically.[65] Results highlighted enduring misperceptions about NRT that likely undermine usage. Despite apprehensions of cessation medication, there were two themes that offer an opportunity to promote wider NRT utilization, and both are highly relevant to the current proposal. First, many smokers expressed trust in physicians, with a common view that "I would use it if my doctor said it was ok." Second, a strong number of smokers, particularly African American smokers, expressed willingness to try NRT if free samples were available: "**If I could go to the doctor, and he could tell me the right amount of dosages to quit smoking, I would try it.**" Together, these beliefs strongly support the notion that NRT sampling, particularly within the context of a lung screening clinic, could significantly promote wider uptake of evidence-based treatment.
Our second study of attitudes towards cessation pharmacotherapy was a phone-based cross-sectional survey of South Carolina ever-smokers.[66] Current smokers (N=697), attitudes towards pharmacotherapy are presented in **Table 2**. Even among never users of cessation medication, within whom there was disregard for pharmacotherapy, there was strong willingness to try a free sample if a healthcare provider gave it to them.

Table 2: Attitudes towards Cessation Medications: Current Smokers[1]

	Ever User[2]	**Never User[2]**
How well do medications work to help smokers quit?	61%	53%
How concerned are you about medication safety?	51%	63%
How concerned are you that you might get addicted?	19%	50%
How concerned are you about cost?	65%	42%
How likely would you use a sample of medication if provided by your healthcare provider?	78%	61%

[1] percent endorsing ≥4 on Likert scale of 1 (not at all) to 5 (a lot) [2] ever/never users of any pharmacotherapy

Expertise and Ability of the Research Team

Our research team has the requisite experience and expertise to conduct this study:
Principal Investigator (PI): Benjamin Toll, Ph.D. **Dr. Toll** is an Associate Professor of Public Health Sciences at MUSC, a member of the Hollings Cancer Center (HCC), Chief of Tobacco Cessation and Health Behaviors at HCC, and Co-Director of the HCC Lung Cancer Screening Program. The Tobacco Treatment Program team at HCC (which consists of a full time secretary/patient scheduler, a clinical pharmacist, and Dr. Toll) is tasked with assessing all HCC patients with regard to tobacco use and offering all patients smoking cessation treatment. He has extensive experience conducting randomized controlled studies of interventions that promote smoking cessation, and has completed and published 4 large randomized controlled smoking cessation trials.[5,6,67,68] He is also the Co-PI of a Yale Lung SPORE project evaluating personalized gain-framed feedback and biofeedback for smoking cessation among lung nodule patients. Further, prior to his position at MUSC, Dr. Toll was an Associate Professor at Yale and thus has a pre-existing relationship with the cancer programs and lung cancer screening program at Yale Cancer Center/Smilow Cancer Hospital at Yale-New Haven (YCC).

MUSC Co-Investigators: **Dr. Carpenter** is an Associate Professor of Psychiatry and Behavioral Sciences. His research interests include nicotine dependence, smoking cessation (including harm reduction), and tobacco

control. He has extensive experience in smoking cessation/tobacco research, across the continuum of human-lab, clinical trial/treatment outcome, and policy-based studies**. Dr. Tanner** is an Assistant Professor of Medicine Pulmonary and Critical Care and the Co-Director of the HCC Lung Cancer Screening Program. She was one of 8 site leads for the VA National Lung Cancer Screening demonstration project and is an expert on various aspects of lung cancer screening including generalizability and shared decision making. Dr. Tanner is also a pulmonologist and member of the Multidisciplinary Thoracic Oncology Clinic at the Charleston VAMC. She is the head of the lung cancer screening program at the VA. **Dr. Silvestri** is a Professor of Medicine in Pulmonary and Critical Care, and is the President Designate of the American College of Chest Physicians. He is a health services researcher with expertise in all aspects of lung cancer diagnostics, screening and pulmonary nodule evaluation. He has written a number of guidelines on the diagnostic approach to lung cancer. He has published 3 *NEJM* articles related to lung cancer screening including risk assessment, patient selection and cost-efficacy. **Dr. Cummings** is a Professor of Psychiatry and Behavioral Sciences at MUSC. His research interests are in the field of health related behaviors, especially tobacco use prevention and cessation. Over the course of his professional career, he has received more than 50 grants and contracts totaling over $60 million. His most recent research is investigating the delivery and success of tobacco cessation interventions in oncology patients. **Dr. Warren** is an Associate Professor of Radiation Oncology and conducts research evaluating the epidemiology and health behaviors related to tobacco use and other exposures by cancer patients, the clinical effects of exposure to tobacco on therapeutic response as well as both cancer-related and non-cancer related health outcomes, and policy considerations for standard clinical practice and clinical trials design. **Dr. Hughes-Halbert** is a Professor of Psychiatry and Behavioral Sciences and the Program Leader in Cancer Control at HCC. Her research program focuses on identifying sociocultural, psychological, and environmental determinants of cancer prevention and control, translating this information into interventions, and disseminating efficacious strategies into clinical and community settings. **Dr. Rojewski** is a Postdoctoral Scholar in the Department of Public Health Sciences at MUSC. Her research interests are tobacco treatment, behavioral interventions for cessation (e.g., contingency management), and integrating cessation interventions in medical settings. Dr. Rojewski will work under the overall supervision of Dr. Toll to act as the Project Coordinator of the study.

Yale Co-Investigators: **Dr. Fucito** is an Assistant Professor of Psychiatry at Yale and the Program Director of the Tobacco Treatment Service at Smilow Cancer Hospital at Yale-New Haven/Yale Cancer Center (YCC). Dr. Fucito's Tobacco Treatment Service team [which consists of a full time secretary/patient scheduler, 2 nurse practitioners, and a physician (Dr. Bernstein listed below)] is tasked with assessing all YCC patients with regard to tobacco use and offering all patients smoking cessation treatment. Dr. Fucito conducts research on novel interventions for smoking and moderators and mechanisms of smoking treatment response. Through a NIAAA Career Award, she is currently developing an integrated smoking and alcohol treatment for heavy-drinking smokers that emphasizes personalized feedback about health biomarkers. Her other research has identified nicotine dependence as an important moderator of framed smoking message effects. **Dr. Bernstein** is a Professor in the Department of Emergency Medicine at Yale. He pioneered the delivery of screening and treatment interventions for smokers in the emergency department (ED).[69-72] His most recently published NCI-funded study, on which Dr. Toll is a co-investigator, tested the efficacy of a multicomponent intervention for smokers in the ED. The 3-month biochemically confirmed quit rates for that study are: Intervention vs. Usual Care arms, 12.2% vs. 4.9% (P<0.001).[73] In addition, Dr. Toll serves as a co-investigator on Dr. Bernstein's current NHLBI-funded study examining the effectiveness of a novel Integrated Tobacco Order Set (ITOS) in an Electronic Medical Record in promoting sustained smoking abstinence in adult inpatients. As noted above, Dr. Bernstein works closely with Dr. Fucito on all medical aspects of patient care and smoking cessation treatment as part of the Tobacco Treatment Service at YCC. **Dr. Tanoue** is a Professor in the Department of Medicine Section of Pulmonary and Critical Care Medicine, Co-Director of the YCC Thoracic Oncology Program, and Director of the Yale Lung Cancer Screening and Nodule Program (*see attached letter of support from Dr. Tanoue*). She also is the Principal Investigator for the Yale Lung Cancer Biorepository. Her research interests are focused on early detection and risk stratification for lung cancer, and the development of quality metrics for lung cancer evaluation and lung cancer screening.

Statistician: Nathaniel Baker, M.S. **Mr. Baker** is a statistician and Research Instructor at MUSC. He is an expert in methodological issues in the design, conduct, and analysis of clinical studies. As a long-standing collaborator of Dr. Carpenter's, Mr. Baker has assisted our tobacco research group in developing appropriate

research designs, power analyses, randomization lists, analyses of adverse events, and outcome analyses for our smoking cessation studies.

We considered a single site study but believe: a) recruitment feasibility is enhanced by more sites, and b) there are added benefits of geographic and demographic diversity. All analyses will control for site effects. MUSC and Yale have a long history of collaborative work. Dr. Toll has worked with investigators at both Yale and MUSC for many years, having published extensively with them,[53,54,68,73-79] worked on collaborative projects,[80,81] and submitted grants. We are now working to establish a collaborative relationship with the VA.

Design and Methods:

General overview:

We propose a group comparison study (gain-framed intervention vs. unframed intervention, starter package of 2 weeks of nicotine patches and lozenges vs. no medication) to evaluation methods to boost rates of smoking cessation for a high-risk group of smokers (N=367) with varying levels of motivation across 3 study sites (MUSC, Ralph H. Johnson Veteran Administration and Yale). All eligible study participants will be randomized to receive either: 1) Unframed Messaging (hereafter referred to as UM) with no medication, or 2) Gain-framed Messaging + Meds (i.e., 1 gain-framed video and print materials + 2 week starter pack of NRT; hereafter referred to as GM+M).

