Title: Tobacco treatment in the context of lung cancer screening: NRT and text messaging

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SPECIFIC AIMS – RESEARCH STRATEGY

Screening for lung cancer at earlier, more treatable stages has the potential to reduce mortality from the U.S.'s most deadly cancer.[83] Annual screening with low-dose computed tomography (LDCT) is now recommended for high risk individuals based on age and smoking history.[52] Comprehensive programs include a shared decision making visit, counseling on smoking cessation, and a LDCT for patients who wish to receive the scan.[20] Lung cancer screening (LCS) has the potential to engage high risk patients who smoke in tobacco treatment, particularly those who may be geographically difficult to reach in traditional clinic-based counseling. Indeed, due to the geographical location of many medical centers, the LCS visit may be the only time rurally-located patients are able to come to a medical visit, unless they require medical follow-up based on the results of their LDCT. Tobacco treatment interventions should be packaged in a novel way to: a) increase the reach of a tobacco treatment intervention after LCS, b) improve cessation rates following LCS, and c) establish a treatment protocol that is translational and easy to implement in the context of LCS. The clinical ramifications of smoking cessation following a LDCT could be profound. Indeed, data from my Co-Mentor Dr. Silvestri's group from the NLST showed that the combination of smoking abstinence and LDCT screening resulted in a 38% risk reduction for lung cancer mortality.[84]

The independent research herein will inform the design of more effective smoking cessation treatments for LCS patients as it will: 1) utilize a mailed NRT model to distribute medication and improve the likelihood of a successful quit attempt, and 2) evaluate gain-framed and medication reminder text messaging as a way to increase adherence with the intervention and overall cessation rates.

The specific aims of the Research Strategy are:

Aim 1: Conduct a 2-arm pilot randomized clinical trial with patients referred for LCS who smoke (N = 80) to evaluate 7-day point prevalence abstinence rates and determine effect size estimates among participants who receive a standard intervention (single, brief counseling session at time of LCS) versus an enhanced medication and text messaging intervention (MTI; standard intervention + 8 weeks NRT + gain-framed messages with medication use reminders).
Hypothesis 1.1: Compared to the standard intervention, NRT and gain-framed text messaging will produce higher rates of smoking cessation at the end of Week 8.

Secondary Aim 2: To develop effect size estimates for rates of smoking cessation at the 3-month follow-up.
Hypothesis 2.1: Compared to the standard intervention, NRT and text messaging will produce higher rates of smoking cessation at the 3-month follow-up.

Exploratory Aim 3: To examine mediators and moderators of smoking cessation outcomes (i.e., nicotine dependence, medication adherence, positive lung finding from the scan [e.g., nodule is present]).
Hypothesis 3.1: Patients with greater nicotine dependence will have lower rates of cessation compared to those who have less nicotine dependence. Those who are more adherent with medication regimens in general (as assessed at baseline), as well as those who are adherent with the NRT regimen throughout the intervention, will have higher rates of cessation compared to those who are less adherent. Patients with a positive lung nodule finding after LDCT will be more likely to quit smoking than those who have a normal LDCT scan.

Exploratory Aim 4: To conduct exploratory analyses of cost-effectiveness of the intervention.
Hypothesis 4.1: I expect that the treatment intervention will be more cost-effective than standard counseling alone.

Summary: In the proposed study, I will integrate two complementary approaches: NRT and a gain-framed text messaging intervention specifically designed for LCS patients. The model has the potential to be highly translatable to other LCS settings. I am proposing easily translational behavioral (text messaging) and pharmacotherapy (NRT) interventions that would not need a specialized service. This study will also serve as a complement to my career development plan in furthering my training in cancer prevention and control, and health services research. Further, this pilot randomized study has the strong potential to provide a critical foundation for an R01 grant application, which is essential to launching my career as an independent researcher.

RESEARCH STRATEGY

A. Significance:

A1. Smoking and Lung Cancer Screening: Smoking causes 30% of all cancer deaths and nearly 90% of all lung cancer deaths.[21] Lung cancer screening (LCS) with low-dose CT scans (LDCT) identifies lung cancer at earlier, more treatable stages 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 year quit-time, and 55-74 years of age) conferred a 20% reduction in mortality for those patients who received 3 annual low dose CT (LDCT) scans.[22] These findings led the U.S. Preventive Services Task Force (USPSTF) to recommend annual screening with LDCT in persons at high risk for lung cancer based on age and smoking history,[23] with CMS and many private insurers now covering screening for this population. Continued smoking, particularly for high-risk groups (like LCS patients), leads to worse clinical outcomes and survival. 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.[24,25] In a recent study, CT scanning prompted smoking cessation shortly following the scan, especially when the results were abnormal, but this outcome was not sustained over time.[26] Likewise, referral to a physician for an abnormal finding may increase initial quit attempts but this is not always sustained.[27,28]

