Smoking Cessation Versus Long-Term Nicotine Replacement among High-Risk Smokers

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A. ABSTRACT

Background: Smokers who continue to smoke despite being diagnosed with chronic obstructive pulmonary disease (COPD) may have particular difficulty quitting. Long-term nicotine replacement therapy (LT-NRT) might provide an alternative strategy for patients who are not ready or are unable to quit immediately, providing either a strategy for risk reduction or a pathway for later cessation.
Objectives: The purpose of this study was to determine whether LT-NRT compared with standard smoking cessation (SSC) would reduce overall exposure to cigarette smoke, reduce harm related to smoking, and ultimately lead to greater quit rates.
Methods: Smokers with clinically diagnosed COPD (n = 398) were randomly assigned to receive either (1) SSC consisting of cessation counseling at baseline, with 4 follow-up counseling calls and 10 weeks of combination NRT provided to support those who set a quit date; or (2) LT-NRT with up to 12 months of combination NRT and 4 counseling calls and 3 in- person sessions focused on titrating their NRT dosage to reduce cigarette consumption prior to setting a quit date and to support quitting and abstinence maintenance 6 months post quitting. Follow-up at 3, 6, and 12 months assessed smoking status, exposure to carbon monoxide (CO), a smoking-related carcinogen (4-[methylnitrosamino]-1-[3-pyridyl]-1- butanol [NNAL]), functional status, and smoking-related hospitalizations. The primary outcome was 7-day, CO-verified (< 10 ppm), point prevalence abstinence at 12 months. Input into the design and conduct of the study was provided by patients and community stakeholders.
Results: Groups were similar at baseline; participants were 60% female and, on average, 56 (SD = 9.28) years old with a COPD history of 6.9 (SD = 7.52) years, who smoked an average of 23.1 (SD = 12.26) cigarettes per day (CPD). At 12 months, CO-verified, 7-day point prevalence abstinence was 11.7% and 12.2% in the SSC and LT-NRT groups, respectively (P = .88). The continuing smokers in the SSC and LT-NRT arms, respectively, reduced their self-reported cigarette consumption by 12.4 and 14.5 CPD, exhaled CO by 5.5 and 7.8 ppm, and mean urinary NNAL by 21.7% and 23.0%. Over the course of the 12-month follow-up, these changes were significantly different from baseline but did not differ significantly between treatment arms. Respiratory symptoms, functional status, and hospitalizations and emergency department visits were also not significantly different between the 2 groups over the 12-month follow-up period. LT-NRT recipients had more gastrointestinal and skin-related side effects of treatment; major adverse cardiac events were similar in the 2 groups.
Conclusions: Smokers with COPD treated with either SSC or LT-NRT had similar reductions in tobacco exposure and similar, modest rates of cessation. Because SSC has a shorter duration of treatment and fewer side effects, it appears to be the preferred treatment for smokers ready to quit. LT-NRT leads to

comparable results and would appear to be an option for
smokers who are not immediately willing to make a quit attempt.

Limitations and subpopulation considerations: Most participants in the SSC arm (96%) were willing to set a quit date; findings might be different in actual clinical practice, which might include more smokers not interested in quitting in the immediate future. Low rates of cessation overall limited the potential for analyses of differential effects in subpopulations.

B. BACKGROUND

Cigarette smoking is the leading cause of preventable disease and death in the United States, accounting for more than 480 000 deaths every year.[1] Smoking is also the primary cause of chronic obstructive pulmonary disease (COPD) which, in turn, can profoundly affect quality of life, resulting in difficulty breathing, chronic cough, poor exercise tolerance, disability, hospitalizations, and death.[2,3] Approximately one-third of deaths associated with smoking can be attributed to COPD.[4]

Quitting smoking is the cornerstone of COPD treatment. For patients with COPD, quitting smoking can reduce the risk of further lung deterioration as well as the risk of COPD-related hospitalizations, death, and disability.[5-7] Although smoking cessation is strongly recommended for all patients with COPD, these patients have a particularly high dependence on nicotine and find it extremely difficult to quit.8 Despite the ongoing damage to their lungs, more than 39% of people who suffer from COPD continue to smoke.9 These smokers recognize the danger10 and the majority would like to quit,11 but only about 3% of smokers each year who try to quit actually succeed.[12]

The current standard of care for smoking cessation in the United States directs smokers to quit completely on a selected quit date, ideally with the aid of smoking cessation pharmacotherapy such as varenicline, bupropion, or nicotine replacement therapy (NRT).[13]

This approach may be unrealistic and unhelpful for smokers who find the idea of quitting completely daunting.[14] At any given time, only 10% to 20% of smokers in the United States are ready to quit and willing to make a quit attempt.[15] Even for the motivated smokers who are willing to quit right away, 80% fail in the attempt and quickly resume smoking.[13] Many smokers would like to have alternatives to the “cold turkey” approach and are interested in a gradual tapering of the number of cigarettes that

they smoke until they are ultimately able to quit.[16] Smokers who fail in an initial quit attempt might similarly benefit from ongoing treatment with pharmacotherapy and supportive counseling that might help them reduce their cigarette use and prepare for a subsequent cessation attempt.

Several investigators have looked at extending treatment with NRT for 6-12 months among smokers willing to quit.[17-19] These studies have had mixed results; 2 studies showed improvements in smoking cessation at 6 months, but these improvements were not sustained at 1 year.[18,19] Another study failed to demonstrate differences at 6 months but did show improvements in cessation rates 12-18 months after study enrollment.[17] None of these studies examined smoke exposure or harm reduction among continuing smokers.

Other investigators have examined the possibility of using long-term NRT (LT-NRT) prior to quitting completely as a method to reduce the harm from cigarettes or as a pathway of cutting down gradually prior to quitting (reduce to quit). A meta-analysis of these studies, performed among smokers not willing to quit, showed that it was safe to use NRT while continuing to smoke and that the "reduce to quit" approach could double the chances of eventually being able to quit and sustain abstinence for 6 months.[20] In response to these findings, many countries have incorporated the "reduce to quit" strategy into their national tobacco control programs.[21] In 2013, the US Food and Drug Administration updated its guidance on the use of NRT by removing cautions about using NRT while continuing to smoke.[22-24]

Given this guidance on NRT, LT-NRT could be offered to all smokers, regardless of their current interest in quitting, with NRT treatment and counseling focused on cutting down prior to quitting. LT-NRT might have the potential to dramatically expand treatment options for recalcitrant smokers, such as smokers with COPD who continue to smoke and may be intimidated by the idea of quitting immediately; it might give smokers who relapse during a quit attempt the support they need to quit again. LT-NRT could result in lower exposure to toxic cigarette smoke and improvements in smoking cessation.[20,25-27]

None of the previous studies that used NRT to "reduce to quit" focused on patients with COPD, and none directly compared a standard smoking cessation (SSC) intervention with a reduce-to-quit approach with NRT independent of a smoker's initial willingness to quit. The

purpose of this study was to compare an SSC program with LT- NRT for patients with COPD who continue to smoke.

C. PARTICIPATION OF PATIENTS AND STAKEHOLDERS

We engaged patient partners, including former and current smokers with COPD, to form a Patient Advisory Board. We also engaged key stakeholders, including regional representatives of organizations engaged in smoking cessation, health care providers, and public health experts, in a Stakeholder Advisory Board. The membership of both boards fluctuated over time. Our initial group of 9 stakeholders was identified through a network of representatives of organizations whose primary focus was to address tobacco use in Kansas (the Tobacco Free Kansas Coalition). We later added a local leader in the respiratory therapy community to enhance engagement of local providers caring for COPD patients. Our initial 3 Patient Advisory Board members were smokers with COPD who received care in a local hospital. Additional patient advisors were recruited from patients who were not eligible to participate in the study but expressed interest in joining the board. Later, we added additional participants who had completed the study, including former study participants from both arms, some who had quit and some who had continued to smoke. We engaged stakeholders 1 to 2 times each year through conference calls and webinars, in addition to email and telephone contact with individual members on an ad hoc basis as needed. Our Patient Advisory Board convened in person every 6 months.

Our patient and stakeholder advisors were engaged during all phases of research: study planning, implementation, and interpretation/dissemination of findings. Before the study began, we conducted structured interviews with smokers with COPD and used the results to guide discussions with the Patient and Stakeholder Advisory Boards on issues related to the design of the research project and intervention, formulation of the research questions, and refinement of the outcome measures. Patients reviewed different interventions for smoking cessation, discussed their prior experiences with cessation, and expressed a strong interest in trying combination NRT. They were particularly intrigued with the possibility of using NRT while still smoking. Patient concerns about varenicline led to the choice of using combination NRT, which had quit rates similar to varenicline but fewer anticipated side effects. Additionally,

patient advisors prompted researchers to incorporate extensive information about combination NRT in both the health education materials and the baseline counseling session. They recommended informing the participants' primary health care providers of their involvement in the study, owing to lack of information among providers about combination NRT and the ability to use NRT while continuing to smoke. Stakeholders supported continuing to treat our long-term nicotine replacement group 6 months after abstinence was achieved. Stakeholders also recommended that our standard smoking cessation arm be consistent with treatment guidelines in the United States; that we assess each smoker's willingness to quit; and, for those willing to make a quit attempt, that we provide pharmacotherapy and help them develop a cessation plan.[13,28] Those not ready to quit would receive motivational counseling but would not receive pharmacotherapy and follow-up cessation treatment unless they were ready to set a quit date.