Participants: Our target sample will be 367 lung screening patients who currently smoke at each of 3 study sites: MUSC), Ralph Johnson VA, and Yale Cancer Center); Total N=367. The following eligibility criteria will ensure that we obtain our study sample of lung screening patients. **Inclusion:** 1) 50 years or older (we see no reason for an upper limit given supportive evidence for cessation among elderly),[82] 2) at least a 20 pack year history of smoking (i.e., the base population of high risk smokers to get screened) as assessed by the patients ordering healthcare provider or the research team, 3) current smoker (defined as any smoking in the past 30 days – this is the criteria our lung cancer screening programs will use to trigger tobacco treatment interventions), 4) willing to be randomized, 5) English speaking; **Exclusion:** 1) unstable psychiatric/medical conditions such as suicidal ideation, acute psychosis, severe alcohol dependence, or dementia, and 2) known allergy to adhesives, and 3) current participation in another tobacco treatment program (e.g., using medication from a primary care doctor, quitline, etc).

Procedures:

Participants will be identified through the established lung cancer screening programs at all 3 sites (MUSC, VA, and Yale). The differences in study procedures for MUSC and VA patients will be the Intake, Consent Process, medication dispersal, and location of study visits as described below. All other study procedures will be the same for MUSC and VA study participants.

Intake and Consent Process:

For MUSC Charleston patients:

If the electronic medical record identifies them as a smoker, or if they report being a smoker at the time of their scan, they will meet or speak by phone with one of our study research assistants. Patients who express interest in the study will set up an intake appointment with a research staff member within 60 days of the date of their shared decision making visit. Patients who decline to participate in the study will be asked why and will be asked if we can collect basic demographic data from their medical record (e.g., age, gender, race, ethnicity, pack years). All eligible lung cancer screening patients will receive a postcard prior to their appointment informing them that they may be eligible to participate in a research study. The study staff will call these patients prior to their appointment to gauge interest in the study. If the patient would like more information, a study staff member will either meet the patient at the scanner on their proposed scan date, at another agreed upon time and place, or speak by phone. If the patient is interested in enrolling or getting more information about the study, a research assistant will speak to them or set a date with the patient to enroll them into the study. Study eligibility will be determined in concert with a clinic staff member and the site PI (Dr. Toll at MUSC or Dr. Fucito at Yale) following completion of baseline assessments, a review of the electronic medical record for health information (if necessary), and the eligibility checklist.

Informed consent will be obtained prior to any other procedures. We will provide participants with the option to complete consent and/or baseline session 1) in person, 2) via an MUSC approved HIPAA compliant video

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We chose to change our inclusion of potential participants from the day of the scan to the day of the shared decision making visit because although these 2 events generally occur on the same date, it is possible that patients may engage in a shared decision making visit and decline participation in the scan. We feel this is an important population to include in the study.

platform (teleconsent) or via REDCap electronic consent (e-consent) combined with a phone discussion, 3) by mail combined with a phone discussion, or 4) a combination of these options. Below is an overview of the procedures for each of these options.

1) In person consent – Research staff will meet with the patient at a specified time and place to review the consent form and obtain a signature.
2) Electronic consent - Signatures on the consent form may be obtained electronically via a HIPAA compliant secure connection platform (i.e., Doxy.Me, REDCap). Patients will be sent the link to the electronic consent form. The research staff will review the consent by phone or video and answer any questions before the patient signs the consent form. The patient will be asked if they are in a private place where they can discuss personal information. If they are, the research staff will continue with the consent process. If they are not, patients will be asked to move to a private place if there is one readily available or the call will be rescheduled for a time when the patient has access to a private space. The REDCap e-consent form will advise the participant to scroll to the bottom of their screen to input their electronic signature.
3) Mail – If patients are unable or unavailable to complete the consent process by any of the above options, they will be sent via mail two copies of the consent, a baseline questionnaire, and a pre-addressed, pre-stamped return envelope. All mailed materials will include our contact information and encourage individuals to call our office with any questions. A member of the research staff will speak with the patient over the phone to review the consent form and answer any questions. The person obtaining consent will have a copy of the consent, and once the patient has reviewed the consent and asked any questions, the person obtaining consent will sign and date their copy and ask the participant to sign and date their copy. The consent will be fully executed when the participant mails back their copy and the two consents are combined.

If a patient, using the remote study visit option, is randomized into a group receiving NRT, the medications will be mailed to the participant as soon as possible. If a patient is randomized into the gain-framed group, they will be asked to view the gain-framed video via an emailed or texted link and the gain-framed materials will be mailed to them as soon as possible. Following the consent process, patients will also be asked to complete the baseline assessments during their first meeting. If they are unable to complete these during this appointment, research staff will remind them to complete these assessments within a week. Additionally, after consent has been obtained and eligibility has been established, we will offer participants the option to complete the baseline assessments at another time (including by phone) within a week of the start of the intake session to allow for greater flexibility to accommodate participant schedules. The study visit will be done at the clinic, at a public location convenient for the participant, or via phone. Participants will be paid $50 for completion of all intake assessments.

For MUSC Lancaster, MUSC Chester, MUSC Florence, and MUSC Columbia patients:
If an eligible patient from either MUSC Lancaster/Chester/Florence/Columbia is interested in enrolling into the study, all study procedures will take place remotely. It is not feasible to perform study procedures in person due to the far distance from study staff, who are located at MUSC Charleston. Recruitment and all study procedures will follow the same procedures as described above for MUSC Charleston sites, with the exception of using in-person methods. If the electronic medical record identified the patient as a smoker, or if the patient reports being a smoker at the time of their scan, the nurse practitioner will speak with the patient regarding the study and/or the patient will speak by phone with one of our study research assistants. The nurse practitioner will be given study flyers to hand out to eligible patients. Patients who express interest in the study will set up an intake appointment with a research staff member 60 days of the date of their shared decision making visit. Patients who decline to participate in the study will be asked why and will be asked if we can collect basic demographic data from their medical record (e.g., age, gender, race, ethnicity, pack years). All eligible lung cancer screening patients will receive a postcard prior to their appointment informing them that they may be eligible to participate in a research study. The study staff will call these patients to gauge interest in the study. If the patient would like more information, the study staff will meet with the patient virtually. All study visits from the MUSC Lancaster/Chester/Florence/Columbia sites will be conducted remotely. After the patient is

randomized into the study, they will be mailed study intake materials (i.e., wellness bag, written materials, and NRT if applicable). Study participants from this site will be paid using Amazon e-gift cards.

For patients at the VA:
All eligible patients, identified through the CPRS system, will be sent a postcard explaining that they are eligible for a research study and the study staff may be in contact with them. Those patients will receive a phone call after being sent a postcard from a study team member. The study member will gage the patient's interest in the study, answer any questions the patient may have, and set up a meeting time at the VA or via phone. Additionally, the patients will have a phone call shared decision making visit with their Nurse Practitioner (NP). During this phone conversation, if the patient is a smoker the VA NP will inform the patient about the smoking cessation study we are offering and ask if they are interested in participating. If the patient is interested in participating, they will schedule their scan for the Lung Cancer screening clinic at the VA and inform us of the patient's interest via our VA email that is encrypted behind the VA firewall of the date and time of the scan. Once a patient is scheduled, the study team member will inform Dr. Tanner, and she we place a pending medication order so that the medication will be available at the time of randomization even if Dr. Tanner is not available. A study team member will meet the patient at the VA and give them the flyer and any additional information about the study they may need to make a decision and further confirm their willingness to participate in the study. If a patient is unavailable to meet at the VA, the study staff will offer to email or mail the flyer and discuss the details over the phone. The consent process will take place at the Charleston VAMC or via teleconsent (see section below). The initial baseline assessment and follow-up assessments will be conducted either face-to-face at the Charleston VAMC or via telehealth per preference of the patient.

Study staff will be trained to obtain informed consent and complete the initial (baseline) assessments. They will go over the informed consent in detail with each participant and answer any questions the participant may have at the time of consent or at any point during the course of the study. Veterans will not participate in the research procedures until they have had the study carefully explained to them, have had the opportunity to ask questions and demonstrate that they understand the research procedures, and have signed informed consent and HIPAA authorization documents. All consent procedures will take place in person at the Charleston VAMC, or via teleconsent (see below.). Participants will be given a copy of the informed consent for their records and will be able to defer enrollment if they would like to speak with significant others about the study or further review the informed consent documents.

We will provide participants with the option to complete consent and/or baseline session 1) in person, 2) by mail, or 3) a combination of these options. An additional overview of these procedures is included in the previous section about MUSC's consent process.

1) If the patient agrees to participate in our study in person, we will take them into a private consult room where we will thoroughly go over the VA consent and HIPAA form and have them sign these forms. Informed consent will be obtained prior to any other procedures in a private setting, then during the intake session medical and tobacco use histories and breath CO levels will be obtained. If a patient is randomized into a group receiving NRT, a member of the research staff will pick up the prescription from the research pharmacy and will give it to the patient.
2) Mail – If patients are unable or unavailable to complete the consent process by any of the above options, they will be sent via mail two copies of the consent, a baseline questionnaire, and a pre-addressed, pre-stamped return envelope. All mailed materials will include our contact information and encourage individuals to call our office with any questions. A member of the research staff will speak with the patient over the phone to review the consent form and answer any questions. The person obtaining consent will have a copy of the consent, and once the patient has reviewed the consent and asked any questions, the person obtaining consent will sign and date their copy and ask the participant to sign and date their copy. The consent will be fully executed when the participant mails back their copy and the two consents are combined.

Participants will be paid $50 for completion of the intake assessments. All follow up visits with the VA patients will take place at the VA hospital or over the phone if the patient is unable to attend an appointment at the VA. All study activities for participants recruited at the VA will take place at the Ralph H Johnson VA hospital or via phone call per patient request.