One important tobacco treatment-related issue to consider in the context of LCS is patient access. LCS has the potential to capture and engage smokers at high risk for lung cancer, particularly those who may be geographically difficult to reach. Indeed, of all patients between the ages of 55 and 74, who are current or former smokers, who visited MUSC for LCS between 1/1/2015 and 3/10/2016, the average distance traveled to MUSC was 24.62 miles (range: 0.8 - 81.9 miles). Effective treatment for smoking cessation at the point of LCS must be offered in a way that reduces travel burden, and more broadly, increases access to care.

Unfortunately, existing cessation treatments have substantial barriers to access. The PHS Clinical Practice Guidelines indicate that both behavioral (e.g., counseling) and pharmacological (e.g., NRT) interventions are effective treatments for tobacco use.[29] However, interviews conducted on the use of tobacco dependence treatments by the National Health Interview Survey show that only 22.4% of the interviewed smokers who tried to quit in the last year had used any type of cessation aids (21.7% pharmacotherapy aids, and 1.3% behavioral counseling).[30] A review on the barriers to using FDA-approved smoking cessation interventions highlights the vast underuse of approved therapies during a quit attempt.[31] Smokers' misperceptions about the health risks and cost, and incorrect use of medication appear to be related to their underuse, and most providers do not offer tobacco-specific behavioral counseling. Engaging high risk individuals with a tobacco treatment provider at the point of LCS and increasing the access to care after LCS is critical to delivering effective interventions. Therefore, I am proposing to enhance existing tobacco treatment interventions in a novel way to: a) increase the reach of a tobacco treatment intervention after LCS, b) improve cessation rates following LCS, and c) establish a treatment protocol that is translational and easy to implement in the context of LCS in the U.S.

A2. Nicotine Replacement Therapy (NRT). NRT is an evidence-based pharmacological intervention for smoking that is easy for tobacco treatment providers to disseminate at the point of care because no prescription is required. Providing NRT is particularly useful because it can be delivered at LCS, does not require a prescription, and can increase the number of quit attempts and quitting.[32,33] Uptake of cessation treatment is higher when accessibility is increased,[34] as would be the case when NRT is proactively provided at the point of LCS. Dr. Toll's recently funded NCI R01 (Co-Is: Rojewski, Carpenter, Silvestri) will evaluate NRT sampling (a 2-week supply of dual NRT and suggestion to "try" the two medications) in a LCS population. I will be able to leverage the resources from that grant to assist with the conduct of this proposed study. The present study will differ from Dr. Toll's R01 in that I will evaluate an 8-week dual NRT regimen. The first 2-week supply will be delivered at the point of screening in the treatment arm, and I will mail the 3 remaining 2-week supplies of NRT to the participant. This will further increase accessibility, reduce possible waste from non-use, and also reduce participant burden from picking up the medication (similar to a state smokers' quitline model). I will also assess medication adherence through the use of text messages (described below in A3) throughout the 8-week treatment period, and send novel text messaging reminders to use the NRT to enhance adherence.

A3. Text Messaging: Texting is a relatively low-cost way to reach smokers frequently and in the context of their day-to-day lives. Recent evidence shows that smoking cessation behavioral support programs provided by text message are effective.[35] Evidence from the texting literature also suggests that the framing of the text message may have an influence on behavior. Prospect theory[36] suggests that decision-making under conditions of risk is influenced by the way messages are delivered, or framed. The framing implications of

prospect theory suggest that decision makers cognitively organize information relevant to decisions in terms of potential gains (i.e., benefits) or potential losses (i.e., costs). Several previous studies have shown that gain-framed messages are more effective than loss-framed messages for increasing intentions to quit, quit attempts, and smoking cessation in general populations of smokers.[15,37-41] I plan to use text messaging, a novel approach in the context of lung screening, to deliver gain-framed texts regarding smoking cessation to patients after their scan. Further, texting will allow me to deliver other types of messaging, such as medication reminders and medication adherence assessments. The use of messaging and framing to increase medication adherence is also a novel difference from the currently funded LCS R01 and past clinical trials on message framing. Integrating medication reminders with a text intervention may promote medication adherence, which, coupled with the effects of gain-framed messaging, could further promote abstinence. The text messages will be delivered through a system already in place at Hollings Cancer Center (HCC). Thus, this text protocol could be easily implemented as standard care at the HCC LCS Program, and this type of dissemination and implementation work could be the topic of future research endeavors. Further, the potential exists for the programmable texts to be easily disseminated to other sites.