Throughout the study, patients and stakeholders provided feedback on ways to boost recruitment and retention. During the first few months of recruitment, we experienced some setbacks owing to low referral numbers. Patients advised us to ask completing participants to provide referrals to individuals they knew who smoked and had COPD. The respiratory therapist helped us connect with therapists caring for COPD patients throughout the region. Word-of-mouth referrals became a significant referral source. Patient advisors also steered us toward providing a study newsletter to all study participants at month 9, to continue to engage participants during the last 6 months of the study. Our stakeholders provided suggestions on recruitment from other local pulmonary clinics and hospitals. This increased not only recruitment but also the diversity of our participant population.

Upon study completion, our participant advisors provided input about the design of a study website, helped provide feedback on the interpretation of the final results, and helped develop a research report to send to former participants. Most notably, they shared their personal stories and struggles in trying to quit, which provided a context for interpreting the study results. Our stakeholders were disappointed with the low quit rates observed in the study, but they indicated that the study results could expand choices for smokers not yet ready to quit.

D. METHODS

Overview

In this randomized, unblinded trial, we recruited 398 smokers with a self-reported physician diagnosis of COPD and randomly assigned them to receive either (1) a standard smoking cessation intervention consisting of 10 weeks of NRT supported by cessation counseling contingent on willingness to quit or (2) long-term NRT with combination NRT and supportive counseling extended over 12 months regardless of the participant's willingness to quit. Participants completed follow-up assessments at 3, 6, and 12 months post enrollment. The primary outcome was carbon monoxide (CO)-verified smoking abstinence at 1 year. This study was reviewed and approved by the Institutional Review Board at the University of Kansas Medical Center and has been registered at clinicaltrials.gov (NCT02148445).

Participants and Setting

Recruitment occurred from May 2014 to November 2015. We queried electronic health records at 2 academic medical centers in the Kansas City metropolitan area to identify patients with COPD seen within the past year who indicated continued smoking at their most recent assessment. Potential participants were mailed a letter that described the nature of the study and gave them the option to opt out of any further study-related contact. For patients already enrolled in a registry of research participants (Frontiers, CTSA Award #UL1TR000001), this letter came directly from the research team. For other participants, the letter came from the patient's provider. If we did not receive a response within 2 weeks, the letter was followed by a call from a member of the research staff who provided further information about the study and assessed the potential participant's interest.

Participants were also directly referred to the study by other participants and by health care providers in the community. To increase the sample's diversity, we recruited at medical centers that serve a diverse population, at safety-net clinics, and on Spanish-language radio.

Potential participants completed a preliminary screening interview via telephone and a subsequent face-to-face evaluation to assess eligibility. Participants were considered eligible if they were ≥ 18 years of age, smoked 5 or more cigarettes per day (CPD) on ≥ 25 of the last 30

days, spoke either English or Spanish, and reported that a physician had diagnosed them with chronic lung disease. Participation was not contingent on willingness to quit, but participants had to be willing to complete 4 in-person visits, participate in 4 counseling calls, and use nicotine replacement therapy for up to 1 year.

Smokers were excluded if they had a terminal medical condition with a life expectancy < 1 year; were pregnant, breastfeeding, or planning to become pregnant in the next year; resided in a nursing home or other long-term care facility that restricted smoking; exhibited severe cognitive impairment; had another member of the household enrolled in the study; did not have a home address; or had been hospitalized with a heart attack, experienced an irregular heartbeat, or reported increasing angina in the past 30 days.

Randomization

After providing informed consent, eligible participants completed a baseline assessment and were randomly assigned to 1 of 2 study conditions: standard smoking cessation or long-term NRT. Randomization occurred at the participant level in permhidden REDCap table until after the research assistant verified eligibility and the participant completed the baseline assessment.

Interventions

The interventions were conducted via telephone or on-site at 1 of 2 locations: the University of Kansas Medical Center or the medical center's Clinical Research Center. All participants received a health education booklet and an in-person counseling session at baseline. All participants in LT-NRT and those ready to quit in the next 30 days in SSC received combination nicotine replacement therapy. Combination NRT included the nicotine patch plus the patient's choice of ad lib nicotine gum or lozenge. Participants who received NRT also received follow-up counseling calls to support their quitting or NRT use.

Counseling

All counseling sessions were delivered by trained tobacco treatment counselors[30] and provided in the patient's preferred language (English or Spanish).

Standard Smoking Cessation. SSC counseling sessions were designed to emulate services provided in a typical smoking cessation program, such as a state tobacco quitline. The timing, duration, and content of each counseling session were consistent with guideline-based recommendations.[13] During the baseline session, counselors provided basic information about smoking and successful quitting. The counselor explored each participant's readiness to quit using a decisional balance tool to identify what the participant perceived to be the pros and cons of smoking and pros and cons of quitting. The counselor then provided a global summary and asked the participant how ready he or she was to quit. If the participant felt ready to quit, the counselor provided practical support in developing a personalized plan for cessation and long-term abstinence. The counselor helped the participant learn to recognize danger situations, develop problem-solving and coping skills, and make a plan to secure additional social support. The counselor helped the participant set a quit date and provided guidance on use of NRT, as outlined below. Participants who expressed an interest in quitting within the next 30 days were offered free combination NRT and additional telephone-based counseling.

SSC participants who were initially unwilling to make a quit attempt still received counseling at baseline. Counselors used a participant-centered approach to enhance the participant's motivation to quit as recommended in current practice guidelines.[13] Participants were informed that they could contact us at any time during the study if they decided they wanted to quit. If they indicated any interest in quitting within 6 weeks of randomization, they were given the complete SSC intervention, including counseling and free NRT. If they contacted the team with an interest in quitting more than 6 weeks after randomization, they were referred to the state tobacco quitline. If they were not interested in quitting, they received no additional counseling or pharmacologic treatment, but they were included in follow-up and outcomes assessments.

SSC participants who expressed an interest in quitting were proactively contacted by telephone for additional smoking cessation counseling 1, 3, 6, and 10 weeks after the baseline face-to-face counseling session. A minimum of 3 call attempts, including attempts during daytime and evening hours and on alternate days, were made to reach participants for each scheduled session. For each session, the participant's current tobacco-use status guided the

content of each follow-up call. If the participant had quit, the counselor reviewed high-risk situations, coping skills, and stress management to prevent relapse. If the participant had relapsed (returned to daily smoking) or slipped (had an occasional cigarette), the counselor explored circumstances related to the relapse or slip and provided troubleshooting techniques to help avoid these situations in the future. The counselor used cognitive behavioral techniques to build coping skills, with the goal of helping the participant build and implement a new quit plan. For participants who set a quit date but did not attempt to quit, and for those who tried to quit but failed, the counselor used motivational strategies to support the participant in making a new quit attempt.

Long-term NRT. Similar to the SSC intervention, all participants randomized to LT-NRT completed a baseline counseling session with a trained smoking cessation counselor. Participants in LT-NRT set cigarette reduction goals and completed a personalized quit plan, which included discussions about setting a quit date, if they expressed an interest in quitting within the next 30 days.

Follow-up calls were provided at 1, 3, and 6 weeks and at 9 months after the baseline visit. Additionally, participants in LT-NRT received in-person counseling at months 3 and 6 after completing their in-person assessments. At each follow-up session, counselors asked participants about their readiness to quit. For participants who stated they were ready to quit, counselors helped in quit planning; for those who stated they were not, counselors encouraged reduction goals. NRT adherence support was a primary focus to facilitate participant goals of quitting, staying quit, or making further reductions. Counselors asked participants about potential side effects of treatment and provided tips to aid symptom management depending on the nature and severity of reported symptoms. This included addressing barriers to NRT adherence and proper usage.

Combination Nicotine Replacement Therapy

All participants randomized to LT-NRT received combination NRT consisting of nicotine patch plus the participant's choice of ad lib nicotine gum or lozenge, titrated to their level of smoking. Provision of combination NRT for the SSC arm was contingent on the participant's

agreement to set a quit date, in a manner consistent with the current standard for smoking cessation.[13] Participants who at their baseline session set a quit date within the next 30 days were offered a free, 10-week supply of combination nicotine replacement therapy and were instructed to start the NRT on their quit date. In the LT-NRT group, participants got up to a year of combination NRT, receiving a 3-month supply at baseline and at months 3, 6, and 9. They were instructed to start their NRT right away, with patches being placed during the baseline session. Participants in both groups were instructed to use the nicotine patch daily for their entire treatment course, even if they slipped and had a cigarette.

The combination nicotine replacement therapy included nicotine patches plus 2 mg nicotine gum and/or lozenge. The dose of nicotine patches provided to the participant was based on their current cigarette consumption[13,31] and consistent with the combined NRT treatment regimens that have been shown to be effective and safe in clinical trials.[32,33] Initial patch dosage was 14 mg for those who reported smoking less than 10 CPD, 21 mg for 10 to 20 CPD, 35 mg for 21 to 39 CPD, and 42 mg for 40 or more CPD.

During their baseline visit, participants in both groups were invited to sample different types and flavors of nicotine gum and lozenges and select the products of their choice. Participants were asked to anticipate the times of day that they typically smoked and use a 2 mg gum or lozenge before deciding if they should have a cigarette. They were advised to consume at least 6 to 12 doses of gum or lozenge each day, depending on their current smoking history.