Medication Dispersal for patients at the VA:
The research assistant will let the research pharmacist and Dr. Tanner know in advanced when they will be at the VA to screen potential research participants. Dr. Tanner will electronically enter the order for the two-week supply of Nicotine patches and mini lozenges before randomization because she is not always available to enter medication orders at the time of intake. After a patient has been screened and has signed the Informed Consent, the ICF will be sent to the research pharmacist via the VA email or taken to the research pharmacy in person and copy is made. The research assistant will contact the research pharmacist via phone or Vocera to inform them of the randomization. The research pharmacist will fill the order that will then be picked up by the research assistant and given to the patient in person. If the patient is using the remote consent option, the medications will be mailed to the patient after randomization is confirmed by the research pharmacy. If the patient is unable to complete the intake appointment the same day as their lung cancer screening visit, the research assistant will let research pharmacist know when the appointment is scheduled for. Dr. Tanner will put the order in for the NRT within a week of the patient's appointment. If the patient is randomized into a group NOT receiving NRT the order will be cancelled.

Standard Care for Smoking Cessation Advice for All Study Participants:
Upon consent, all participants will be randomized to study group, stratified by study site and level of motivation (low: 0-7 on VAS ladder vs. 8-10). Following randomization, all participants will receive a bag with small smoking cessation tools (i.e., stress ball) and smoking cessation handouts based on practical counseling principles, which is a cognitive-behavioral, evidence-based, smoking cessation treatment modality focused on specific strategies to support quitting smoking. If patients are meeting with research staff via tele-consent, e-consent, or by mail, the wellness bag will be mailed to them with the intervention materials they were randomized to receive. All participants will be encouraged to set a quit date.

Study Interventions:

Gain-Framed Messaging: We will develop 1 gain-framed video and corresponding printed materials. The video will be approximately 4 minutes long and will include individuals of differing racial and ethnic backgrounds representative of our study population. The video will be designed specifically for lung screening patients, addressing how quitting smoking can be helpful given their present situation. To be clear, we are not framing any information to encourage lung screening – the gain-framed intervention will focus on smoking cessation in the context of lung screening. It will highlight Dr. Tanner's recent paper showing that quitting smoking will significantly reduce their risk for lung cancer in conjunction with screening.[28] For example, a gain-framed statement in this regard might say: "Attending this lung screening visit and low-dose CT screen is a great step toward better health and reducing your risk of lung cancer. Even if you decide not to undergo screening, you can still further reduce your risk of developing lung cancer and other diseases by quitting smoking. Research of high risk people who did not have a CT scan shows that by quitting smoking and maintaining abstinence you continue to reduce your risk for lung cancer."

For those in the arm that will receive gain-framed materials, we will disseminate the gain-framed print media to patients at the time of intake. A research assistant will show participants their assigned video via an iPad if they are assigned to the GM+M groups. We chose these procedures for several reasons: a) delivering the gain-framed messages by video allows us keep the content consistent, b) videos are easily disseminable, c) having our research staff administer the videos is consistent with how the videos would be administered at other lung screening programs (i.e., given by support staff and not clinicians), and d) this does not necessitate any special training or procedures with the clinical staff.

The most appropriate comparison group for the gain-framed intervention is debatable; we could have used a loss-framed or general health video/print intervention as a comparator but we decided against this for several reasons: a) it is more translational and more of a "real-world" test to only investigate an intervention that we hypothesize may be better than standard care; b) we do not want to waste participants' time with placebo video and handouts that we expect will not help them; and c) notably, our last large smoking cessation trial that

tested message framing was a comparison of standard care to a gain-framed intervention added to standard care,[6] for similar reasons to those described above. Thus, our control condition for the gain-framed message conditions is no message.

NRT sampling: Participants in the medication arm (GM+M) will be given a 2-week long supply of both nicotine patch and lozenge. NRT samples will be delivered in addition to all standard care treatment described above. Given the very brief 'intervention' time (few minutes), we believe that treatment groups will be essentially time-matched. We will provide a 2-week supply of both 4 mg lozenge and 21mg nicotine patches provided in the original packaging. Detailed information on each product, including instructions for use, will be provided in the take-home packet, which will include FAQs and related information intended to dispel medication misperceptions. Patients who are receiving nicotine patches and lozenges will be given the option to try these over-the-counter products (i.e., a patch and a lozenge) at the time of their study visit with aid from the research staff and will receive handouts and instructions about proper use of the NRT. We provide both patch and lozenge for four reasons. First, a number of studies demonstrate their efficacy when used singularly.[84] Second, they are both over the counter, increasing their utility in various populations, particularly within lung cancer screening settings where eligibility is minimal and instructions on use require nominal discussion. Third, whereas the patch provides a steady dose of nicotine throughout the day, the lozenge is used ad libitum and provides acute nicotine administration. These two mechanisms might appeal to smokers differently. Fourth, two studies have shown that combined use of patch + lozenge is superior over placebo and single NRT products.[11,85,86] We neither explicitly advise nor discourage combined use. Thus, this is an opportunity for smokers to learn about two NRT products, to be used individually or together (participant choice, including none at all). We will caution all participants on signs of receiving too much nicotine (nausea, dizziness), and will monitor adverse events, expected to be rare/mild. Given our inclusive study criteria, some study participants who have low nicotine dependence will receive the starter package of NRT. However, given recent evidence that dual NRT benefits most low dependence smokers, we feel this is appropriate.[87] We do not offer a placebo comparison because we are interested in the provision of medication vs. not (and not to determine if effects are pharmacologic). However, participants not receiving the starter kit of NRT will still be advised to use evidence based medications, including NRT, per standard guidelines. The NRT for MUSC patients will be stored in a cabinet in the Tobacco Treatment Program offices. The door to the office suite locks. The NRT for VA patients will be obtained via the research pharmacy at the Ralph H Johnson VA Medical Center.

Follow-up: Participants will complete assessments at a 1, 3, and 6 month follow-up session. Research staff will meet the MUSC Charleston participant in a public location that is convenient to the participant or conduct the follow-up via phone call. MUSC Charleston patients will also have the option of coming in to the clinic at Hollings Cancer Center for the follow-up meeting. All participants recruited from MUSC Lancaster, MUSC Chester, MUSC Florence, and MUSC Columbia will complete all visits remotely. If the participant has an in-person meeting, we will complete a breath CO test and a battery of assessments. If patients elect to complete these vists via phone call and report that they continued to smoke, a CO breath test will not be obtained. However, if the patient reports having quit smoking during the phone call, the research staff will schedule a visit to obtain the CO breath test. CO will be collected using the Bedfont Smokerlyzer for in-person visits or the Bedfont iCO smokerlyzer for remote visits. If CO is obtained remotely, we will mail a breath CO monitor to the participants with instructions for use. At a prearranged time, participants will be sent a link to a HIPAA Compliant video platform. Participants will virtually meet with research staff and will complete the breath CO sample live so that we can be sure it was the participant who provided the sample and reduce the chance of sample falsification. The CO device will also email a report of the CO sample to research staff. We plan to pay participants $10 for completion of the 1- and 3-month follow up visits and $30 for the completion of the 6-month visit. If the study participant is not available to meet in person or by phone, we will mail the follow up questionnaire to them to fill out and return via mail to us. Additionally, we can also send patients a link to the questionnaires via REDCap and contact them over the phone to get their timeline followback.

Safety protocol: To ensure the safety of the research assistant they will adhere to the following safety guidelines:

Confirm with participants by phone before the visit
Send meeting information to the Study Coordinator prior to leaving for the meeting
Meet in public buildings where you feel safe, and not in parking lots, or public parks

Send a message to the Study Coordinator to confirm that the meeting has ended and you are leaving the meeting location

Never meet a participant after dark

Keep your phone charged and on your person at all times in case of emergency

To ensure the safety and privacy of the MUSC participant:

We will try to meet in a public location that has an area that is in clear sight of others but semi-private area where we can obtain research data as confidentially as possible.

We will not use the patient's name in public at this location.

We will speak in low volume to communicate with the participant as not to share information with those in the surrounding area.

To ensure the safety and privacy of the VA participant:

We create a VA REDCap database behind the VA firewall where all participant study data will be collected, stored and analyzed.

Assessments (Items with an asterisk will be tested as a mediator or moderator):

Demographic and Smoking History Questionnaire: As in our previous studies, this questionnaire will obtain: 1) basic demographic information and 2) basic smoking status and history.[5,67,88] At baseline this will assess basic smoking status and history which will allow us to personalize the messages for participants in the study groups receiving gain-framed messages.

Tobacco and Alcohol Use Calendar (Timeline Followback): This standardized, validated, and reliable experimenter-administered rating scale[89-91] will be used to obtain quantity and frequency estimates of cigarette consumption for a 30-day period prior to treatment. As in our previous clinical trials, we will use the calendar to record tobacco use on a daily basis throughout the 6 months of the study.[5,67,88]

Abstinence: For our primary outcome, consistent with our past clinical trials, abstinence will be defined as 7-day point prevalence abstinence, meaning no cigarettes (or other tobacco products) for 7 days, confirmed by CO breath test less than or equal to 10 ppm.[5,67,88]

CO levels: Expired breath CO will be monitored at each in-person visit to verify abstinence during treatment. Levels of CO will be measured using a Bedfont Micro+ Smokerlyzer Monitor (Innovative Medical Marketing, Williamsburg, VA), which is a precision instrument for detecting CO in exhaled breath. Both study sites are currently using these devices and have several on hand. If smoking status is verified remotely, participants will be mailed a Bedfont iCO Smokerlyzer with instructions for use. They will complete the breath test live on a HIPAA compliant video platform and results will be emailed to study staff.

