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A Randomized Clinical Trial of Counseling and Nicotine Replacement Therapy for Treatment of African American Non-Daily Smokers: Design, Accrual, and Baseline Characteristics

Nicole L. Nollen,
Department of Preventive Medicine and Public Health, University of Kansas School of Medicine, Kansas City, Kansas

Lisa Sanderson Cox,
Department of Preventive Medicine and Public Health, University of Kansas School of Medicine, Kansas City, Kansas, lcox@kumc.edu

Matthew S. Mayo,
Department of Biostatistics, University of Kansas School of Medicine, Kansas City, Kansas, mmayo@kumc.edu

Edward F. Ellerbeck,
Department of Preventive Medicine and Public Health, University of Kansas School of Medicine, Kansas City, Kansas, eellerbe@kumc.edu

Sheshadri Madhusudhana, and
Department of Hematology/Oncology, Truman Medical Center, Kansas City, Missouri, sheshadri.madhusudhana@tmcmed.org

Jasjit S. Ahluwalia
Department of Behavioral and Social Sciences, Brown University, Providence, Rhode Island, jasjit_ahluwalia@brown.edu

Abstract

BACKGROUND: Non-daily smokers (NDS) who smoke on some but not all days are a growing subset of United States (US) tobacco users. Racial/ethnic minorities are more likely to be NDS.

CORRESPONDING AUTHOR: Nicole L. Nollen, Department of Preventive Medicine and Public Health, University of Kansas School of Medicine, 3901 Rainbow Boulevard, Mail Stop 1008, Kansas City, Kansas, 66160, 913-588-3784, nnollen@kumc.edu.

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TRIAL STATUS
The final participant was enrolled in May 2017. The active treatment and follow-up phases are ongoing, with the final week 26 follow-up visit scheduled for January 2018. Outcomes data have not been examined and will not be available until December 2018.

COMPETING INTERESTS
None to report

African American NDS have strikingly high levels of nicotine and carcinogen exposure, making treatment of this high risk group a priority.

METHODS: The current study is one of three ongoing federally-funded clinical trials of NDS and, to our knowledge the only RCT focused on racial/ethnic minority NDS. The design has been guided by input from Patient and Stakeholder Advisory Panels who helped develop the research questions, design the intervention, and select the outcomes. The objective is to compare the effectiveness of smoking cessation counseling alone (C) or smoking cessation counseling plus participant's choice of nicotine replacement therapy (NRT; C+NRT) for African American NDS. Two-hundred seventy-eight African American NDS will be randomized in a 2:1 fashion to C+NRT or C. All participants receive five sessions of smoking cessation counseling; those randomized to C+NRT receive their choice of nicotine gum, patch, and/or lozenge. Treatment in both groups lasts for 12 weeks. We hypothesize that C+NRT will be more effective than C on the primary outcome of biochemically-confirmed abstinence from smoking at week 12. Secondary aims will compare C +NRT and C on patient- and provider-desired outcomes including abstinence from smoking at week 26, change in biochemically-verified nicotine and carcinogen exposure, days abstinent, and treatment process measures (e.g., NRT use and side effects). Predictors of abstinence will also be explored.

DISCUSSION: Findings will illuminate effective treatment options for African American NDS and contribute to development of evidence-based guidelines for treating the 8.9 million US adult NDS for whom no guidelines currently exist.

Keywords

Non-daily smokers; African American; smoking cessation; nicotine replacement therapy; smoking cessation behavioral counseling

1. Introduction

Non-daily smokers (NDS) report smoking on some but not all days and constitute 8.9 million adults or 24.3% of all adult smokers in the US [1]. Prevalence of NDS has increased almost 30% in the last decade. NDS are at risk for the same health consequences of smoking as daily smokers (DS) [2, 3], are nicotine dependent [4], and want to quit smoking [5], yet they are overlooked by health care providers and largely have been excluded from clinical trials. As a result, there is an almost complete paucity of information on effective treatments for this growing subgroup of smokers whose smoking patterns challenge traditional nicotine dependence treatment paradigms [5, 6]. NDS average 15–20 smoking days per month and routinely abstain for periods of 5–10 days without experiencing significant withdrawal or craving [7, 8], contributing to perceptions that NDS do not identify as smokers, are uninterested in quitting, are not addicted enough to warrant the use of smoking cessation medications, and concern that, if nicotine replacement therapy (NRT) is used, the amount of nicotine delivered could exceed the levels achieved through smoking [4, 6, 8]. These perceptions are not supported by the literature [6, 9, 10]; nonetheless, NDS are less likely than DS to be asked about their smoking status or advised to quit by a physician, have low utilization of smoking cessation pharmacotherapy or behavioral counseling, and experience

difficulty in quitting; 73–82% of NDS who attempt to quit resume smoking within 90 days [5].