Smokers who were unable to tolerate using the nicotine patch were given a 4 mg gum or lozenge if they smoked within 30 minutes of waking or smoked more than 20 CPD.

At each counseling call, the counselor assessed NRT usage, side effects, and the adequacy of the current dosing. The counselor worked with the participant to mitigate any side effects, improve medication adherence, and adjust the dosage, to minimize symptoms of withdrawal or craving. Additionally, staff instructed participants to call the study hotline if they experienced side effects or needed a dosage adjustment.

Written Health Education Materials

All participants received written education materials similar to material offered by a tobacco quitline but adapted to provide in-depth information on combination NRT, including how NRT works, how to use the products, and how to troubleshoot side effects. Additional topics covered included health benefits of quitting smoking, coping with withdrawal and smoking triggers, creating a personalized quit plan, managing stress, creating a smoke-free home, and cognitive-behavioral strategies for quitting smoking and preventing relapse. The materials provided a number that the participants could call 24/7 if they had problems related to their treatment. Materials were offered in the participant's language of choice (English or Spanish) and were reviewed with participants at enrollment.

Staff Training and Fidelity Monitoring

Trained staff provided the intervention and collected data and specimens at clinical and lab visits. Counselors were required to either completed an accredited Tobacco Treatment Specialist program or an 8-hour online program for basic skills in Tobacco Treatment, pass a proficiency exam, and complete additional skills training until competency was met.

Additional training specific to the counseling protocol was provided by 2 doctoral-level psychologists (KR, NN). Counselors completed mock sessions and had to demonstrate proficiency in tobacco treatment skills and protocol delivery for both treatment arms prior to providing the intervention. Supervision included direct observations and review of audio-taped sessions. Any deficiencies were identified, and strategies were developed to enhance protocol adherence.

Outcomes, Measures, and Follow-up

Research assistants collected data at baseline and during face-to-face follow-up assessments at 3, 6, and 12 months post enrollment. All participants, regardless of their interest in quitting, were included in these follow-up assessments. Participants were

reimbursed $50 for each study visit. Assessments were performed on site at either the University of Kansas Medical Center or the University of Kansas Clinical Research Center.

All data were directly entered into a REDCap database with edit checks to reduce the risk of out-of-range and missing data.[29] REDCap is a secure web-based application designed to support data capture for research studies. Completeness of data entry was automatically verified before each assessment was completed. To reduce the risk of missing data, participants received telephone and postcard reminders prior to study visits. For participants we could not reach by phone, we sent letters and contacted prespecified "key contacts." For participants unable or unwilling to come to the study site for assessments, we conducted assessments via phone, by mail, or in the participant's home.

Outcomes. The primary outcome was 7-day point prevalent smoking abstinence at 12 months (ie, self-reported abstinence over the previous 7 days) confirmed by exhaled carbon monoxide $\leq$ 10 ppm[34] (Table 1). Secondary outcomes included outcomes related to smoking cessation, harm reduction, and respiratory function. Secondary cessation-related outcomes included 6-month sustained abstinence, defined as confirmed quit by CO or proxy at both 6 and 12 months, and the cumulative number of 24-hour quit attempts over 12 months. Secondary outcomes related to harm reduction included the average number of CPD smoked over 12 months, exposure to CO over 12 months as measured with a portable smoke analyzer, and carcinogen exposure over 12 months as measured by NNAL (4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol).

Table 1. Outcomes and Covariates

OUTCOMES	
Smoking abstinence	7-day point prevalence abstinence, confirmed by exhaled carbon monoxide (CO) or proxy validation; primary outcome at 12 month follow-up
6-month sustained smoking abstinence	6 month sustained abstinence defined as confirmed quit by exhaled CO or proxy validation at both 6 and 12 month follow-ups
Average cigarettes per day (CPD)	Self-reported cigarettes smoked per day was assessed at all time points; a repeated measures analysis analyzed differences between groups over time controlling for baseline values.
Smoke exposure -Carbon Monoxide exposure (CO)	Expired CO was measured at all time points; a repeated measures analysis analyzed differences between groups over time controlling for baseline values.
Carcinogen exposure (NNAL)	Urinary NNAL (pg per mg creatinine) was measured at all time points; a repeated measures analysis analyzed differences between groups over time controlling for baseline values.
Quit attempts	Number of self-reported quit attempts lasting at least 24 hours were measured at all time points. Baseline values, which assessed the number that occurred during the year prior to study enrollment, provided a control for a repeated measure analysis comparing differences between groups over time.
Respiratory function	Simple spirometry was performed at baseline and at the 12 month follow-up visit. Group differences at month 12 were assessed controlling for baseline values.
Respiratory symptoms	Respiratory symptoms were measured using the COPD Assessment Test (CAT), with scores ranging from 0 - 40, at all time-points; a repeated measures analysis analyzed differences between groups over time controlling for baseline values.
Respiratory-related hospitalizations and ED visits	Intercurrent hospitalizations and emergency department visits were assessed at each follow-up visit and summed. Baseline values, which assessed the number that occurred during the year prior to study enrollment, provided a control for a repeated measure analysis comparing differences between groups over time.

CO-VARIATE MEASURES		BL	M3	M6	M12
Demographics/social history	Gender, age, race, ethnicity, income, education, employment, marital status, smokers in the home, home smoking rules, health history, anxiety (GAD-2), depression (PHQ-2)	X			
Tobacco/nicotine use history	Quantity smoked, quitting history, use of other tobacco and nicotine products, including e-cigs and nicotine replacement therapy (NRT)	X	X	X	X
Readiness to quit	Interest in quitting assessed via 30-day and 12-month anchor	X	X	X	X
Nicotine dependence	Heaviness of Smoking Index (HSI)	X	X	X	X
Nicotine intake	Urinary cotinine (ng per mg creatinine)	X	X	X	X
Respiratory function	FEV1 (% of predicted) using simple spirometry	X			X
COPD symptoms	COPD Assessment Test (CAT)	X	X	X	X
NRT use	3-day recall of NRT use		X	X	X
Counseling adherence	Total number of follow-up counseling sessions completed		X	X	X

Concentrations of total cotinine, 3-hydroxy-cotinine, and total NNAL were measured in urine samples using fully validated liquid chromatography-mass spectrometry (LC-MS/MS) methods. Analytical procedures, including beta-glucuronidase treatment, sample preparation, and LC-MS/MS procedures, were based on established methods for cotinine and 3-hydroxy-cotinine[35] and for NNAL.[36] Limits of quantitation were 15 ng/ml for cotinine and 3-hydroxy-cotinine and 30 pg/mL for NNAL. Values that fell below the level of quantitation were imputed as half the lower limit of quantitation.[37]

Additional secondary outcomes included the change in respiratory function as measured by simple spirometry at baseline and 12 months using a portable spirometer (Spiropalm, Future Med) and taking the values from the best of 3 trials,[38] respiratory symptoms over 12 months as measured by the 8-item COPD Assessment Test (CAT),[39,40] and the cumulative number of respiratory-related hospital admissions and emergency department visits over 12 months.

Demographics, smoking characteristics, health history, and other measures. At baseline, we assessed basic demographic data including age, gender, race, ethnicity, marital status, education level, employment status, and insurance status (Table 1). Smoking history included CPD, number of 24-hour quit attempts in the past year, a single stage-of-change question (readiness to quit smoking in the next 30 days),[41] interest in quitting or cutting down in the next 12 months,[16] presence of home smoking restrictions,[42,43] presence of other smokers in the home, e-cigarette use, other tobacco use, and use of cessation pharmacotherapy in previous quit attempts. Motivation and confidence to quit were each measured with a 10-point Likert scale. We assessed nicotine dependence using the Heavy Smoking Index, which combines 2 items (the number of cigarettes smoked per day and time to first cigarette of the day) from a larger scale measuring nicotine dependence (The Fagerstrom Test of Nicotine Dependence).[44] Health status measures included the length of time since participants' COPD was diagnosed, prior history of diabetes or heart disease, and the number of hospitalizations and emergency department visits in the past 12 months for heart disease or respiratory problems. Anxiety was assessed using the 2-item Generalized Anxiety Disorder Scale,[45] and depression was assessed using the Patient Health Questionnaire.[46] We also assessed adherence to nicotine replacement

therapy usage via 3-day recall.

We tracked adverse events potentially related to NRT use, including major adverse cardiac events. Major adverse cardiac events were defined as a cardiovascular-related death, including sudden death; myocardial infarction; unstable angina requiring hospitalization; revascularization resulting from increasing ischemia; an arrhythmia resulting in hospitalization or placement/modification of a device; a stroke; a transient ischemic attack resulting in hospitalization; and a hospitalization for congestive heart failure.

Monitoring Procedures

A Data Safety and Monitoring Committee consisting of a statistician, pulmonary physician, and cardiologist provided oversight to the study and reviewed the safety monitoring procedures, the frequency of adverse events, and major adverse events. Adverse events related to NRT were primarily identified during the counseling calls, while trouble-shooting problems with the participant's nicotine replacement therapy. We specifically queried participants about cardiovascular events, including hospitalizations and emergency department visits, during follow-up assessments at 3, 6, and 12 months. Medical records were reviewed to confirm any major adverse cardiac events as defined in the previous paragraph.