Evaluation of Framed Intervention: This manipulation check asks participants to report whether the session focused on the costs of continuing to smoke or the benefits of smoking cessation.[6]

*Outcome expectancies: Expectancies regarding the benefits of smoking cessation are important determinants of quitting.[92-94] We anticipate that gain-framed texts will enhance expectations of the benefits of quitting smoking; so outcome expectancies will be evaluated as a mediator. We will administer 6 items from the Benefits subscale of the Perceived Risks and Benefits Questionnaire (health, well-being, self-esteem, finances, physical appeal, social approval).[95] Participants will rate their perceptions of the benefits of quitting on a 7-point scale from 1 (*no chance*) to 7 (*certain to happen*). A similar brief measure of outcome expectancies has been shown to be a mediator of our framed message intervention with NY Quitline callers.[30]

*Fagerström Test for Nicotine Dependence (FTND) and Heaviness of Smoking Index (HSI): The HSI scale, which assesses 2 items from the FTND scale about amount smoked and time-to-first-cigarette, is a commonly used scale for the measurement of severity of dependence on nicotine.[96] The HSI has been shown to predict both behavioral and biochemical indices of smoking.[96-98] In line with findings from our previous research[53,54] and from other groups,[99,100] we plan to test both the FTND and HSI as moderators of treatment.

*Self-efficacy: Tailored messages have been found to increase self-efficacy for smoking cessation;[30] thus, we will examine self-efficacy as a mediator of treatment. We will measure self-efficacy using a single item. Participants will rate their confidence to quit smoking within the next month from 0 (*not at all confident*) to 10 (*completely confident*).[101] A similar, single item self-efficacy measure has demonstrated predictive validity in smoking cessation studies, and in our previous research with the NY Quitline.[9]

Use of NRT and Other Pharmacotherapy: We will determine the amount and frequency of NRT used (per product), and will determine use of products we provide (lozenge + patch) vs. additional purchase of products. We will ascertain the context in which the product is used (e.g., places with smoking restrictions vs. other) using prior methods.[102] We will specifically ask if the NRT is used "not to quit, but to reduce the amount you smoke" or "not to quit or reduce smoking, but to get you through times when you cannot smoke."

*Attitudes Towards NRT: Based largely on prior work in this area,[32-34,93,103] we have published[10] on 1) positive, and 2) negative attitudes towards NRT, as well as 3) general knowledge of NRT.

*Motivation and Confidence to Quit: We will separately assess motivation and confidence to quit smoking. We will do so using our modification of the Contemplation Ladder[104] to measure readiness to quit in the next 1 and 6 months. Our ladders have adequate test-retest stability and predictive validity.[105] This measure will of motivation will be used for stratification, as well as to assess motivation throughout treatment.

Findings from screening: Lung screening findings will be defined as pulmonary findings (nodule, cancer, emphysema, enlarged lymph nodes) and coronary findings (calcification).

*Lung Cancer Distress Questionnaire: Higher baseline distress, as measured by the LCDQ has been associated short-term smoking cessation.[114] We plan to use a single item from this questionnaire.

Statistical Considerations

Power and Sample size:

We propose to test the primary hypothesis that rates of smoking cessation will be significantly higher 6-months after lung screening for the smoking cessation strategy involving a gain-framed intervention + 2 weeks of nicotine patches and lozenges compared to a strategy of an unframed behavioral intervention + no medication. We assume a biologically confirmed 7-day point prevalence abstinence rate at the 6 month follow up visit of 10-13% for the participants randomized to receive no NRT or gain framed messaging based on USPHS guidelines (Table 6.7 and 6.8 of USPHS Guidelines).[15] In studies with a similar 2 week NRT exposure, 6 month abstinence rates varied from 16-34 %[46,107-109] and a conservative estimate of a 20% abstinence rate in those receiving NRT only will be assumed. Based on previous work[5,6] we estimate that the abstinence rate of in those receiving both NRT and gain framed messaging will be 10-11% increased over those with unframed messaging. Based on these estimates, we will have 80% power with a type 1 error rate of 5% to detect the conservative difference of between those receiving gain framed messaging + NRT (28%) and those receiving unframed messaging and no NRT (13%) with 123 participants randomized to each of the 4 treatment groups (total n=492 Participants). This assumes that the two treatment sites are moderately correlated (ICC=0.85) and randomize equal numbers of patients to each treatment cell. Additionally, we anticipate that 15-20% of our participants will fail to report 6 month follow up outcome data (LTF, death, moved out of area), accounting for a 20% attrition during the study follow up, we would need to randomize **n=367 participants** across all sites (179 randomized at Yale and 179 between MUSC and the VA) to maintain adequate power to detect the clinically meaningful difference stated. Assuming an abstinence rate of 14-17% in the group receiving unframed messages, we will have >80% power with a type 1 error rate of 5% to detect an 11% increase in abstinence in those receiving gain framed messages with the sample size stated for aim 1. We considered but opted against powering our trial on the treatment interaction, as this would require >5,000 participants.

Anticipated abstinence rates – 6 months	Gain-framed Intervention	No Message Intervention	
2 week starter pack NRT	**28-30%**	**18-20%**	23-25%
No Medication	**20-23%**	**10-13%**	15-18%
	24-27%	14-17%	

Statistical Analysis:

Categorical clinical and demographic variables will be assessed by chi-square tests of independence, while continuous variables will be assessed using Student's *t*-test. In addition to baseline group differences, preliminary analysis of baseline characteristics with outcomes of interest will examine significant correlates of abstinence in the study population. Characteristics found to be significantly associated with smoking outcomes will be included as covariates in the initial stages of model development. *Our primary aim is to determine if the rate of smoking cessation among lung screening patients may be improved by delivering gain-framed smoking cessation messages and delivery of a free starter package of medication (gain-framed behavioral intervention + 2 weeks of nicotine patches and lozenges vs. unframed behavioral intervention + no medication).* We hypothesize that rates of smoking cessation will be significantly higher at 6-months after lung screening for the smoking cessation

strategy involving a gain-framed intervention + 2 weeks of nicotine patches and lozenges compared to a strategy of an unframed behavioral intervention + no medication. Primary and secondary models will be developed including the effects of both randomized conditions; gain framed vs. unframed messaging and NRT vs. no medication, and a cluster effect of study site. Models will be computed both unadjusted and adjusted for significant covariates found in the preliminary analysis. For these efficacy analyses, 7-day point prevalence abstinence will be defined as having no cigarettes (or other tobacco products) for 7 days, confirmed by CO breath test less than or equal to 10 ppm. All randomized participants will be included in the analyses (intent-to-treat approach), and participants will be considered non-abstinent at any missed visit (drop-out/lost-to-follow-up included). To comprehensively analyze the longitudinal efficacy of gain framed messages and NRT sampling, the entire study time course will be analyzed with repeated measures logistic regression using a Generalized Estimating Equation framework. Continuous abstinence (CA) from the time of lung screening to the 1 and 3 month follow-ups (Weeks 4 and 12) and to final follow-up visit (Week 26) will be assessed using logistic regression analysis. Time to first lapse (puff) and time to relapse (first of 3 consecutive days smoking ≥1 cigarette) will be analyzed using Cox Proportional Hazard models with effects of both randomized conditions in a 2x2 design; gain framed vs. unframed messaging and NRT vs. no medication, and a cluster effect of study site. In addition to the primary intent-to-treat analyses, additional exploratory approaches (e.g., modified intent-to-treat models, per protocol analysis, and completer analysis) will be undertaken as indicated and a sensitivity analysis comparing these models to the ITT model will be completed.

We have an exploratory aim in which we plan to examine moderators of treatment to determine which subgroups are most likely to respond to the gain-framed and medication interventions, and we will explore differential effects of the study factors across treatment groups. Procedures from MacKinnon et al[110] will be used to test mediators. We hypothesize that changes in self-efficacy, smoking cessation outcome expectancy, familiarization with NRT, motivation, and autonomy will act as mechanisms for the smoking cessation effects (i.e., will act as mediators of treatment). Variables that predict the outcome variable (smoking cessation) differently between treatments will be considered to be moderators using the model outlined by Kraemer et al.[111] In order to be considered a moderator, the variable must be present prior to randomization and must not be related to the independent variable. We hypothesize that lung screening findings (e.g., presence of a nodule, cancer, etc.), nicotine dependence, and health disparities will modify treatment response (i.e., will act as baseline moderators of treatment). Variables that predict the outcome variable but do not significantly interact with treatment condition (i.e., influence outcome regardless of treatment condition) will be classified as nonspecific pre-randomization predictors.

Our other exploratory aim will examine additional treatment endpoints: patient reach, intervention fidelity, patient acceptance and engagement, cost, and the ease of delivery and feasibility. We hypothesize that we will reach a majority of qualified patients who are current smokers, adherence to the critical elements of the intervention design and delivery methods will be successfully met, patient acceptance and engagement will be greater in the gain-framed messaging and NRT arms, the cost will be higher in the NRT arms, and both the gain-framed messages and dispensing of the 2-week starter pack of NRT will be easily delivered and feasible as part of the lung screening clinic work flow. Patient adherence, exposure to study content, acceptance/responsiveness to content and noted distinguishing factors will be assessed within the study and across study groups.[112,113] Associations between treatment status and these exploratory endpoints will be assessed using general linear mixed models with data appropriate residual distribution assumptions (Gaussian, Poisson, etc.) and transformations where necessary.