A4. Summary of Primary and Secondary Aims. In the proposed study, I will investigate 2 complementary treatments: NRT and gain-framed text messaging designed for LCS patients. The primary aim is to determine an effect size estimate for the intervention at the end of treatment. I will also examine abstinence rates among the two treatment arms. I hypothesize that an NRT intervention plus gain-framed text messaging will produce higher rates of smoking cessation at the end of treatment compared to standard care for LCS patients. As a secondary aim, I plan to develop effect size estimates for rates of smoking cessation at the 3-month follow-up.

A5. Mediators, Moderators, and Exploratory Analysis. This study will also evaluate important mediators and moderators of response to the intervention. Several message framing studies from both our group and others have found that nicotine dependence can moderate treatment efficacy.[42-45] Thus, I will evaluate nicotine dependence as a moderator of treatment outcomes. Further, research has evaluated the effect of LCS findings (presence/absence of nodule) on smoking behavior,[26-28] but no studies have evaluated how LCS findings moderate a smoking cessation intervention. Thus, I will carefully evaluate these factors and determine if LCS findings moderate outcomes. In addition, because consistent medication use may increase NRT efficacy,[46,47] I will also evaluate medication adherence as a moderator and mediator of treatment outcomes. Finally, on an exploratory basis, I will evaluate the cost-effectiveness of the intervention compared to standard care.

B. Innovation:

1. This is the ***first*** study to test a gain-framed texting intervention in LCS. Although texting and gain-framed messaging have both been independently shown to be effective for smoking cessation, whether gain-framed text messages will improve quit rates for LCS patients is an empirical question. Delivery of gain-framed texts has the potential to enhance quit rates above those reported in prior studies because I plan to: 1) make the messages specific to a LCS population and 2) include reminders about medication use to increase the likelihood of medication adherence, and thus increase participant engagement with the intervention.
2. The model has the potential to be highly translatable to other LCS settings. I am proposing an easily translational behavioral (text messaging) and pharmacotherapy (NRT) intervention. A subsequent R01-funded full scale clinical trial could evaluate the intervention further for potential dissemination.
3. An assessment of mediators and moderators is also an innovative feature of this study as nicotine dependence, medication adherence, and lung screening findings are understudied in LCS patients.

C. Approach:

C1a. Preliminary Data on Gain-Framed Messaging

Quit4Hlth: R21CA181471 (PI: B. Toll, Co-I: Rojewski). The goal of this study, funded in October 2015, is to address tobacco control by increasing smoking cessation rates through the use of framed text messages among smokers who enroll in treatment with the NY Quitline. We are comparing quit rates for smokers who receive 30 weeks of tailored, gain-framed text messages with those who receive 30 weeks of tailored, unframed text messages, both combined with standard quitline treatment, to develop an effect size estimate for 7-day point prevalence abstinence smoking cessation at 30 weeks. I was involved in the development and testing of the text message bank for this study, and will use the bank to build off of and tailor to LCS patients for the text messaging in the present proposal.

C1b. Preliminary Data on Lung Cancer Screening and Smoking

Nicotine Dependence, Smoking Variables, and Clinical Outcomes in LCS. I recently began a collaborative endeavor with Drs. Silvestri, Toll, and 3 additional colleagues, Drs. Tanner, Ravenel, and Gebregziabher to

conduct secondary data analyses on the NLST data from the American College of Radiology Imaging Network (ACRIN) subset. In the ACRIN subset of the NLST, 14,125 patients were screened for lung cancer and 7,057 were current smokers at baseline. The average Fagerström Test for Nicotine Dependence (FTND)[48,49] score was 6.1, and the average Heaviness of Smoking Index (HSI)[50] score was 4.2. LCS patients who had higher FTND scores had higher rates of cancer (2.3% for very low dependence smokers vs. 6.1% for very high dependence, $p < 0.01$), higher rates of mortality (5.9% for very low dependence smokers vs. 11.0% for very high dependence, $p < 0.01$), and higher rates of lung cancer-specific mortality (1.0% for very low dependence smokers vs. 2.9% for very high dependence, $p < 0.01$). Similar patterns emerged for the HSI. Further, those who were smoking at the time of LCS and had high dependence scores were less likely to quit smoking after LCS (very high dependence vs very low dependence; Odds Ratio= 0.59, 95%Confidence Interval = 0.48-0.73). These data show that people presenting for lung cancer screening with high levels of nicotine dependence are more likely to die from lung cancer and all other causes than those less dependent. Further, those with high nicotine dependence are less likely to quit smoking after lung screening. I was invited to the Lung Cancer Specialized Program of Research Excellence (SPORE) Workshop to present the initial data in June 2016. This shows strong evidence of: 1) my appreciation of LCS as an opportunity to deliver a smoking cessation intervention, 2) my understanding of smoking among the LCS population, 3) my ability to collaborate with senior faculty on tobacco control research with LCS patients, 4) my motivation to contribute to the literature on tobacco use among LCS patients, and 5) the interest of the research and medical community in smoking cessation among LCS patients. The manuscript detailing these data is currently in preparation for submission.