Sample Size Determination

Our sample size was based on our primary outcome, point prevalence abstinence at 12 months, using an intent-to-treat approach. Based on our prior efforts to recruit smokers at all stages of readiness into a smoking cessation study,[47] we estimated that (1) 60% of participants in the SSC arm would be interested in quitting smoking at the time of recruitment and would receive active treatment and (2) the 12-month cessation rate in this group would be about 10%. Based on prior studies that used NRT among smokers not ready to quit, we estimated a 2-fold increase in cessation outcomes in the LT-NRT group compared with the SSC group.[20,25,27,48] With a 12-month cessation rate of 10% in the SSC group and a 20% 12-month cessation rate in LT- NRT, we needed a sample size of 398 participants to achieve a power of 80% to detect a 2-fold difference or greater with a type 1 error of 5%.

Data Analyses

Study data were managed using REDCap electronic data capture tools hosted at the University of Kansas Medical Center.[29] Data were analyzed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina). We generated descriptive statistics for each of the baseline measures and assessed for imbalance between the treatment groups using chi-square analyses and Student's *T* test for bivariate and continuous data, respectively.

For the primary outcome, we used the Pearson chi-square test to compare the verified 7-day point prevalence abstinence at month 12 between the 2 groups. For the secondary outcomes, we used the Pearson chi-square to test for group differences in sustained abstinence and self-report and verified abstinence at 3, 6, and 12 months. For respiratory events and quit attempts, we conducted a repeated measures analysis using a generalized linear mixed model that allowed us to model the number of events as count data after accounting for the appropriate correlation structure across time by adding baseline counts as a covariate and applying offset variables to account for varying exposure times. The change in respiratory function (FEV1) from baseline to month 12 was computed and changes were compared between groups using Student's *T* test. We tested for differences between groups, and across time for CO readings and respiratory symptoms measured at baseline, 3, 6, and 12 months, using linear mixed model repeated measures analysis.[49] Our modeling structure accounted for the fact that longitudinal measurements across time are auto- correlated, which allowed us to test for significant differences both over time and between the 2 study arms. Because NNAL measurements were found to be highly skewed, a similar approach was used for modeling the logarithm of creatinine-adjusted NNAL measurements. In all the repeated measures analyses mentioned earlier, we also assessed whether potential effects over time varied by study arm (that is, a study arm–time interaction). We used a flexible approach in our modeling and did not assume linear trends over time. All statistical tests were conducted at the 0.05 level of significance.

In all our analyses, we did not experience more than 7% missing data at any given time point for either the primary or secondary outcomes. For our primary outcome, we treated participants with missing data as continued smokers. We conducted a variety of sensitivity

analyses on the primary outcome, including a completers-only analysis and an analysis that made the unlikely assumption that all nonrespondents had actually quit smoking. We also performed logistic regression analyses controlling for variables that were unbalanced across treatment arms at baseline. In our analyses that used linear and generalized linear mixed models, the modeling framework addressed missing data under the missing-at-random assumption using likelihood-based analyses.[50]

We used a classification and regression tree (CART) analysis[51,52] to identify subgroups of participants whose personal characteristics might affect cessation outcomes. This exploratory CART analysis was not driven by prespecified hypotheses of specific subgroup differences in treatment response. Candidate variables, which were initially identified by the research team and reviewed with the Patient Advisory Board and the Stakeholder Advisory Board, included age, gender, nicotine dependence, severity of COPD, and psychiatric comorbidities. These candidate variables, along with treatment assignment (LT-NRT versus SSC) were entered into a recursive partitioning model as described by Brieman and Freidman using the JMP statistical software.[51] Strategies for building the tree (using appropriate splitting criteria and assessment using the logworth statistic), pruning the tree, and handling missing data (using surrogate variables) were employed using the techniques described by Therneau and Atkinson.[53] Similar methods were used to generate CART model/decision trees for (1) 6-month sustained abstinence, (2) 50% reduction in carcinogen (NNAL) exposure, (3) 50% reduction in exhaled CO, and (4) COPD-related hospitalization (0; 2 or more).

E. RESULTS

Participant Characteristics

Of the 667 potential participants screened, 269 (40.3%) were excluded (Figure 1)—of whom 153 failed to meet the eligibility criteria and 102 initially deemed eligible failed to show up for the face-to-face screening. The remaining 398 eligible participants consented to participate, completed the baseline assessment, and were randomized to either SSC (n = 198) or LT-NRT (n = 200).

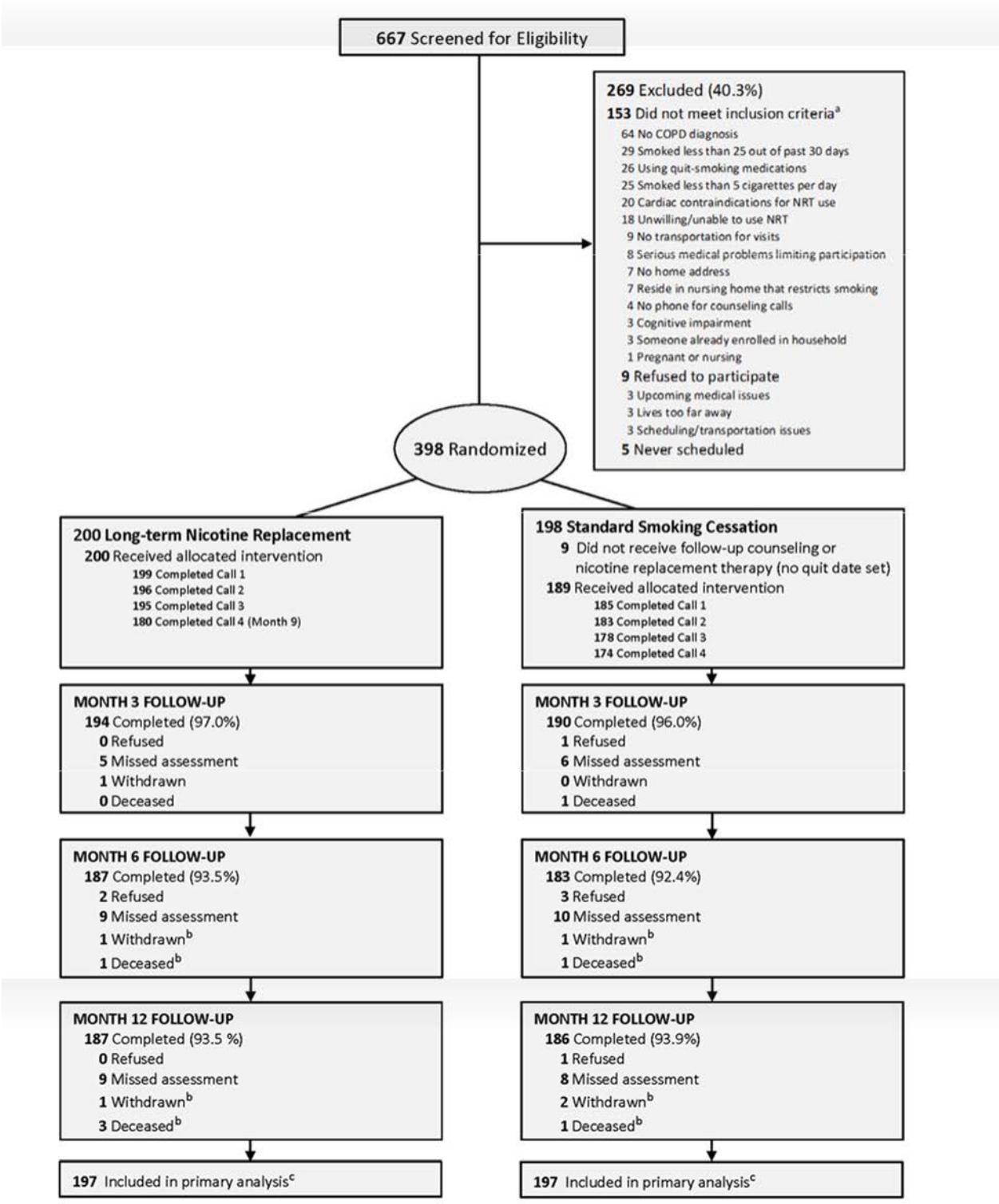
Participant characteristics across the 2 study arms were mostly similar at baseline

(Table 2), except that participants assigned to LT-NRT were less likely to prohibit smoking in the home and less likely to have had 2 or more COPD exacerbations in the past year. The majority of participants were female (59.8%), Caucasian (69.6%), and not employed (79.9%). Participants were an average of 56.0 (SD = 9.28) years old and had been diagnosed with COPD for an average of 6.9 (SD = 7.52) years; 58% had a CAT score > 20, indicating a high level of symptomatology from their COPD. Participants reported smoking an average of 23.1 CPD (SD = 12.26), with 94% smoking within 30 minutes of waking. The majority (81.4%) had used 1 or more types of cessation pharmacotherapy in the past, 54.8% had made 1 or more quit attempts in the past year, and 81.9% indicated an interest in quitting within the next 30 days.