Adverse Events (AE) and Serious Adverse Events (SAE) will be recorded during the duration of the treatment period. All cause treatment emergent adverse event and serious adverse event frequencies will be compared through the use of analysis of variance models. Of particular interest will be (S)AEs that lead to treatment suspension or study discontinuation. Study retention will be assessed by two methods; total number of treatment visits attended will be compared using Poisson regression for count data, while the number of days retained will be assessed using Cox Proportional Hazards regression models.

Recruitment, Feasibility, and Timeline

Patients eligible for this study come from our lung cancer screening programs at our 3 study sites (MUSC, VA and Yale). Because the smoking cessation treatment programs led by Dr. Toll and Dr. Fucito are clinical services, we have access to any and all of these patients for recruitment and are able to easily identify them through the Epic Medical Record (which is used at both study sites). Moreover, because Dr. Toll is the Co-Director of the Lung Cancer Screening Program at MUSC and with the support of Dr. Tanoue (see attached

letter), who is the Director of the Lung Screening and Nodule Program at Yale, we have full access to all lung screening patients at those study sites. Dr. Tanner is the director of the lung cancer screening program at the VA and will be able to assist us in identifying all eligible participants that come through the lung cancer screening program. Because the USPTF recently recommended lung cancer screening for high-risk individuals and CMS covered lung screening as a benefit, many insurers are now covering lung cancer screening for high-risk patients, so these numbers should continue to grow rapidly. At HCC, Between March 1, 2015 and September 1, 2015, we have had 50 patients screened under physician referral to the screening program (approximately 8 per month). We have engaged the primary care physicians at MUSC (University Internal Medicine) and are conducting outreach with these physicians to increase referrals for lung cancer screening at MUSC. Dr. Toll's Co-Director of the Lung Cancer Screening Program at MUSC, Dr. Nichole Tanner (a co-investigator on this grant), conducted similar outreach activities this past year at the Charleston VA and was able to screen 400 patients in the first year the program was open. Thus, we anticipate that our number of patients we are able to recruit will grow rapidly in the coming year. At YCC, there are 100 patients scheduled for screening over the next 4 months. Given the start date of this grant project and the time needed to prepare for the trial after the grant is awarded, we are highly confident that we will easily be able to meet our recruitment goal of approximately 1 participants per month (7 patients per month per site, VA/MUSC and Yale). This seems quite feasible given the large (and quickly growing) pool of patients available. The study timeline is described below:

Months 1–6: Create gain-framed intervention materials, obtain study medication, train staff on study procedures, and finalize IRB approval.
Months 7–51: Actively recruit 367 participants (approximately 14/month) and follow for 6 months.
Months 50–60: Complete follow-up interviews, data analyses, prepare presentations and publications.

Strengths and Overall Impact

The proposed research has numerous strengths including: a) an experienced multi-disciplinary team; b) a timely research question, namely how to optimally enhance smoking cessation in growing populations of current smokers who are receiving lung cancer screening; c) gain-framed smoking cessation messages specifically developed for lung screening patients; d) an innovative pharmacotherapy strategy for all smokers; and e) ability to easily translate our findings to the growing number of lung cancer screening programs across the country. The findings from this research will have high overall impact by filling gaps in our knowledge of tobacco cessation in this high-risk population of smokers. These findings and the sharing of materials developed as part of this research will assist cancer centers and other healthcare organizations to maximize management of lung cancer screening patients with proven interventions for cessation, to have the greatest possible impact on lung cancer incidence and mortality.

PROTECTION OF HUMAN SUBJECTS

RISKS TO THE SUBJECTS

Human Subjects Involvement and Characteristics

In this experiment, participants will be recruited to participate in a smoking cessation study in the context of lung cancer screening. For the randomized controlled study, we will use the following inclusion and exclusion criteria. Inclusion: 1) 50 years or older (we see no reason for upper limit given supportive evidence for cessation among elderly), 2) 20 pack year history of smoking (i.e., the base population of high risk smokers to get screened), 3) current smoker (defined as any smoking in the past 30 days – this is the criteria our lung cancer screening programs will use to trigger tobacco treatment interventions), 4) willing to be randomized, 5) English speaking; Exclusion: 1) unstable psychiatric/medical conditions such as suicidal ideation, acute psychosis, severe alcohol dependence, or dementia, and 2) contraindications to NRT. We intend to enroll 616 participants across 3 sites (MUSC, VA and Yale).

Sources of Materials. The sources of data for participants in this project is open-ended questions through interviewer-administered self-report questionnaires of background, behavior (eg, smoking), and cognitions (eg, motivation). Questionnaires will be administered at the time of intake (i.e., the lung cancer screening appointment), and at 1, 3, and 6 months for follow-up. All responses will be collected on a secure, password-

protected, electronic Web-based form. The data will be sent to a secure database in REDCap. Only research staff members have access to the database. The data obtained from VA participants will be house in the VA REDCap database.
We will collect demographic information, as well as diagnostic medical information related to their screening. Identifiable information will be collected and used to enroll, treat, and contact participants. It will only be used for this purpose.

Research data will be collected using in-person interviews and self-reports. All identifiable information will be stored in a locked file cabinet. All identifiable information collected from VA patients will be stored in a locked cabinet in Dr. Tanner's office room C405 at the Ralph H Johnson VA Hospital. All participants will be assigned a study participant ID made up of numbers and letters. Subsequently, participants will be identified in the Case Report Forms (CRFs) only by that number (e.g., CM24). A list of MUSC IDs and the corresponding names will be maintained by the Principal Investigator and stored on the MUSC BOX.Com site. Digital data with PHI will be stored on a secured server. A list of VA IDs and the corresponding names will be maintained by the site Principal Investigator, Dr. Tanner, and stored on the V drive behind the VA firewall. Digital data without PHI may be stored and analyzed on a laptop or desktop computer.

Potential Risks. The risks to participating in these studies are minimal. Participants are informed in advance about the content of the educational materials that they will receive and the kinds of questions that they will be asked. They are also informed that they may terminate participation without penalty. Moreover, they are informed that, if any pre- or post-intervention question seems too personal or if they prefer not to respond for any reason, they can skip the question without penalty. There is also the risk of loss of confidentiality and privacy. Some participants will be offered nicotine replacement therapy (NRT), and there are risks in taking NRT. The NRT used in this study (patch and lozenge) is a standard smoking cessation intervention and is available over-the-counter. The most common adverse effect of nicotine transdermal delivery is topical skin irritation, ranging from mild erythema to a more generalized skin reaction, frequently in subjects with a history of eczematous dermatitis. The most common adverse effects of nicotine replacement lozenges are upset stomach and heartburn.

ADEQUACY OF PROTECTIONAGAINST RISKS

Recruitment and Informed Consent
Participants will be recruited through the lung cancer screening programs at Hollings Cancer Center and Yale Cancer Center/Smilow Cancer Hospital at Yale-New Haven and the Ralph H. Johnson Veteran Administration. Informed consent will be obtained prior to beginning the study.

Protection Against Risk. We will take the following steps to reduce the direct risk of participating in the study:

(a) If offended in any way, participants can terminate any part of participation without penalty. In all of the preliminary experiments reported in this proposal, no participant reported being unduly distressed or upset about his or her participation, although occasionally participants do drop out because they are no longer interested in the study or because it is taking too long and they have other obligations. To date, no one has expressed significant regret about having participated.

(b) If a participant or potential participant appears extremely distraught or clearly preoccupied, investigators will use their discretion as to whether or not to attempt to enroll the individual into the study or suggest that their participation stop.

(c) If a participant reports an adverse effect of the NRT, we will work with them to ensure that they are using the medication properly. If it is determined that they have been using the medication properly and are still experiencing an adverse effect, they will be encouraged to discontinue use of the NRT.

d) Several steps will be taken to safeguard the confidentiality of subjects and their data. All research data that is collected will be assigned a study participant number and that number will only identify participants in digital databases. The names of participants will not be associated with this data and assessments will be maintained

according to participant study number. A master list connecting participant study numbers to participant names will be kept online on the Box MUSC approved encrypted website where only senior level project staff will have access to the information. Any information published as a result of the study will be such that it will not permit identification of any participant. For VA patients, their consent forms will be stored in a locked cabinet in Dr. Tanner's space on VA premises and their MUSC consent and HIPAA will be stored in a locked cabinet on MUSC premises.

Medical records are maintained under the person's name, but the study number is not entered anywhere into that record. Right to privacy for participation in this research will be protected through coding of data and proper storage of research records. The Principal Investigator will maintain a list of IDs and the corresponding names online on the BOX MUSC approved encrypted website. Consistent with mandated reporting requirements for health providers, we advise participants that in the case of child abuse or neglect, threat of injury to self or others, or intention to destroy property, that we may need to intervene and report that information to the proper authorities. Subjects will be informed of this limit to confidentiality as it is stated in the informed consent document. For VA patients, there will be a note entered in the CPRS system that they have been consented to participate in an MUSC study but no other notations of study procedures will appear in their medical records.

The data will be stored in a locked room for 7 years after the final data is collected. The PI and the research staff will have access to PHI. Organizations that have a responsibility for protecting human participants, including the MUSC IRB, may have access to subjects' medical records containing PHI. Additionally, the funding agency (National Cancer Institute) may have access to subjects' medical records containing PHI.

POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

Participants will receive advice about quitting smoking. Subjects participating in this study may benefit from the information provided to them the counselor by having their motivation to quit smoking bolstered and by receiving advice that helps them to quit smoking. Although the investigators cannot know for sure whether this study will be of any direct benefit to participants, the results of the study will facilitate the development of more effective smoking cessation intervention materials, which will promote tobacco and cancer control.

IMPORTANTCE OF THE KNOWLEDGE TO BE GAINED

Although the proposed research poses minimal risks to participants, it has high potential for advancing knowledge in the field of smoking cessation. The proposed research will augment current knowledge on the efficacy of interventions administered in the context of lung cancer screening. Administering a sample of NRT and gain-framed messages may help to identify a low-cost method for increasing the effectiveness of a moderate-intensity intervention for smoking cessation that has the potential to reach smokers at high risk of lung cancer, thereby bolstering tobacco and cancer control efforts across the United States. Given the minimal risks in the study and the potentially great benefit to science, the risk/benefit ratio in this study appears quite favorable.

DATA AND SAFETY MONITORING PLAN

Monitoring for data integrity and safety will be the responsibility of the investigators, the MUSC Institutional Review Board, and the Yale University Human Investigation Committee.

Data Monitoring. For this review process, we evaluate a semiannual report of aggregate data that contains screening data, baseline demographics, retention data, adverse events data, accrual status including projections, times to milestones, and any other data that will help in the assessment of the experiments. Based on this report, we will decide whether we will: 1) continue recruitment unchanged; 2) continue with a protocol amendment; 3) stop the study pending further investigation. If after assessment, we feel that a protocol amendment is needed, the MUSC IRB and the Yale HIC will be immediately informed by the site PIs.

Safety Monitoring. This protocol presents minimal risks to participants. The study involves receiving gain-framed messages and/or a 2-week sample of NRT, and to complete follow-up interviews. The only risk that can be anticipated from this study is loss of confidentiality, and this will be protected using the procedures described

in the “Sources of Materials” section above. Nonetheless, because we anticipate that behavior change (which will pose minimal risk to participants) will be a product of participating, we have developed a safety monitoring plan to report adverse events resulting from behavioral changes.

Monitoring to identify adverse events. Prior to implementing the randomized study, research staff will be trained to identify adverse events. Research staff will be instructed to provide the Project Coordinator a detailed description of the event. The Project Coordinator will grade the event in conjunction with the PI within 24 hours. The following additional individuals will be informed immediately of serious adverse events: (a) all Co-investigators; (b) the National Cancer Institute; (c) the MUSC Institutional Review Board; and (d) the Yale University Human Investigation Committee. All of these individuals and committees will receive a copy of an SAE Form within 48 hours.

Plan for grading adverse events. Serious Adverse Events (SAE). The FDA’s definition of serious adverse events (21 CFR 312) will be used. Serious Adverse Events include any untoward medical occurrence that at any dose results in death or the immediate risk of death, hospitalization or the prolonging of an existing hospitalization, persistent or significant disability/incapacity or a congenital anomaly/birth defect, new cancer, or medication overdose. Adverse events will be defined and graded for risk as follows:

Coding of Severity:
0 = No adverse event or within normal limits
1 = Mild adverse event
2 = Moderate adverse event
3 = Severe, resulting in psychiatric or medical hospitalization
4 = Life-threatening adverse event
5 = Fatal adverse event

Coding of Attribution will be made for adverse events grade 3 and above (ie, serious adverse events):
1 = Unrelated to study interventions
2 = Unlikely relationship to study interventions
3 = Possible relationship to study interventions
4 = Probable relationship to study interventions
5 = Definite relationship to study interventions

Plans for reporting serious unanticipated and anticipated adverse events. Serious adverse events, whether unanticipated or anticipated, will be reported immediately (within 24 hours) to the MUSC Institutional Review Board, the Yale University Human Investigation Committee, and to the National Cancer Institute, and a written report will be submitted within 48 hours. The PI will evaluate the adverse event and determine whether the adverse event affects the Risk/Benefit ratio of the study and whether modifications to the protocol or the consent procedures are required.

Plans for reviewing and reporting nonserious anticipated or unanticipated adverse events. Any participants' experiences of anticipated and unanticipated adverse events will be reported on an annual basis to the MUSC Institutional Review Board, the Yale University Human Investigation Committee, and the National Cancer Institute as part of an annual progress report (NCI) and annual re-approval (MUSC Institutional Review Board and the Yale University Human Investigation Committee).

References

1. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *The New England journal of medicine.* 2011;365(5):395-409.
2. Moyer VA. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Annals of internal medicine.* 2014;160(5):330-338.
3. Mazzone P, Powell CA, Arenberg D, et al. Components necessary for high-quality lung cancer screening: American College of Chest Physicians and American Thoracic Society Policy Statement. *Chest.* 2015;147(2):295-303.
4. Tversky A, Kahneman D. The framing of decisions and the psychology of choice. *Science.* 1981;211:453-458.
5. Toll B, SS O'Malley, NA Katulak, et al. Comparing gain- and loss-framed messages for smoking cessation with bupropion: A randomized controlled trial. *Psychology of Addictive Behaviors.* 2007;21:534-544.
6. Toll BA, Martino, S., Latimer, A., Salovey, P., O'Malley, S. S., Carlin-Menter, S., Hopkins, J., Wu, R., Celestino, P., & Cummings, K. M. Randomized trial: Quitline specialist training in gain-framed vs standard care messages for smoking cessation. *Journal of the National Cancer Institute.* 2010;102:96-106.
7. McKee S, O'Malley S, Steward W, Neveu S, Land M, Salovey P. How to word effective messages about smoking and oral health: Emphasize the benefits of quitting. *Journal of Dental Education.* 2004;68:569-573.
8. Schneider T, Salovey P, Pallonen U, Mundorf N, Smith N, Steward W. Visual and auditory message framing effects on tobacco smoking. *Journal of Applied Social Psychology.* 2001;31:667-682.
9. Steward W, Schneider T, Pizarro J, Salovey P. Need for cognition moderates responses to framed smoking-cessation messages. *Journal of Applied Social Psychology.* 2003;33:2439-2464.
10. Carpenter M, Hughes J, Gray K, Wahlquist A, Saladin M, Alberg A. Nicotine Therapy Sampling to Induce Quit Attempts Among Smokers Unmotivated to Quit A Randomized Clinical Trial. *Archives of Internal Medicine.* 2011;171:1901-1907.
11. Carpenter M, Jardin B, Burris J, et al. Clinical Strategies to Enhance the Efficacy of Nicotine Replacement Therapy for Smoking Cessation: A Review of the Literature. *Drugs.* 2013;73:407–426.
12. Jardin B, Cropsey K, Wahlquist A, et al. Evaluating the Effect of Access to Free Medication to Quit Smoking: A Clinical Trial Testing the Role of Motivation. *Nicotine & Tobacco Research.* 2014;Online first(doi:10.1093/ntr/ntu025).
13. US Surgeon General. *The Health Consequences of Smoking-50 Years of Progress: A Report of the Surgeon General*. Atlanta (GA)2014.
14. Shopland D, Eyre H, Pechacek T. Smoking-attributable cancer mortality in 1991: is lung cancer now the leading cause of death among smokers in the United States? . *Journal of the National Cancer Institute.* 1991;83:1142-1148.
15. Fiore M, Jaén C, Baker T, et al. *Treating Tobacco Use and Dependence 2008 Update: Clinical Practice Guideline.* Rockville, MD: USDHHS; 2008.
16. Siegel R, Naishadham D, Jemal A. Cancer Statistics, 2012. *CA Cancer J Clin.* 2012;62:10–29.
17. National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *New England Journal of Medicine.* 2011;365:395-409.
18. U.S. Preventive Services Task Force. Screening for Lung Cancer: U.S. Preventive Services Task Force Final Recommendation Statement December 2013; http://www.uspreventiveservicestaskforce.org/uspstf13/lungcan/lungcanfact.pdf. Accessed January 28, 2014.
19. Mayne ST LS. Cigarettes: a smoking gun in cancer chemoprevention. *Journal of the National Cancer Institute.* 2005;97:1319-1321.