C2. Design and Methods:

General overview: A 2-arm randomized controlled pilot study is proposed to evaluate a treatment package to increase rates of smoking cessation for LCS patients (N=80). Eligible participants will be randomized to receive either: 1) standard care (SC) or 2) Medication and Texting Intervention (MTI) after LCS. A description of the arms is presented in Table 1. The current standard of care in the HCC LCS program is standard counseling. One potential wekaness of this design is that we will not know if differences between MTI and SC are due to specific components of the MTI package (i.e., NRT or texting), or a combination. A fractional (Multiple Optimization Strategy [MOST]) design[51] may be preferred to assess the components of the treatment package, but such an approach seems unwise for this K07. I hope to disintangle any effects of the combined intervention in future grant endeavors.

Table 1. Description of Treatment Arms

Arm	Intervention
Standard care (SC)	Standard counseling
Medication and Texting Intervention (MTI)	Standard counseling + 8 weeks of NRT + gain-framed text messages with medication reminders

Text Message Development and Testing: I will create a library of gain-framed and medication reminder texts by adapting messages from a selection of the 300 texts used in the NCI R21 that Dr. Toll and I are currently conducting. I created the text messaging bank alongside Dr. Toll, and was closely involved in the iterative process that was undertaken to develop and test the messages. The messages for the present proposal will include content regarding health, self-esteem, finances, physical appeal, social approval, quitting smoking in the context of LCS, and reminders to use the medication. Any new messages developed will be sent to experts in the field for their opinion on the framing of the message. Edits to the text message bank to ensure appropriate framing will be made based on expert reviews. A sample of 15 smokers attending LCS, and meeting the criteria for LCS, will be recruited to provide feedback on the text messaging program. I do not plan to target specific patient characteristic goals for these 15 participants. By enrolling current LCS patients, we can assume a representative sample with respect to sex, nicotine dependence, etc. Further, I would not expect any of these variables to have an impact on the participant's opinion regarding the framing of the messages. A survey will be distributed to each participant, with several questions regarding their current text message use, their preferences regarding texting, and the degree to which they may like certain types or frequency of messages. They will be compensated $20. This survey feedback model was employed in the R21 study we are currently conducting, and was successful in gathering feedback regarding the messages.

Participants and Randomization

Participants: Our target sample will be 80 patients who currently smoke and are attending the LCS program at MUSC for the intervention, and an additional 15 patients for the message testing portion of the developmental phase. The following key eligibility criteria will ensure that we obtain our study sample of LCS patients. Inclusion criteria will follow the USPSTF screening guidelines[52]: 1) 50 years or older (no reason for upper limit given supportive evidence for cessation among elderly),[53] 2) 20 pack year history of smoking, 3) current

smoker (defined as self-report any smoking in the past 7 days), 4) willing to be randomized, 5) English speaking; 6) access to device(s) that allows for text messaging and downloading apps; Exclusion: 1) unstable psychiatric/medical conditions such as suicidal ideation, acute psychosis, severe alcohol dependence, substance abuse, or dementia, 2) in the immediate (within 2 weeks) post myocardial infarction period, 3) serious arrhythmias, 4) unstable angina pectoris,5) hemodynamically or electrically unstable, or 6) currently taking part in any other tobacco treatment program or using cessation medication (i.e., taking NRT or other cessation medications, enrolled in the Quitline, in another drug study). Exclusion criteria will be assessed through participant interview and/or medical record review.

Randomization. Given the goal of establishing an effect size, and the relatively small N in each group, we will use block randomization in an effort to ensure equal numbers in each treatment arm.[54] We considered using a stratified randomization procedure, but the aim of establishing effect sizes does not necessitate a randomization procedure that controls for covariates. If we observe imbalance on confounders by treatment group, we will adjust for these confounders in our analysis using regression modeling.