Follow-up and Adherence to Therapy

Retention was comparable across treatment arms, with 96.5%, 93.0%, and 93.7% completing follow-up assessments at months 3, 6, and 12, respectively. Four participants died during follow-up and were excluded from the primary and secondary analyses. Of those assigned to the SSC arm, 9 (4.5%) indicated that they were not interested in setting a quit date after the baseline counseling session and did not receive any further counseling or pharmacotherapy. The remaining participants completed 96.3% and 95.2% of the scheduled counseling calls in the LT-NRT and SSC arms, respectively.

Figure 1. Study Flow (CONSORT) Diagram



[a] Multiple categories could be selected. [b] Categories are cumulative. [c] Deceased participants were excluded from analysis.

Table 2*. Baseline Characteristics of Study Participants

	TOTAL n = 398		LT-NRT n = 200		SSC n = 198	
Characteristics	**No.**	**%**	**No.**	**%**	**No.**	**%**
Age (years), mean (SD)	56.0	(9.28)	55.6	(9.87)	56.3	(8.65)
Female	238	59.8	127	63.5	111	56.1
Race						
White	277	69.6	145	72.5	132	66.7
African American	113	28.4	52	26.0	61	30.8
American Indian/Alaskan Native	7	1.8	2	1.0	5	2.5
Native Hawaiian/Other Pacific Islander	1	0.3	1	0.5	0	0.0
Ethnicity, Hispanic	13	3.3	5	2.5	8	4.0
Employment						
Employed	80	20.1	40	20.0	40	20.2
Disabled	197	49.5	99	49.5	98	49.5
Other[a]	121	30.4	61	30.5	60	30.3
Education, high school graduate	202	50.8	101	50.5	101	51.0
Health insurance	333	83.7	167	83.5	166	83.8
Medicaid	169	42.5	80	40.0	89	44.9
Prescription insurance	321	80.7	156	78.0	165	83.3
Cigarettes smoked per day, mean (SD)[b]	23.1	(12.26)	24.0	(12.58)	22.1	(11.87)
Smoke 1st cigarette within 30 minutes of waking	374	94.0	188	94.0	186	93.9
Heavy Smoking Index, score 4'	255	64.1	129	64.5	126	63.6
Smoking prohibited in home	71	17.8	28	14.0	43	21.7
Previous use of e-cigarette	280	70.4	142	71.0	138	69.7
E-cigarette use in past 7 days	51	12.8	27	13.5	24	12.l
Other tobacco use in past 7 days	41	10.3	19	9.5	22	11.1
M arital status						
Married/partner	145	36.4	78	39.0	67	33.8
Divorced/separated	146	36.7	76	38.0	70	35.4
Widowed	34	8.5	17	8.5	17	8.6
Never been married	73	18.3	29	14.5	44	22.2
Living status						
Lives alone	133	33.4	72	36.0	61	30.8
Other smokers in household	155	38.9	77	38.5	78	39.4
Only nonsmokers in the home	110	27.6	51	25.5	59	29.8
Confidence to quit, mean (SD)[d]	6.6	(2.77)	6.6	(2.88)	6.6	(2.66)
Planning to quit in next 30 days	326	81.9	169	84.5	157	79.3
Planning to quit in next year	353	88.7	174	87.0	179	90.4
Believe quitting will improve breathing•	377	94.7	187	93.5	190	96.0
Rate current health as “fair” or “poor”	231	58.0	118	59.0	113	57.1
Length of COPD diagnosis in years, mean (SD)	6.9	(7.52)	7.1	(7.51)	6.7	(7.54)
CAT Score >20, high impact level[1]	231	58.0	124	62.0	107	54.0
MRC Breathlessness Scale, mean (SD)'	1.9	(1.20)	2.0	(1.23)	1.8	(1.17)
Diabetes	132	33.2	69	34.5	63	31.8
Heart disease	87	21.9	48	24.0	39	19.7

Table 2. Baseline Characteristics of Study Participants (continued)

Characteristics	TOTAL n =398 No.	%	LT-NRT n= 200 No.	%	SSC n=198 No.	%
BMI, mean (SD)	30.0	(8.37)	30.5	(8.70)	29.6	(8.02)
Underweight ≤ 18.5	13	3.3	9	4.5	4	2.0
Normal 18.5 to < 25	116	29.1	57	28.5	59	29.8
Overweight 25 to < 30	106	26.6	44	22.0	62	31.3
Obese 30 to < 40	113	28.4	61	30.5	52	26.3
Morbid obese ≥ 40	50	12.6	29	14.5	21	10.6
PHQ-2 score ≥ 3[h]	133	33.4	70	35.0	63	31.8
GAD-2 score ≥ 3[I]	166	41.7	88	44.0	78	39.4
Hospitalization for breathing past 12 months	89	22.4	42	21.0	47	23.7
ED visit for breathing past 12 months	92	23.1	38	19.0	54	27.3
COPD exacerbation (2 or more in past year)[J]	76	19.1	30	15.0	46	23.2
Hospitalization for heart past 12 months	36	9.0	20	10.0	16	8.1
ED visit for heart past 12 months	27	6.8	16	8.0	11	5.6
Quit attempts in the past 12 months, mean[b]	2.1	(4.70)	1.9	(4.29)	2.2	(5.09)
Prior use of NRT to cut down	149	37.4	76	38.0	73	36.9
Prior use of cessation pharmacotherapy, any	324	81.4	163	81.5	161	81.3
Nicotine patch	234	58.8	116	58.0	118	59.6
Nicotine gum	110	27.6	56	28.0	54	27.3
Nicotine lozenge	43	10.8	21	10.5	22	11.1
Bupropion	86	21.6	44	22.0	42	21.2
Varenicline	162	40.7	88	44.0	74	37.4
Bupropion and nicotine patch in combination	11	2.8	4	2.0	7	3.5
Nicotine patch and short acting in combination	32	8.0	16	8.0	16	8.1
Exhaled CO, ppm, mean (SD)	22.5	(13.81)	22.7	(14.48)	22.2	(13.12
Exhaled CO, < 10 ppm	54	13.6	29	14.5	25	12.6
Exhaled CO, 10 to < 20 ppm	136	34.2	68	34.0	68	34.3
Exhaled CO, 20 to < 30 ppm	120	30.2	57	28.5	63	31.8
Exhaled CO, 30 to < 40 ppm	51	12.8	25	12.5	26	13.1
Exhaled CO, 40 to < 50 ppm	19	4.8	11	5.5	8	4.0
Exhaled CO, ≥ 50 ppm	18	4.5	10	5.0	8	4.0
Spirometry, FEV1/FVC < .70 (actual)[k]	242	60.8	119	59.5	123	62.1
GOLD GRADE 1: FEV1, >/= 80% of predicted	60	15.1	34	17.0	26	13.1
GOLD GRADE 2: FEV1, 50 to < 80% of	187	47.0	81	40.5	106	53.5
GOLD GRADE 3: FEV1, 30 to < 50% of	119	29.9	66	33.0	53	26.8
GOLD GRADE 4: FEV1, < 30% of predicted	32	8.0	19	9.5	13	6.6

[a]Other category includes currently not employed, homemaker, student, and retired; *p*-value for employment is comparing employed to all other categories combined. [b]Smoking history questions from stage of change questionnaire.[41] [c]Heavy Smoking Index scores range from 0 to 6. Scores of 4 or greater indicate moderate to high nicotine dependence.[54] [d]Confidence to quit smoking scores range from 0 to 10. [e]Rate agreement based on a response of 6 or 7 on a 7-point Likert scale. [f]COPD Assessment Test (CAT) scores range from 0 to 40. Scores greater than 20 indicate high impact of COPD.[39,40] [g]The MRC Breathlessness Scale scores range from Grade 0 (no respiratory disability) to Grade 4 (almost complete incapacity).[55] [h]PHQ-2 scores range from 0 to 6. Scores of 3 or greater indicate presence of depressive symptoms.[46] [i]GAD scores range from 0 to 6. Scores of 3 or greater indicate possible presence of general anxiety disorder.[45] [j]COPD exacerbation was calculated by adding COPD related hospitalizations and ED

visits in the year before baseline. [k]Spirometry categories used GOLD 2017 criteria.[56]

**Adapted version of this table published in: Ellerbeck EF, Nollen N, Hutcheson TD, et al. Effect of Long-term Nicotine Replacement Therapy vs Standard Smoking Cessation for Smokers With Chronic Lung Disease: A Randomized Clinical Trial. JAMA Netw Open. 2018;1(5):e181843. doi:10.1001/jamanetworkopen.2018.1843*

Based on 3-day recall at 3, 6, and 12 months, respectively, 77.5%, 77.8%, and 61.4% of LT-NRT participants and 61.2%, 26.5%, and 15.7% of the SSC participants indicated using at least 1 type of NRT daily. The LT-NRT and SSC participants, respectively, reported an average of 39.1 weeks (n = 176; SD = 11.24) and 15.9 weeks (n = 169; SD = 9.90) of nicotine patch use and 36.7 weeks (n = 176; SD = 13.34) and 20.4 weeks (n = 170; SD = 12.38) of nicotine gum or lozenge use across the 12 months.