20. Clark MM. Change in smoking status after low-dose spiral chest CT screening for lung cancer: opportunity for smoking intervention. *Thorax.* 2009;64(5):371.
21. Cox LS. Change in smoking status after spiral chest computed tomography scan screening. *Cancer.* 2003;98(11):2495.
22. Anderson CM. Smoking cessation and relapse during a lung cancer screening program. *Cancer epidemiology, biomarkers & prevention.* 2009;18(12):3476.
23. Styn MA. Smoking behavior 1 year after computed tomography screening for lung cancer: Effect of physician referral for abnormal CT findings. *Cancer epidemiology, biomarkers & prevention.* 2009;18(12):3484.
24. Townsend CO. Relation between smoking cessation and receiving results from three annual spiral chest computed tomography scans for lung carcinoma screening. *Cancer.* 2005;103(10):2154.
25. Zeliadt SB, Heffner JL, Sayre G, et al. Attitudes and Perceptions About Smoking Cessation in the Context of Lung Cancer Screening. *JAMA internal medicine.* 2015;175(9):1530-1537.
26. Rothman A, Salovey P. Shaping perceptions to motivate healthy behavior: The role of message framing. *Psychological Bulletin.* 1997;121:3-19.
27. McCall L, Martin Ginis K. The effects of message framing on exercise adherence and health beliefs among patients in a cardiac rehabilitation program. *Journal of Applied Biobehavioral Research.* 2004;9:122-135.
28. Tanner N, Kanodra N, Gebregziabher M, et al. The association between smoking abstinence and mortality in the National Lung Screening Trial. *American journal of respiratory and critical care medicine.* in press.
29. Enright A. Samples eliminate fear factor. *Marketing News*2005:October; 43&49.
30. Latimer A, Fucito L, Carlin-Menter S, et al. How do perceptions about cessation outcomes moderate the effectiveness of gain-framed smoking cessation telephone counseling intervention? *Journal of Health Communication.* 2012;17:1081-1098.
31. Balmford J, Borland R, Hammond D, Cummings KM. Adherence to and reasons for premature discontinuation from stop-smoking medications: Data from the ITC Four-Country Survey. *Nicotine & Tobacco Research.* 2011;13(2):94-102.
32. Bansal MA, Cummings KM, Hyland A, Giovino GA. Stop-smoking medications: Who uses them, who misuses them, and who is misinformed about them? *Nicotine & Tobacco Research.* 2004;6(Suppl 3):S303-S310.
33. Cummings KM, Hyland A, Giovino GA, Hastrup JL, Bauer JE, Bansal MA. Are smokers adequately informed about the health risks of smoking and medicinal nicotine? *Nicotine & Tobacco Research.* 2004;6(Suppl 3):S333-S340.
34. Etter JF, Perneger TV. Pharmacoepidemiology and drug utilization: Attitudes toward nicotine replacement therapy in smokers and ex-smokers in the general public. *Clinical Pharmacology Therapy.* 2001;69:175-183.
35. Hammond D, McDonald PW, Fong GT, Borland R. Do smokers know how to quit? Knowledge and perceived effectiveness of cessation assistance as predictors of cessation behaviour. *Addiction.* 2004;99:1042-1048.
36. Carpenter MJ, Hughes JR, Solomon LJ, Callas PW. Both smoking reduction with nicotine replacement therapy and motivational advice increase future cessation among smokers unmotivated to quit. *Journal of Consulting and Clinical Psychology.* 2004;72:371-381.
37. Velicer WF, DiClemente CC, Rossi JS, Prochaska JO. Relapse situations and self-efficacy: An integrative model. *Addictive Behaviors.* 1990;15:271-283.
38. Zapawa LM, Hughes JR, Benowitz NL, Rigotti NA, Shiffman S. Cautions and warnings on the US OTC label for nicotine replacement: What's a doctor to do? *Addictive Behaviors.* 2011;36:327-332.
39. Gwaltney CJ, Metrik J, Kahler CW, Shiffman S. Self-efficacy and smoking cessation: A meta-analysis. *Psychology of Addictive Behaviors.* 2009;23:56-66.

40. Williams GC, Niemiec CP, Patrick H, Ryan RM, Deci EL. The importance of supporting autonomy and perceived competence in facilitating long-term tobacco abstinence *Annals of Behavioral Medicine.* 2009;37:315-324.
41. Williams GC, McGregor HA, Zeldman A, Freedman ZR, Deci EL. Testing a self-determination theory process model for promoting glycemic control through diabetes self-management *Health Psychology.* 2004;23:58-66.
42. Fiore MC, McCarthy DE, Jackson TC, et al. Integrating smoking cessation treatment into primary care: An effectiveness study. *Preventive Medicine.* 2004;38:412-420.
43. Cox JL, McKenna JP. Nicotine gum: Does providing it free in a smoking cessation program alter success rates? *Journal of Family Practice.* 1990;31:278-280.
44. Walker N, Howe C, Bullen C, et al. Does improved access and greater choice of nicotine replacement therapy affect smoking cessation success? Findings from a randomised controlled trial. *Addiction.* 2011;106(6):1176-1185.
45. Cummings KM, Fix BV, Celestino P, et al. Does the number of free nicotine patches given to smokers calling a quitline influence quit rates: Results from a quasi-experimental study. *BMC Public Health.* 2010;10:181.
46. McAfee TA, Bush T, Deprey TM, et al. Nicotine patches and uninsured quitline callers. A randomized trial of two versus eight weeks. *American Journal of Preventive Medicine.* 2008;35(2):103-110.
47. Tinkelman D, Wilson SM, Willett J, Sweeney CT. Offering free NRT through a tobacco quitline: Impact on utilisation and quit rates. *Tobacco Control.* 2007;16(Suppl 1):i42-i46.
48. Schillo BA, Wendling A, Saul J, et al. Expanding access to nicotine replacement therapy through Minnesota's QUITLINE partnership. *Tobacco Control.* 2007;16(Suppl 1):i37-i41.
49. Hollis JF, McAfee TA, Fellows JL, Zbikowski SM, Stark M, Riedlinger K. The effectiveness and cost effectiveness of telephone counselling and the nicotine patch in a state tobacco quitline. *Tobacco Control.* 2007;16(Suppl 1):i53-i59.
50. Cummings KM, Hyland A, Carlin-Menter S, Mahoney MC, Willett J, Juster HR. Costs of giving out free nicotine patches through a telephone quit line. *J Public Health Manag Pract.* 2011;17(3):E16-23.
51. Borland R, Segan CJ. The potential of quitlines to increase smoking cessation. *Drug and Alcohol Review.* 2006;25:73-78.
52. Zhu SH, Anderson CM, Tedeschi GJ, et al. Evidence of real-world effectiveness of a telephone quitline for smokers. *New England Journal of Medicine.* 2002;347:1087-1093.
53. Fucito L, Latimer A, Salovey P, Toll B. Nicotine dependence as a moderator of message framing effects on smoking cessation outcomes. *Annals of Behavioral Medicine.* 2010;39:311-317; PMID: 20502997; PMCID: PMC22749968.
54. Fucito L, Latimer A, Carlin-Menter S, Salovey P, Cummings K, Toll B. Nicotine dependence as a moderator of a quitline based message framing intervention. *Drug and Alcohol Dependence.* 2011;114:229-232; PMID: 21036492.
55. Moorman M, van den Putte B. The influence of message framing, intention to quit smoking, and nicotine dependence on the persuasiveness of smoking cessation messages. *Addictive Behaviors.* 2008;33:1267-1275.
56. Szklo A, Coutinho E. The influence of smokers' degree of dependence on the effectiveness of message framing for capturing smokers for a Quitline. *Addictive Behaviors.* 2010;35:620-624.
57. Okuyemi KS, Reitzel LR, Fagan P. Interventions to Reduce Tobacco-Related Health Disparities. *Nicotine & Tobacco Research.* 2015;17(8):887-891.
58. Croyle R. Increasing the effectiveness of tobacco quitlines (Editorial). *Journal of the National Cancer Institute (JNCI).* 2010;102:72-73.
59. Carpenter MJ, Alberg AJ, Gray KM, Saladin ME. Motivating the unmotivated for health behavior change: A randomized trial of cessation induction for smokers. *Clinical Trials.* 2010;7:157-166.
60. Heckman CJ, Egleston BL, Hofmann MT. Efficacy of motivational interviewing for smoking cessation: A systematic review and meta-analysis. *Tobacco Control.* 2010;19(5):410-416.

61. Hettema JE, Hendricks PS. Motivational interviewing for smoking cessation: A meta-analysis review. *Journal of Consulting and Clinical Psychology.* 2010;78:868-884.
62. Lai DTC, Cahill K, Qin Y, Tang JL. Motivational interviewing for smoking cessation. *Cochrane Database of Systematic Reviews*. Oxford: John Wiley & Sons; 2010.
63. Stead LF, Bergson G, Lancaster T. Physician advice for smoking cessation (Cochrane Review). *The Cochrane Library, Issue 3*. Oxford: Wiley Publishers; 2008.
64. Bansal-Travers M, Cummings KM, Hyland A, Brown A, Celestino P. Educating smokers about their cigarettes and nicotine medications. *Health Education Research.* 2010;25:678-686.
65. Carpenter MJ, Ford ME, Cartmell KB, Alberg AJ. Misperceptions and misconceptions of nicotine replacement therapy within racially and ethnically diverse smokers. *Journal of the National Medical Association.* 2011;103:885-894.
66. Ryan KK, Garrett-Mayer E, Alberg AJ, Cartmell KB, Carpenter MJ. Predictors of cessation pharmacotherapy use among African American and non-Hispanic white smokers. *Nicotine & Tobacco Research.* 2011;13:646-652.
67. Toll BA, White, M., Wu, R., Meandzija, B., Jatlow, P., Makuch, R., & O'Malley, S. S. Low-dose naltrexone augmentation of nicotine replacement for smoking cessation with reduced weight gain: A randomized trial. *Drug and Alcohol Dependence.* 2010;111(3):200-206.
68. Toll BA, Martino S, O'Malley SS, et al. Randomized trial of brief alcohol intervention for hazardous drinking smokers calling a tobacco quitline. *Journal of Consulting and Clinical Psychology.* 2014;Online First Publication, November 24, 2014. http://dx.doi.org/10.1037/a0038183
69. Bernstein S, Boudreaux E, Rhodes K, et al. Tobacco Control Interventions in the Emergency Department: A Joint Statement of Emergency Medicine Organizations. *Annals of Emergency Medicine.* 2006;48:417-426.
70. Bernstein S, Cannata M. Nicotine dependence, motivation to quit, and diagnosis in emergency department patients who smoke. *Addictive Behaviors.* 2006;31:288-297.
71. Bernstein S, Boudreaux E, Cabral L, et al. Efficacy of a Brief Intervention to Improve Emergency Physicians' Smoking Cessation Counseling Skills, Knowledge, and Attitudes. *Substance Abuse.* 2009;30:158-181.
72. Bernstein S. The impact of smoking-related illness in the emergency department: an attributable risk model. *American Journal of Emergency Medicine.* 2002;20:161-164.
73. Bernstein S, Rosner J, O'Malley S, et al. Successful tobacco dependence treatment achieved via pharmacotherapy and motivational interviewing in low-income emergency department patients *Annals of Emergency Medicine.* in press.
74. Gritz E, Toll B, Warren G. Tobacco use in the oncology setting: Advancing clinical practice and research. *Cancer, Epidemiology, Biomarkers, and Prevention.* 2014;23:3-9.
75. Peters E, Torres E, Toll B, et al. Tobacco assessment in actively accruing National Cancer Institute (NCI) Cooperative Group clinical trials. *Journal of Clinical Oncology.* 2012;30:2869-2875.
76. Warren G, Marshall J, Cummings K, et al. Assessing tobacco use and tobacco cessation support by members of the American Society of Clinical Oncology (ASCO). *Journal of Oncology Practice.* 2013;1:258-262.
77. Warren G, Marshall J, Cummings K, et al. Practice patterns and perceptions of thoracic oncology providers on tobacco use and cessation in cancer patients *Journal of Thoracic Oncology.* 2013;8:543-548.
78. Fucito L, Toll B, Salovey P, O'Malley S. Beliefs and attitudes about bupropion: Implications for medication adherence and smoking cessation treatment. *Psychology of Addictive Behaviors.* 2009;23:373-379; PMID: 19586156.
79. Toll BA, Rojewski AM, Duncan LR, et al. "Quitting Smoking Will Benefit Your Health": The Evolution of Clinician Messaging to Encourage Tobacco Cessation. *Clinical Cancer Research.* 2014.
80. Balogh E, Dresler C, Fleury M, et al. Reducing tobacco-related cancer incidence and mortality: summary of an institute of medicine workshop. *Oncologist.* 2014.