Intervention Procedures: Participants will be identified through the established lung cancer screening programs at MUSC. Interested LCS patients who meet the intake criteria will speak with a research assistant. Patients who want to enroll in the study will be screened, consented, and randomized. Additionally, other recruitment methods might be used such as postcards, flyers, Craigslist ads, radio ads, billboard ads, and newspaper ads to assist with recruitment to the study as well as for the LCS program in general. A postcard may be sent informing individuals that they may be eligible to participate in a research study. Study personnel may obtain information to send postcards through chart reviews and/or marketing strategies. The research staff will call these patients prior to their appointment to gauge interest in the study. If the patient would like more information, a research staff member will either meet the patient on their proposed scan date, at another agreed upon time and place, or speak by phone. The flyers will be placed around the community in areas that our potential participant pool will see (i.e. community centers, senior centers, patient rooms in family medicine at MUSC, etc.). Study eligibility will be determined in concert with a clinic staff member and myself (with guidance from Dr. Toll as necessary).

Informed consent Process

For MUSC Charleston participants: Informed consent and HIPAA authorization 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 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) Redcap electronic consent - Signatures on the consent form may be obtained electronically via REDCap. Patients will be sent the redcap link to the consent form. The research staff will review the consent by phone and answer any questions before the patient signs the consent form via redcap. 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 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 call the patient to discuss the consent form and answer any questions after the consent is mailed. The person obtaining consent will sign and date their copy and then ask the participant to sign and date their copy. Once the MUSC researcher receives the participant's signed copy, the two copies will be combined together to make a fully executed consent document.

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.

For MUSC Lancaster, MUSC Chester, MUSC Florence, and MUSC Columbia participants:
If an eligible patient from MUSC Lancaster, MUSC Chester, MUSC Florence, or MUSC 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 for MUSC Charleston sites, apart from 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 a virtual intake appointment with a research staff member. All participants recruited through these sites will complete the consent and baseline session using either 1) REDCap electronic consent (e-consent) combined with a phone discussion, 2) by mail combined with a phone discussion, or 3) a combination of these options.

All participants will have a smoking cessation counseling session with the lung screening nurse practitioner as part of standard clinical care. Of note, the treatment provided to study participants by the smoking cessation counselor in this study is a reimbursable service. This is important for 2 reasons: 1) NCI grant funds are not needed to support these high-cost services provided in this project, and 2) this increases the future translational possibilities of the intervention, as these methods will be sustainable at other cancer centers because insurance reimbursement will pay for these services. The counseling provided by the nurse practitioner will be based on practical counseling, which is a cognitive-behavioral, evidence-based, smoking cessation treatment modality.[55] The counseling session will last approximately 30 minutes, and all participants will be encouraged to set a quit date.

NRT. In addition to the standard counseling described above, participants in the MTI arm will receive dual NRT (nicotine patch plus lozenge). An initial 2-week supply of 21 mg patches and 4 mg lozenges will be provided at the time of counseling or will be mailed to the participant within a week of randomization, and 3 additional 2-week supplies will be mailed out over the course of the subsequent 8 weeks. This mail-out model will allow us to assess participant use of the medications because participants will be contacted and asked how much NRT they used and if they would like to receive the next 2-week dose. Detailed information on each product, including instructions for use, will be provided in the take-home packet or emailed to the participant. We will inform patients about both single NRT use, as well as combined use, and participants will be given the opportunity to use the medications individually or together (participant choice, including none at all). Both patch and lozenge will be provided for four reasons. First, a number of studies demonstrate their efficacy when used singularly.[56] Second, they are both over the counter, increasing their utility within LCS 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, the majority of studies [57-60] have shown that combined use of patch + lozenge is superior over placebo and single NRT products. Finally, the National Comprehensive Cancer Network Smoking Cessation Guidelines list combination NRT as first line pharmacotherapy. Those in the SC condition will receive standard counseling but no medications, and we will contact them every 2 weeks to inquire about use of any pharmacotherapies that they purchased on their own. At the time of patient contact regarding medications, research assistants will also assess point prevalence abstinence.

These two week check-ins will occur either by phone or through MUSC REDCap's automated survey feature. Surveys can be automatically sent to patients for each two-week follow-up and patients can fill out the questions to indicate whether they would like more medications to be mailed to them. After the completion of the two-week check-ins, patients will be sent an Amazon gift code as a form of compensation. The payment will be as follows: $10 for each completed two-week check-in and $25 at the completion of the 3-month visit. If a participant completes at least 3 of the 4 check-ins, a $30 bonus amazon gift code will be provided.