Smoking Cessation

Self-reported smoking cessation at 3, 6, and 12 months was not significantly different across treatment arms (Table 3). At 12 months, the CO-verified 7-day abstinence (primary outcome) was 12.2% among LT-NRT participants and 11.7% among SSC participants (risk difference 0.5% [95% CI, –5.9%, 6.9%]; based on an intent-to-treat analysis with those with missing data imputed as smokers). Six-month sustained abstinence was likewise similar across treatment arms. Sensitivity analyses, including a completers-only analysis and an analysis that made the unlikely assumption that all nonrespondents had actually quit smoking, provided similar results, as did analyses controlling for participant characteristics that differed across treatment arms at baseline.

Secondary Outcomes

Although participants' respiratory function (FEV1) measurements remained unchanged over the course of the study (Table 4), both groups experienced significant improvements in respiratory symptoms over time, with the average CAT score improving by 4.6 points in the LT-NRT arm and 3.6 points in the SSC arm, but these improvements were not significantly different between the treatment arms. Similar numbers of participants in the 2 treatment arms had 1 or more respiratory-related emergency department visits or hospitalizations during the 12 months of follow-up. Both groups reported similar frequency of quit attempts that

lasted for at least 24 hours.

Table 3. Smoking Cessation Outcomes between Standard Smoking Cessation and Long-term NRT

	Total n = 394 No. (%)	Smoking Cessation n = 197 No. (%)	Long-term NRT n = 197 No. (%)	Risk Ratio (95% CI)	Risk Difference (95% CI)
Primary Outcomes at Month 12					
Self-reported 7-day abstinence	53 (13.5)	25 (12.7)	28 (14.2)	1.12 (0.68, 1.85)	1.5% (-5.2, 8.3)
Biochemically verified 7-day abstinence[a]	47 (11.9)	23 (11.7)	24 (12.2)	1.04 (0.61, 1.78)	0.5% (-5.9, 6.9)
Secondary Outcomes					
6-Month sustained abstinence[b]	27 (6.9)	15 (7.6)	12 (6.1)	0.80 (0.38, 1.67)	-1.5% (-6.5, 3.5)
Self-reported 7-day abstinence Month 3	43 (10.9)	27 (13.7)	16 (8.1)	0.59 (0.33, 1.06)	-5.6% (-11.7, 0.6)
Biochemically verified abstinence Month 3[a]	39 (9.9)	25 (12.7)	14 (7.1)	0.56 (0.30, 1.04)	-5.6% (-11.5, 0.3)
Self-reported 7-day abstinence Month 6	48 (12.2)	28 (14.2)	20 (10.2)	0.71 (0.42, 1.22)	-4.1% (-10.5, 2.4)
Biochemically verified abstinence Month 6[a]	44 (11.2)	25 (12.7)	19 (9.6)	0.76 (0.43, 1.33)	-3.1% (-9.3, 3.2)

[a] Abstinence confirmed by exhaled CO ≤10 ppm, except 1 participant at Month 12 and 2 at Month 6 verified by proxy. Non-respondents and those who did not provide verification were treated as smokers. [b] 6-month abstinence defined as biochemically verified quit at both Month 6 and Month 12 follow-up.

Among the participants at 12 months who continued to smoke, both groups reported similar reductions in self-reported CPD from baseline (LT-NRT: –14.5; SSC: –12.4 CPD), expired CO (LT-NRT: –7.8 and SSC: –5.5 ppm), and NNAL (LT-NRT: –23.0%; SSC: –21.7%) between baseline and 12 months. During the 12-month follow-up, these differed significantly from baseline but did not differ significantly between groups (Table 4).

Classification and Regression Tree Analyses

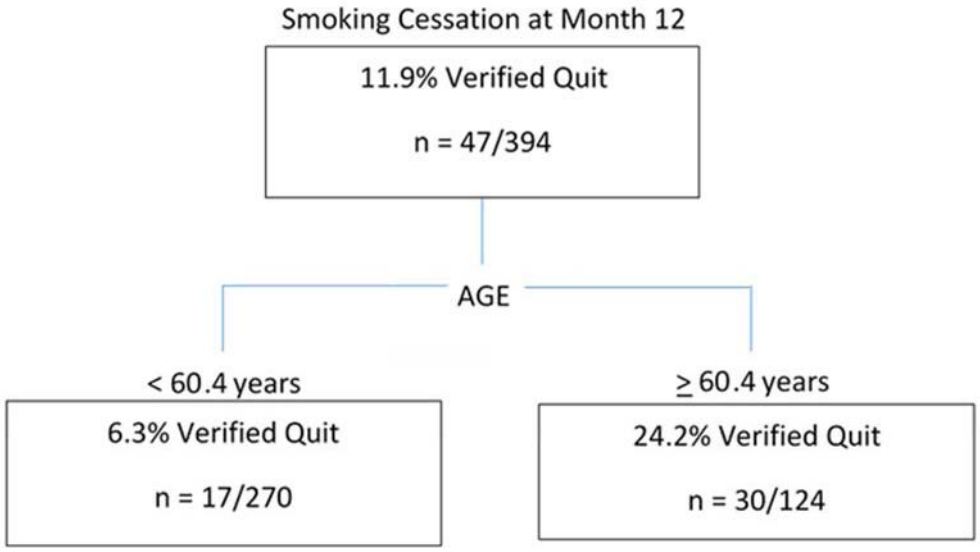
According to our prespecified analytic plan, we performed classification and regression tree analyses to identify any patient- or treatment-related factors associated with our primary or secondary outcomes. Based on these analyses, treatment arm was not identified as a major determinant of outcomes in any subgroup of participants. For abstinence at 12 months, we did identify differences in cessation associated with age, with 30 (24.2%) of 124 participants $\geq$ 60.4 years of age abstinent compared with 17 (6.3%) of 270 participants < 60.4 years of age (Figure 2; risk difference 17.9%; [95% CI, 9.8%, 26.0%]). The remaining CART analyses did not find any other patient-related factors that were significantly associated with treatment outcomes.

Table 4. *Secondary Outcomes By Arm and Timepoint*

		Baseline		Month 3		Month 6		Month 12		*p* value[a]		
All Participants		*n*	mean (SD)	*n*	mean (SD)	*n*	mean (SD)	*n*	mean (SD)	Group	Time	G*T
Cigarettes per day	SSC	197	22.1 (11.90)	189	7.9 (8.64)	182	8.1 (8.52)	186	8.5 (7.84)	.16	<.0001	.05
	LT-NRT	197	23.9 (12.52)	191	10.5 (8.64)	185	9.1 (9.45)	185	8.1 (8.33)			
Carbon monoxide (ppm)	SSC	197	22.3 (13.13)	174	15.0 (12.62)	164	14.6 (11.85)	175	15.5 (11.14)	.75	<.0001	.05
	LT-NRT	197	22.8 (14.58)	185	17.4 (13.69)	167	15.4 (12.58)	176	13.8 (11.14)			
NNAL (pg/mg creatinine)[b]	SSC	197	322.4 (269.23)	188	279.0 (353.42)	180	178.2 (221.26)	183	190.4 (233.22)	.79	<.0001	.39
	LT-NRT	197	311.7 (301.63)	190	320.1 (350.59)	184	186.0 (236.21)	180	183.5 (223.94)			
Quit Attempts (# of 24-hour or longer attempts)[c]	SSC	197	2.2 (5.10)	189	4.6 (6.54)	181	4.5 (6.86)	185	5.7 (8.59)	.55	--	.40
	LT-NRT	197	1.9 (4.31)	191	3.7 (5.48)	185	4.8 (8.97)	183	6.2 (11.31)			
Respiratory function, FEV1 (% of predicted)[d]	SSC	197	57.4 (18.63)		--		--	175	55.4 (19.25)	--	--	.42
	LT-NRT	197	56.9 (21.09)		--		--	175	56.8 (19.78)			
Respiratory symptoms[e]	SSC	197	21.1 (8.83)	189	17.8 (9.25)	181	17.9 (9.48)	185	17.5 (9.33)	.18	<.0001	.27
	LT-NRT	197	22.8 (8.31)	191	19.3 (8.68)	185	18.1 (8.51)	184	18.2 (9.37)			
Respiratory events[c, f]	SSC	197	1.0 (1.65)	189	0.1 (0.38)	181	0.2 (0.82)	185	0.2 (0.66)	.69	--	.06
	LT-NRT	197	0.7 (1.43)	191	0.2 (0.51)	185	0.2 (0.66)	183	0.2 (0.62)			
Continuing Smokers Only [g]												
Cigarettes per day	SSC	174	22.1 (11.33)	166	8.7 (8.84)	159	9.1 (8.62)	163	9.7 (7.64)	.21	<.0001	.05
	LT-NRT	173	23.8 (12.16)	167	11.4 (8.53)	161	9.9 (9.52)	161	9.3 (8.27)			
Carbon monoxide (ppm)	SSC	174	22.9 (13.34)	152	16.4 (12.56)	142	16.0 (11.68)	153	17.4 (10.57)	.74	<.0001	.08
	LT-NRT	173	23.6 (15.13)	161	18.8 (13.23)	143	17.0 (12.49)	152	15.8 (10.73)			
NNAL (pg/mg creatinine)[b]	SSC	174	328.1 (267.13)	165	314.6 (373.23)	158	219.8 (236.30)	160	257.0 (234.83)	.96	<.0001	.77
	LT-NRT	173	321.4 (305.62)	166	337.6 (363.80)	160	217.1 (251.82)	156	247.5 (230.64)			

[a] Table displays raw means for actual respondents at each time-point; p-values are based on model-based means for repeated measure analyses. [b] Geometric means and SD around the Geometric mean calculated using Delta method are reported. [c] Quit attempts and respiratory events are measured as number reported in the past year at baseline; past 3 months at Month 3 and 6; and past 6 months at Month 12. [d] P-value based on t-test difference from baseline to Month 12 and includes 175 participants per arm who had data at both time points. [e] COPD Assessment Test (CAT) scores range from 0 to 40 with higher scores indicating greater symptom severity. [f] Respiratory events included both ED visits and hospitalizations. [g] Continuing smokers analyses exclude all participants who were verified as quit at Month 12.