81. Toll B, Brandon T, Gritz E, et al. Assessing and Stopping Cancer Patients' Tobacco Use: An American Association for Cancer Research (AACR) Policy Statement. *Clinical Cancer Research.* 2013;19:1941-1948.
82. Gellert C, Schöttker B, Brenner H. Smoking and all-cause mortality in older people: Systematic review and meta-analysis smoking and All-cause mortality in older people. *Archives of Internal Medicine.* 2012;172:837-844.
83. Webb MS, Hendricks PS, Brandon TH. Expectancy priming of smoking cessation messages enhances the placebo effect of tailored interventions. *Health Psychol.* 2007;26(5):598-609.
84. Fiore M, Jaén C, Baker T, et al. *Treating Tobacco Use and Dependence 2008 Update: Clinical Practice Guideline.* Rockville, MD: USDHHS; 2008.
85. Piper M, Smith S, Schlam T, et al. A randomized placebo-controlled clinical trial of 5 smoking cessation pharmacotherapies. *Archives of General Psychiatry.* 2009;66:1253-1262.
86. Smith S, McCarthy D, Japuntich S, et al. Comparative effectiveness of 5 smoking cessation pharmacotherapies in primary care clinics. *Archives of Internal Medicine.* 2009;169:2148-2155.
87. Loh W-Y, Piper M, Schlam T, et al. Should all smokers use combination smoking cessation pharmacotherapy? Using novel analytic methods to detect differential treatment effects over 8 weeks of pharmacotherapy. *Nicotine & Tobacco Research.* 2012;14:131–141.
88. Toll BA, Leary, V., Wu, R., Salovey, P.,Meandzija, B., & O'Malley, S. S. A preliminary investigation of naltrexone augmentation of bupropion to stop smoking with less weight gain. *Addictive Behaviors.* 2008;33:173-179.
89. Sobell L, Sobell M. Alcohol consumption measures. In: Allen J, Wilson V, eds. *Assessing Alcohol Problems: A Guide for Clinicians and Researchers, Second Edition*. Bethesda, MD: NIAAA; 2003:75-99.
90. Toll B, Cooney N, McKee S, O'Malley S. Do daily Interactive Voice Response (IVR) reports of smoking behavior correspond with retrospective reports? *Psychology of Addictive Behaviors.* 2005;19:291-295; PMID: 16187808; PMCID: PMC12527779.
91. Brown R, Burgess E, Sales S, Whiteley J, Evans D, Miller I. Reliability and validity of a smoking timeline followback interview. *Psychology of Addictive Behaviors.* 1998;12:101-112.
92. Toll B, Salovey P, O'Malley S, Mazure C, Latimer A, McKee S. Message framing for smoking cessation: The interaction of risk perceptions and gender. *Nicotine & Tobacco Research.* 2008;10:195-200; PMID: 18188760; PMCID: PMC12527723.
93. Hammond D, McDonald P, Fong G, Borland R. Do smokers know how to quit? Knowledge and perceived effectiveness of cessation assistance as predictors of cessation behaviour. *Addiction.* 2004;99:1042-1048.
94. Norman P, Conner M, Bell R. The theory of planned behavior and smoking cessation. *Health Psychology.* 1999;18:89-94.
95. McKee SA, O'Malley SS, Salovey P, Krishnan-Sarin S, Mazure CM. Perceived risks and benefits of smoking cessation: Gender-specific predictors of motivation and treatment outcome. *Addictive Behaviors.* 2005;30(3):423-435.
96. Kozlowski L, Porter C, Orleans T, Pope M, Heatherton T. Predicting smoking cessation with self-reported measures of nicotine dependence: FTQ, FTND, and HSI. *Drug and Alcohol Dependence.* 1994;34:211-216.
97. Heatherton TF, Kozlowski LT, Frecker RC, Rickert W, Robinson J. Measuring the Heaviness of Smoking: using self-reported time to the first cigarette of the day and number of cigarettes smoked per day. *British Journal of Addiction.* 1989;84(7):791-800.
98. Heatherton T, Kozlowski L, Frecker R, Fagerström K. The Fagerström Test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire. *British Journal of Addiction.* 1991;86:1119-1127.
99. Szklo AS, Coutinho ESF. The influence of smokers' degree of dependence on the effectiveness of message framing for capturing smokers for a Quitline. *Addictive Behaviors.* 2010;35(6):620-624.

100. Moorman M, van den Putte B. The influence of message framing, intention to quit smoking, and nicotine dependence on the persuasiveness of smoking cessation messages. *Addictive Behaviors.* 2008;33(10):1267-1275.
101. Yong H, Borland R, Siahpush M. Quitting-related beliefs, intentions, and motivations of older smokers in four countries: Findings from the international tobacco control policy evaluation survey. *Addictive Behaviors.* 2005;30:777-788.
102. Glaser BG. *Doing grounded theory: issues and discussions.* Mill Valley, CA: Sociology Press; 1998.
103. Borland R, Cooper J, McNeill A, O'Connor R, ., Cummings KM. Trends in beliefs about the harmfulness and use of stop-smoking medications and smokeless tobacco products among cigarettes smokers: Findings from the ITC four-country survey. *Harm Reduct J.* 2011;8:21.
104. Giardina TD, Hyland A, Bauer UE, Cummings KM. Which population-based interventions would motivate smokers to think seriously about stopping smoking? *Am J Health Promot.* 2004;18:405-408.
105. Borland R, Yong HH, O'Connor RJ, Hyland A, Thompson ME. The reliability and predictive validity of the Heaviness of Smoking Index and its two components: findings from the International Tobacco Control Four Country study. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2010;12(Supp 1):S45-S50.
106. Williams GC, Gagne M, Ryan RM, Deci EL. Facilitating autonomous motivation for smoking cessation. *Health Psychology.* 2002;21:40-50.
107. Jolicoeur D, Richter K, Ahluwalia J, Mosier M, Resnicow K. Smoking cessation, smoking reduction, and delayed quitting among smokers given nicotine patches and a self-help pamphlet. *Substance Abuse.* 2003;24:101-106.
108. Fellows J, Bush T, McAfee T, Dickerson J. Cost effectiveness of the Oregon quitline "free patch initiative". *Tob Control.* 2007;16(Suppl 1):i47-i52.
109. Bush T, McAfee T, Deprey M, et al. The impact of a free nicotine patch starter kit on quit rates in a state quit line. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* 2008;10:1511-1516.
110. MacKinnon D, Fritz M, Williams J, Lockwood C. Distribution of the product confidence limits for the indirect effect: program PRODCLIN. *Behavior Research Methods.* 2007;39:384-389.
111. Kraemer H, Wilson G, Fairburn C, Agras W. Mediators and moderators of treatment effects in randomized clinical trials. *Archives of General Psychiatry.* 2002;59:877-883.
112. Dane A, Schneider B. Program integrity in primary and early secondary prevention: Are implementation effects out of control *Clinical Psychology Review.* 1998;18:23-45.
113. Nelson M, Cordray D, Hulleman C, Darrow C, Sommer E. A Procedure for Assessing Intervention Fidelity in Experiments Testing Educational and Behavioral Interventions. *The Journal of Behavioral Health Services & Research.* 2012;39:374-396.
114. Brain K, Carter B, Lifford KJ, Burker O, Deveraj A, Baldwin DR, Duffy S, Field JK, Impact of low-dose CT screening on smoking cessation among high-risk participants in the UK Lung Cancer Screening Trial *Thorax* 2017;**72:**912-918.