Text Messaging: Based on previous research[35] and our current R21, participants in the MTI condition will receive 3 messages per day for the 8 week treatment period following LCS. The messages will be gain-framed to highlight the improved health benefits of quitting and they will also give reminders for participants to use their medication. A subset of texts will also be interactive to assess their craving or medication use, and some will specifically refer to their LCS nodule outcome and risk. To be clear, we are not framing any information to encourage LCS – the gain-framed intervention will focus on smoking cessation in the context of LCS. For example, the messages would highlight that quitting smoking will significantly reduce their risk for lung cancer in conjunction with screening.[61] A gain-framed text message in this regard might say: "Even if your screening does not show any nodules, quitting smoking is the single best thing you can do to reduce your risk of lung cancer." Some texts will involve interactivity between us and the participant. For example, participants may be asked to reply to a text such as "Did you use your NRT patch today? Reply: YES or NO". The next text sent to the participant will be tailored to their medication use. For instance, if a participant says "NO" then the reply text may read "NRT will help with managing cravings. Apply your patch to clean, dry skin." If the participant says "YES", the reply text may read "We are glad you are using the NRT to manage your cravings! You are on your way to a healthier new you!" Interactive texting will also allow us to also assess smoking status at the follow-up time points. For example, consistent with the outcome definition (defined below) the text may read: "Did you have a cigarette, even a puff in the past 7 days?" and the participant will be able to text back with a reply of "YES" or "NO." We will assess the interactive texting data to determine if they corroborate (or enhance) smoking outcome data collected by written or verbal assessment at each of the 2-week "check in" timepoints, the end of treatment, and the 3-month follow-up. The comparison of text message data to written data in this trial will allow us to ascertain if data collection by text is viable for use in a larger trial. The texting protocol we design will be programmed and delivered via the MUSC REDCap database. MUSC's REDCap database allows us to send SMS text messages with an assigned phone number with the protection of MUSC's firewall. The REDCap database has the ability to auto reply based upon the message received and to broadcast messages to various lists.

Follow-up: Participants will complete either online or paper assessments (no return clinic visit) at the end of treatment and 3 month follow-up session. Point prevalence abstinence will be established. At the 3-month follow-up all of the participants will also complete a biochemical verification of abstinence (see Outcome Definition below). Participants will be paid $25 in the form of Amazon gift card codes for completion of the 3 month follow-up interview.

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

Demographic, Smoking History, and Current Medications Questionnaire: This questionnaire will obtain: 1) basic demographic information and 2) basic smoking status and history.[12,15,62]

Tobacco Use Calendar (Timeline Followback): This standardized, validated, and reliable experimenter-administered rating scale[63-65] will be used to obtain quantity and frequency estimates of cigarette consumption for a 30-day period prior to treatment and to retrospectively record daily use at each participant contact point.

*Fagerström Test for Nicotine Dependence (FTND) and Heaviness of Smoking Index (HSI): The FTND is a commonly used scale for the measurement of severity of dependence on nicotine.[48] The HSI assesses 2 items from the FTND regarding amount smoked and time-to-first-cigarette.[49] The HSI has been shown to predict both behavioral and biochemical indices of smoking.[48-50] In line with findings from our previous research[42,43] and from other groups,[66,67] we plan to test both the FTND and HSI as moderators of treatment.

*Medication Adherence Questionnaire (MAQ): The MAQ is a self-report instrument composed of four items that assess participants' history of medication adherence,[68,69] *which may moderate treatment outcomes.*[70] Using the MAQ score, medication adherence will be assessed as a baseline moderator of treatment outcome.

*Use of Pharmacotherapies: We will determine the amount and frequency of NRT used (per product), and will also determine use of products we provide vs. purchase of additional products. *For all participants*, at each refill or contact point during the 8-week time frame, we will ask how many total patches and lozenges were used since the last contact, and how many were used each day. I will also incorporate a text-message based medication use assessment, as previously described. This *novel approach* will allow us to collect a daily medication diary from each participant, instead of relying on retrospective report. After calculating a percentage of medications taken, *medication adherence will be assessed as a mediator of treatment outcomes.*[70,71]

Attitudes Towards NRT: Attitudes towards NRT may differ depending on the amount of NRT they elect to receive, the types of NRT selected, and the patient experience with the medication. We will assess 1) positive, and 2) negative attitudes towards NRT, as well as 3) general knowledge of NRT.[32,72-76]

Motivation and Confidence to Quit: We will assess motivation and confidence to quit smoking using our modification of the Contemplation Ladder[77,78] which assesses readiness to quit in the next month.