Figure 2. Classification and Regression Tree Including All Participants, Excluding Those Deceased at Month 12 (n = 394), to Identify Subgroups Predicting Abstinence at Month 12



Adverse events

A total of 17 major adverse cardiac events occurred during the study—9 in the SSC group and 8 in the LT-NRT group—with 4 hospitalizations for heart failure, 4 for arrhythmias, 5 for exacerbations of angina or cardiovascular disease, 3 for cerebrovascular symptoms, and 1 death related to mesenteric ischemia. Six events occurred while participants were using NRT and 11 occurred when participants were not using NRT. Medical record review did not identify any adverse cardiac events that were likely related to treatment. Three additional study deaths were reported and attributed to complications of COPD, lung cancer, and aspiration leading to cardiopulmonary arrest.

The most commonly reported symptoms of therapy (Table 5) were skin reactions (ie, itching or rash) at the patch site; upper gastrointestinal symptoms, such as nausea or upset stomach; problems sleeping or vivid dreams; oral symptoms related to gum or lozenges; headache; and change in affect or state of arousal (eg, restlessness, depression, irritability, fatigue). Overall, symptoms occurred more frequently among LT-NRT participants than among SSC participants.

Table 5. Symptoms Reported During Yearlong Study Providing Combination Nicotine Replacement

	Total n = 398		Standard Smoking Cessation n = 198		Long-term NRT n = 200		Risk Ratio		Risk Difference	
Symptoms Reported	No.	%	No.	%	No.	%	Ratio	(95% CI)	%	(95% CI)
Local skin reactions from patch	125	31.4	44	22.2	81	40.5	1.82	(1.34, 2.48)	18.3%	(9.3, 27.2)
Upper GI symptoms	94	23.6	32	16.2	62	31.0	1.92	(1.31, 2.80)	14.8%	(6.6, 23.0)
Problems sleeping/vivid dreams	64	16.1	23	11.6	41	20.5	1.76	(1.10, 2.83)	8.9%	(1.7, 16.0)
Irritation or pain in mouth	39	9.8	13	6.6	26	13.0	1.98	(1.05, 3.74)	6.4%	(0.6, 12.2)
Change in affect or state of arousal	31	7.8	12	6.1	19	9.5	1.57	(0.78, 3.14)	3.4%	(-1.8, 8.7)
Headache	25	6.3	7	3.5	18	9.0	2.55	(1.09, 5.96)	5.5%	(0.7, 10.2)
Cardiovascular symptoms	20	5.0	7	3.5	13	6.5	1.84	(0.75, 4.51)	3.0%	(-1.3, 7.2)
Hiccups	18	4.5	7	3.5	11	5.5	1.56	(0.62, 3.93)	2.0%	(-2.1, 6.0)
Bad taste	15	3.8	4	2.0	11	5.5	2.72	(0.88, 8.41)	3.5%	(-0.2, 7.2)
Dizziness	14	3.5	3	1.5	11	5.5	3.63	(1.03, 12.82)	4.0%	(0.4, 7.6)
Diarrhea	10	2.5	4	2.0	6	3.0	1.49	(0.43, 5.18)	1.0%	(-2.1, 4.1)
Muscle aches	7	1.8	1	0.5	6	3.0	5.94	(0.72, 48.89)	2.5%	(-0.1,5.1)
Sweating/night sweats	7	1.8	0	0.0	7	3.5	--	--	3.5%	(1.0, 6.0)
One or more symptoms	260	65.3	97	49.0	163	81.5	1.66	(1.42, 1.95)	32.5%	(23.7, 41.3)

Note: NRT was provided for one year for the long-term guided maintenance NRT intervention (LT-NRT) and 10 weeks for the standard intervention (SSC). In SSC, 9 did not receive any NRT. Some symptoms were reported when Pt. was no longer using NRT, but all symptoms were recorded. LT-NRT counseling focused on NRT use, adherence and side effect management. SSC counseling included some troubleshooting, but focused more on quitting strategies.

G. DISCUSSION

Decisional Context

The vast majority of COPD in the United States can be attributed to smoking, and smoking cessation is the primary method for slowing the progression of the disease.[56] Compared with those who quit, patients with COPD who continue to smoke have a higher mortality rate[5] and more rapid decline in pulmonary function.[7] Patients with COPD have an urgent need to quit but have more difficulty in doing so. Patients with COPD who continue to smoke may have particularly high levels of nicotine dependence[8,57,58] and lower self-efficacy related to quitting[59]; they may also find it more difficult to quit.[60] Despite the effectiveness of counseling and smoking cessation pharmacotherapy,[61] smokers with COPD are less likely than other smokers to succeed in their quit attempts[62] and the vast majority will continue to smoke.

The current decisional context for these smokers centers on the question of whether they are ready to quit. If they are ready to quit, health care providers can then offer counseling and pharmacotherapy to assist them in the quit attempt, but the smoker is asked to set a quit date on which they will completely abstain from cigarettes. Although most smokers would like to

quit, when presented with the idea of needing to abstain completely, only a minority are willing to make the decision to quit. Two major strategies have been proposed to alter this decisional context: (1) reduce to quit (cutting down on smoking as a bridge to quitting), and (2) harm reduction (reducing the harms of cigarettes by smoking less or getting nicotine from other sources). The LT-NRT intervention developed for this study was designed to offer smokers with COPD an alternative to immediate cessation.

Study Results in Context

Our study showed that long-term NRT, provided for 12 months, led to comparable rates of smoking cessation at 12 months compared with a traditional smoking cessation program that included 10 weeks of NRT. Despite the intensity of treatment, both groups experienced low quit rates. In a systematic review of randomized trials that used NRT to "reduce to quit," continuous NRT treatment for 6 to 18 months was associated with a 2-fold increase in cessation, although the effect size was small. These studies, conducted primarily among patients without COPD, achieved sustained abstinence of 6.75% in NRT recipients versus 3.28% among controls (NNT = 29).[20]

These previous studies of long-term NRT as a "reduce-to-quit" intervention focused almost exclusively on patients who first indicated that they had no intention of quitting in the short term.[20,63] In contrast, our study sought to enroll a broad spectrum of smokers with COPD. These smokers had made, on average, more than 2 quit attempts in the past year and had failed with a variety of previous pharmaceutical interventions. We anticipated that these patients, who continued to smoke despite their COPD, would find quitting particularly difficult, but the vast majority were willing to try; this willingness may have been stimulated in part by the availability of free combination NRT—a relatively novel intervention for the majority of our participants. Our study also used a different comparator than previous studies that used NRT to "reduce to quit." Whereas previous studies had compared active treatment with NRT to placebo or no treatment,[20] our study compared long-term NRT with an intensive smoking cessation intervention using 10 weeks of combination NRT.

Given the large number of patients in our study who indicated an interest in quitting, our study had much in common with previous studies that extended treatment with NRT for

patients willing to quit.[17-19] In a placebo-controlled trial, Schnoll compared 8 versus 24 weeks of nicotine patches.[18] At 24 weeks, point prevalence abstinence was significantly higher in those who received extended therapy (31.6% versus 20.3%), but by week 52, the rate of abstinence in both groups had declined to 14%. In a second, open-label study,[19] Schnoll compared 8 versus 24 versus 52 weeks of nicotine patch use. At 24 weeks, the patients in the 2 extended treatment groups had significantly higher rates of cessation (AOR 1.70), but at 52 weeks there were no significant differences between the groups—23.8% of those receiving 8 or 24 weeks of NRT were abstinent compared with 20.3% of those receiving 52 weeks of therapy. While our study failed to confirm the increased rates of abstinence that Schnoll's 2 studies demonstrated for extended treatment at week 24, we did observe a similar lack of impact of extended treatment at week 52.

Another study, however, did demonstrate long-term differences in outcomes associated with extended treatment.[17] In this study, Joseph and her colleagues compared 8 versus 48 weeks of treatment using a variety of types of NRT. They found that point prevalence abstinence at 6 months was virtually identical in the 2 groups, but at 18 months, those who received the extended treatment had significantly higher 6-month prolonged abstinence (AOR 1.74). A critical difference in Joseph's study, however, was that attempts were made to contact smokers every 2 to 4 weeks throughout the study and engage them in a new quit attempt if they were still smoking. This ongoing reengagement among relapsed or continuing smokers may be important. In the absence of intensive, ongoing reengagement in the 2 studies by Schnoll, abstinence rates dropped between months 6 and 12. In contrast, in the presence of ongoing reengagement, abstinence rates in Joseph's study actually increased during the same period. Another study that used 8-week courses of pharmacotherapy but reengaged smokers at 6-month intervals over 2 years also demonstrated progressively increasing rates of cessation over time.[47] In our study, where recipients of long-term NRT received counseling at months 6 and 9, confirmed abstinence increased from 9.6% at month 6 to 12.2% at month 12, whereas recipients of the standard smoking cessation intervention experienced a slight decline in abstinence during the same period. Taken together, these findings suggest that pharmacotherapy alone is insufficient and that the benefits of extended therapy with NRT may

depend on ongoing behavioral support and attempts to reengage continuing or relapsed smokers in new cessation attempts.