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

Adverse Events: We will assess adverse events at each NRT refill time point for the MTI group. For the SC group, we will ask about adverse events at each contact point after LCS. We will grade and report the severity of adverse events as described in Protection of Human Subjects. Participants who have significant side effects from NRT use will be encouraged to discontinue NRT use immediately.

Texting Satisfaction Survey: We will assess participant satisfaction with the texting intervention, including frequency, timing, and content of the text messages.

Outcome Definition: For our primary outcome, consistent with Dr. Toll's past quitline clinical trials,[13,15,62] abstinence will be defined as self-reported 7-day point prevalence abstinence. We will ask participants during follow-up, "Have you smoked a cigarette, even a puff, in the past 7 days?" An answer of "no" to this item will be considered abstinence. We will also ask about number of days since the participant quit, to retrospectively compute longer-term quit rates, including 30-day point prevalence abstinence. At the end of treatment and the 3-month follow-up, we will also attempt to obtain smoking status via text. The text to participants will be the same point prevalence question described above. After comparing these data to the interview-based data, we will be able to determine if texting is a viable method for collecting smoking cessation data in a larger trial. I will also attempt to obtain biochemical verification at baseline and the 3-month follow-up using breath carbon monoxide (CO). Biochemical verification is often used in smoking cessation studies to objectively confirm self-reported smoking status.[79] If the baseline visit occurs in person, we will obtain breath CO at the visit. If the baseline visit occurs remotely, then a breath CO monitor will be mailed to the participant. At the 3-month visit, we will mail a breath CO monitor to participants who did not receive one at baseline (i.e., those who completed the baseline visit in person). Breath CO monitors will be mailed with instructions for use. At a prearranged time, participants will be sent a doxy.me link. Doxy.me is a secure, virtual telemedicine "room." 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. Studies examining the validity of smokers' self-reports have noted that differences between self-report and biochemical validation have been relatively small in absolute terms, so we will use self-report for primary abstinence outcomes and CO for secondary analyses of outcomes.[81,82]

C3. Statistical Considerations

See letter of support from consultant, Dr. Garrett-Mayer, Director of the HCC Biostatistics Shared Resource. Sample size justification: Eighty participants (40 per group) will be enrolled. A sample size of 40 will allow us to establish estimates of abstinence with 95% confidence intervals (CI) for each arm, and to assess the precision in our estimates. The goal is to establish reasonably precise effect sizes to power a future study so we do not expect to achieve statistical significance in group comparisons. 95% CI and corresponding half widths for exemplar abstinence rates are provided in Table 2. With 40 patients per arm and an observed abstinence rate of 0.30, we can be 95% confident that the true abstinence rate is between 0.17 and 0.47 for that intervention.

Table 2. Example Effect Size Estimates

Observed Rate of Abstinence	95% CI	Half Width
0.50	(0.34,0.66)	0.16
0.30	(0.17,0.47)	0.15
0.10	(0.03,0.24)	0.10

Statistical Analysis: Aims 1 and 2 will be achieved by estimating abstinence rates with exact 95% CIs. Differences in rates and the 95% CIs for the differences will also be estimated. Baseline clinical and demographic variables will be assessed with summary statistics and reported by group, and compared to evaluate balance across groups. While the main aim of this pilot trial is to establish effect size estimates, we will also conduct a preliminary examination of between group differences in abstinence using logistic regression. With respect to exploratory analyses, logistic regression will also be implemented to evaluate effects of mediators and moderators of treatment on abstinence, and linear regression will be used to compare costs in the two arms. Given the pilot nature of this study, emphasis is on estimating effect sizes and variances and not statistical significance of associations. A sample size of 40 patients per group should provide sufficient preliminary data to guide me in my future research in this area.

C4. Recruitment, Feasibility, and Timeline

Patients eligible for this study will come from the LCS programs at HCC Downtown, Mount Pleasant, North Charleston, West Ashley, Lancaster, Chester, Florence, and Columbia. Dr. Toll is the Co-Director of program, and I will have full access to all LCS patients who smoke. To date, the program has screened more than 300 patients and is expanding outreach efforts. Between 11/1/16 and 2/1/17, 21 current smokers were screened (7 per month). Not all patients may be interested in participating in a research study, so I conservatively estimate that I could recruit 2 current smokers per month. The LCS program is in the midst of launching a $30,000 ad campaign, and the nurse practitioner dedicated to the program is visiting primary care practices every week. Thus, due to these ongoing outreach activities, the program projects screening at least 20 current smokers per month over the next 6 months, and I do not anticipate a problem with recruitment. The study timeline is presented in Table 3.