In our study, both long-term NRT and standard smoking cessation resulted in comparable levels of "harm reduction," even among patients who had not quit smoking. In the 2 study arms, persistent smokers reported similar reductions of 62% to 66% in CPD, 30% to 39% in expired CO, and 19% to 30% in NNAL excretion, respectively; all these changes were statistically significant. These findings suggest that over the course of the study, even if participants didn't quit, both groups reduced their cigarette consumption; but long-term treatment with NRT was not the major factor in achieving these reductions. This is consistent with evidence that addiction-related factors (eg, sensory and environmental stimuli) other than nicotine play a major role in cigarette dependence in patients with COPD.[64] These findings are also consistent with a recent cross-sectional study that showed that, as long as smokers were still smoking, concomitant use of e-cigarettes or NRT was not associated with reductions in carcinogen or toxin exposure.[65] As seen in other studies, the reductions in CPD in our study exceeded the reductions in biological markers of cigarette exposure.[66,67] Nevertheless, the reductions seen in both groups of continuing smokers may be clinically significant.

Reductions of 50% or more in CPD have been linked to improvements in both cardiovascular risk factors and respiratory symptoms.[67] Reductions in smoking may also serve as a bridge to future quit attempts and ultimate cessation.[16]

Implementation of Study Results

Our study highlights critical steps for implementing smoking cessation activities among smokers with COPD, including steps to identify and recruit patients and deliver the intervention. We took advantage of queries of electronic health records, which provided lists of patients with COPD along with their smoking status. These lists allowed us to reach out to smokers through both direct mailings and follow-up telephone calls. Our Patient Advisory Board provided guidance on issues that they felt would be most critical to participant recruitment, including messages about free nicotine replacement therapy and messages that participants did not need to be immediately ready to quit. This type of population-based outreach is emblematic of strategies promoted as part of meaningful use of electronic health records and is now included

as part of the Merit-based Incentive Payment System.[68]

The delivery of both the "standard" smoking cessation intervention and LT-NRT took advantage of both face-to-face and telephone-based counseling sessions. Counseling protocols were largely designed to emulate existing cessation counseling services provided by telephone quitlines, but with greater emphasis on NRT adherence and troubleshooting problems with NRT and, in the LT-NRT arm, less emphasis on a specific quit date. In addition to the details provided in the methods section, counseling protocols, medication protocols, and tips from participants are available at www.kumc.edu/ukb. Participants engaged in approximately 90% of the counseling sessions, a rate of counseling adherence that exceeds that seen in many other smoking cessation trials and is much higher than that seen with telephone quitline interventions.[69] This high rate of participation may reflect the integrated approach to smoking cessation used in this study, in which smoking cessation pharmacotherapy was integrated with both face-to-face and telephone counseling. While this integrated approach is not commonly employed by most health care providers, many insurers now provide reimbursement for face-to-face counseling and cessation pharmacotherapy.[70] Of note, current reimbursement of NRT does not make provisions for combination therapy, and at a maximum dose of 21 mg/day does not provide nicotine replacement at levels consumed by many heavy smokers,[71] including many participants in this study.

Generalizability

Our study was conducted among a group of patients who continued to smoke despite their COPD diagnosis. As a group they had a high burden of symptoms from their COPD and were heavily dependent on nicotine. Only 20% of participants were employed.

The study was geographically isolated to a single region of the United States but included a broad diversity of patients with COPD. One in 3 participants were from underrepresented minority groups, 60% were women, and patients had wide variability in the extent of their respiratory impairment. This study, however, relied on volunteers willing to participate in a research study and may not be generalizable to less motivated smokers with COPD. Although we tried to recruit the full spectrum of smokers, the nature of a randomized controlled study

may substantially reduce participation by unmotivated smokers and smokers not immediately willing to make a quit attempt. Indeed, most smokers in the SSC group took advantage of the offer of NRT and set a quit date, suggesting a much higher motivation to quit than that seen in the community at large. Study findings might be different in a less motivated group of smokers; if so, the small proportion of unmotivated smokers in this study would have reduced the power of this study to detect such differences.

Subpopulation Considerations

Per our a priori analytic plan, we used classification and regression tree analyses to identify subpopulations that might experience better or worse outcomes or might respond to the treatment differently. We analyzed a variety of different outcomes, including abstinence at month 12, 6-month sustained abstinence, and COPD-related hospitalizations. For continuing smokers, we looked at reduction in NNAL exposure and exhaled CO. We looked at the influence of a variety of patient characteristics on these outcomes, including demographic and smoking characteristics, severity of COPD, and psychiatric comorbidities. While older smokers were much more likely to be abstinent at 12 months (Figure 2), there was no interaction between age and treatment allocation. None of the other CART analyses identified major subcategories with differential response rates. The overall low rate of cessation reduced this study's power to detect major differences among subpopulations.

Study Limitations

Our study had several limitations. Our groups differed at baseline in the prevalence of home smoking restrictions and in the frequency of COPD exacerbations during the past year, but adjustment for these differences had no impact on the study findings. Based on input from our Patient and Stakeholder Advisory Boards, we included patients with clinically diagnosed COPD regardless of their spirometry. Almost 40% of patients included in this study did not meet criteria for COPD based on spirometry. These patients did, however, have a high level of respiratory symptoms as has been seen in other smokers with normal spirometry,[72] and we think it is unlikely that strict adherence to spirometry as an inclusion criterion would have

affected the study's results.

Based on self-report, there was substantial crossover between the 2 treatment arms. While 61.4% of the patients randomized to LT-NRT reported that they were adherent to daily NRT at 12 months, 15.1% of those in the SSC arm reported regular NRT use even though it was not part of their designated treatment regimen. This crossover in the intervention may have diminished our ability to identify a treatment effect. Our assessments of NRT use were based on self-report; since participants were still smoking, we could not objectively verify their use of NRT through biochemical assessments. The intensity of treatment in the SSC group may have exceeded the intensity typically offered in clinical practice and may have further limited our ability to detect an impact from LT-NRT. Loss to follow-up could have had a small impact on our study findings, but loss to follow-up was comparable in the 2 treatment arms and overall was less than 7%. The overall low rate of smoking cessation in the study limited our ability to identify differential treatment effects across subpopulations.

Future Research

Impact of altering the decisional context on the reach of smoking cessation efforts. In terms of efficacy, our study demonstrated similar smoking cessation and harm reduction from traditional approaches to smoking cessation and long-term nicotine replacement. Our study, however, only compared the reach of these 2 approaches among smokers with COPD committed enough to take part in a 1-year, longitudinal study. It is still not clear how routinely offering NRT, regardless of willingness to quit, might affect the potential reach of smoking cessation.

Impact of repeated invitations for smoking cessation. Our study compared long-term NRT versus a single, supported attempt at smoking cessation. While the long-term NRT group received ongoing support over 9 months to promote adherence to NRT and guide them in a "reduce to quit" approach, the smoking cessation group received only a single 10- week intervention. Prior work by our group suggests that repeated interventions over the course of 2 years can result in progressively more smokers quitting[47] and that the impact of repeated pharmacotherapy-guided quit attempts may not diminish over time.[73] Future research could

examine the impact of repeated interventions for smoking cessation in COPD or examine the impact of modifying therapy after an initial treatment failure.

Altering the modality of treatment. We chose to use combination NRT in this study based on patient concerns about varenicline and data suggesting rates of cessation that are comparable to those seen with varenicline.[74] Treatment with varenicline has been associated with higher rates of cessation than the nicotine patch alone,[74,75] including among patients with COPD.[8] Varenicline may be particularly effective in rapid metabolizers of nicotine.[76] It may also be more effective in reducing reinforcement from cigarettes and result in higher rates of delayed cessation.[63]

E-cigarettes may also provide an alternative modality for cessation. Although the data about their efficacy are limited, many of the smokers in our study had tried e-cigarettes on their own, and members of our Patient Advisory Board were very interested in whether they might be helpful for them. New control by the FDA over e-cigarettes should enable higher-quality studies on the efficacy of these devices for smoking cessation. Observational studies, however, suggest that unless smokers quit completely, e-cigarettes may not result in meaningful harm reduction.[65]

H. CONCLUSIONS

In this appropriately powered, randomized clinical trial with low attrition to follow- up, conducted in accordance with PCORI methodologic standards, long-term nicotine replacement therapy did not provide any advantages over a traditional smoking cessation program for either smoking cessation or harm reduction among smokers with COPD. Both interventions led to modest rates of smoking cessation, improvements in respiratory symptoms, and reductions in smoke exposure among participants who did not quit. Since the traditional smoking cessation intervention has a shorter treatment duration and fewer side effects, it appears to be the preferred treatment for smokers ready to quit. Long-term NRT can lead to rates of cessation comparable to traditional smoking cessation programs and could provide an alternative option for smokers—an option that might be most appealing to smokers who are not immediately willing to make a quit attempt.

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