Table 3. Study Timeline

Months 1–12:	IRB approval, create texting materials
Months 13-17:	Test the text protocol; obtain medication, train staff
Months 18-49:	Recruit *80* participants and follow for 3 months
Months 50–60:	Follow-up, data analyses, prepare presentations and publications.

D. Summary and Future Directions

The proposed independent research extends the rigorous research methods found in recent studies of NRT and gain-framed text messaging interventions in the general population to the important, yet understudied clinical population of LCS patients. The proposed research has numerous strengths including: a) a timely research question, namely how to optimally enhance smoking cessation in current smokers who are receiving LCS; b) gain-framed smoking cessation text messaging specifically developed for LCS patients; c) a robust pharmacotherapy strategy ; d) a rigorous study design and analyses to establish effect sizes for future research in this area, and e) potential to easily translate the findings to the growing number of LCS programs across the country. Research on tobacco treatment interventions for LCS patients could reduce the future incidence of cancer and mortality for this high-risk patient population. This is an area of research where creative and rigorous research is desperately needed to capitalize on the teachable moment of LCS and extend effective tobacco treatments. Further, this project will allow me to extend my training goals of health services research to an avenue of research. My career development plan and independent research proposed herein will ensure that I am fully capable of achieving my long-term career goal of contributing to the research on tobacco treatment in an oncology setting, and LCS more specifically.

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 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 self report any smoking in the past 7 days), 4) willing to be randomized, 5) English speaking; 6) access to device(s) that allows for text messaging and downloading apps; Exclusion: 1) unstable psychiatric/medical conditions such as suicidal ideation, acute psychosis, severe alcohol dependence, or dementia, 2) in the immediate (within 2 weeks) post myocardial infarction period, 3) serious arrhythmias, 4) unstable angina pectoris, or 5) hemodynamically or electrically unstable, or 6) currently taking part in any other tobacco treatment program or using cessation medication (i.e., taking NRT or other cessation medications, enrolled in the Quitline, in another drug study). We intend to enroll 80 participants.

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, at the end of the 8-week intervention period, and at the 3-month follow-up. All responses will be collected on a secure, password-protected, electronic Web-based form, or on paper forms if the participant does not have access to the internet. The data will be sent or entered into a secure database in REDCap. Only research staff have access to the database.

Potential Risks. The risks associated with 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. Participants in the treatment arm 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 PROTECTION AGAINST RISKS

Recruitment and Informed Consent
Participants will be recruited through the lung cancer screening programs at Medical University of South Carolina/Hollings Cancer Center Downtown, Mount Pleasant, North Charleston, Lancaster, Chester, Florence, and Columbia. 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 in a locked file cabinet where it can only accessed by senior level project staff. Any information published as a result of the study will be such that it will not permit identification of any participant. Right to privacy for participation in this research will be protected through coding of data and proper storage of research records. 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. 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 by 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 text 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, and the MUSC Institutional Review Board (IRB).

Data Monitoring. For this review process, I will compile 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 and discuss the report with my full mentoring committee. Based on this report, each mentor will make 1 of 2 recommendations: 1) maintain the current study protocol; 2) schedule formal meeting immediately with the MUSC IRB. If any committee member recommends a meeting, this will be scheduled within 1 week. The committee will vote on whether the current study should: 1) continue recruitment unchanged; 2) continue with a protocol amendment; 3) stop the study pending further investigation. If after this meeting any committee member votes to request a protocol modification, the MUSC IRB will be immediately informed by Dr. Rojewski.

Safety Monitoring. This protocol presents minimal risks to participants. The study involves receiving gain-framed text messages and NRT, and to complete follow-up interviews. The only risks 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. In addition, participants may experience side effects from NRT (as previously described). 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 Dr. Rojewski with a detailed description of the event. Dr. Rojewski will grade the event in conjunction with Dr. Toll within 24 hours. The following additional individuals will be informed immediately of serious adverse events: (a) the mentoring committee; (b) the National Cancer Institute (NCI); and (c) the MUSC IRB. All of these individuals and committees will receive a copy of a SAE Form within 48 hours, at which point a decision will be made whether to convene a meeting.

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 IRB and the National Cancer Institute, and a written report will be submitted within 48 hours. The PI and mentoring committee 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 IRB and the NCI as part of an annual progress report (NCI) and annual re-approval (MUSC IRB).

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