Racial/ethnic minorities are more likely to be NDS compared to non-Hispanic Whites (Whites) yet they bear a disproportionate burden of smoking-related diseases [11–13]. African Americans, in particular, have higher cardiovascular and cancer-disease risk at lower levels of smoking, including non-daily smoking [14, 15]. Concentrations of NNAL, a metabolite of the potent lung carcinogen NNK, and cotinine, the primary metabolite of nicotine, are three to six times higher in African American NDS compared to White and Hispanic/Latino NDS [16, 17]. This difference persists after adjustment for racial/ethnic variations in smoking level and nicotine metabolism, suggesting that African American NDS incur substantial risk from their intermittent pattern of smoking. African American NDS are also more likely than White and Hispanic/Latino NDS to have made a quit attempt in the past year and to intend to quit in the next 30 days [7], making the treatment of this high risk group a priority.

To date, only two small pilot studies have examined treatment of NDS [18, 19]. The current study is one of three ongoing federally-funded (NIH, PCORI) smoking cessation randomized clinical trials (RCT) examining effective treatments for NDS and the only RCT focused exclusively on racial/ethnic minority NDS. The 3-year study is comparing the effectiveness of smoking cessation counseling alone or smoking cessation counseling in combination with participant's choice of NRT (i.e., nicotine patch, gum, lozenge) on abstinence in African American NDS interested in quitting. The primary aim is to test the hypothesis that 1) African American NDS randomized to C+NRT will have significantly higher biochemically verified smoking abstinence at 12 weeks (end of treatment) than African American NDS randomized to C. Secondary aims are: (2) test the hypothesis that African American NDS randomized to C+NRT will have significantly higher biochemically verified smoking abstinence at 26 weeks (end of follow-up) than African American NDS randomized to C, (3) test the hypothesis that AA NDS randomized to C+NRT will demonstrate significantly greater reductions in nicotine intake and carcinogen exposure and significantly more days abstinent, while experiencing no differences in side effects as participants randomized to C, and (4) identify predictors of successful quitting among African American NDS. Due to the exploratory nature of this aim, no specific hypotheses are proposed for this aim. This paper describes the study design, enrollment, and baseline characteristics of participants in the trial.

2. Methods

2.1. Study design.

The study is an unblinded and open-label RCT of 278 African American NDS randomized to receive either 5 sessions of smoking cessation counseling in combination with 12 weeks of their choice of nicotine patch, gum, or lozenge (C+NRT) or 5 sessions of smoking cessation counseling alone (C). A 2:1 randomization schema was used; for every one patient randomized to C, two were randomized to C+NRT. The schedule of enrollment, intervention, and assessment activities is displayed in Table 1. The primary outcome is biologically-confirmed 30-day point prevalence abstinence (PPA) from smoking at week 12.

All study visits will be completed at the University of Kansas Medical Center or Swope Health Central, a Federally Qualified Health Center that serves a predominately African American clientele. Study procedures are approved and monitored by the University of Kansas Medical Center (KUMC) IRB (#00001602).

2.1. Patient and stakeholder engagement and study design rationale.

The design of this study has been guided by input from Patient and Stakeholder Advisory Panels comprised of nine African American NDS, two physicians serving a predominately African American patient population, and two experts from Optum (formerly Alere), one of the nation's largest provider of cessation quit line services (http://map.naquitline.org/reports/administration/). The panels helped develop the research questions, design the intervention, and select the outcomes. For example, participants receive a choice of nicotine patch, gum, or lozenge because these are the medications that were preferred by our Patient and Stakeholder Advisory Panels. A counseling only control group was chosen because the providers on our Stakeholder Advisory Panel felt uncertain about whether pharmacotherapy conferred any benefits beyond those provided by counseling alone. This is consistent with literature suggesting that NDS, who are more likely to smoke because of the behavioral components of nicotine addiction (e.g., stimuli/cues, positive reinforcing effects) rather than to maintain blood nicotine levels, might benefit more from behavioral counseling focused on management of smoking cues/triggers than pharmacological approaches that replace nicotine in order to reduce withdrawal and craving [4, 18–20]. While our primary outcome, biochemically-confirmed abstinence from smoking, is the scientific 'gold standard,' our Patient and Stakeholder Advisory Panels noted other important outcomes of interest. The Patient Advisory Panel was particularly interested in harm reduction outcomes, including reductions in nicotine intake and carcinogen exposure and number of days abstinent. The Stakeholder Advisory Panel was interested in these harm reduction outcomes in addition to side effects and use of NRT in the intervention group.

The panels reviewed and approved the counseling protocol, quit smoking guide, NRT dosing criteria, recruitment materials, and surveys prior to initiation of the clinical trial. Ongoing input from the Patient Advisory Panel helps guide recruitment and retention strategies, interpretation of findings, and dissemination plans, particularly for reaching a broader, non-academic audience.

2.2. Recruitment.

Recruitment started in May 2015 and ended in May 2017. Final 6-month follow-up will be completed in January 2018. Participants are recruited through clinic- and community-based efforts, including fliers, physician letters, in-clinic recruitment, radio, television, and social media ads, and word-of- mouth referrals from current and former participants.

2.3. Eligibility.

Eligible participants are non-Hispanic African American adults (≥ 18 years) who had smoked at least 100 lifetime cigarettes and met criteria for NDS, defined as smoking cigarettes on 4–27 of the last 30 days and smoking at the current non-daily rate for ≥ 3 months [21]. Individuals are excluded if they are a daily user of non-cigarette tobacco

products, have engaged in a pharmacotherapy-assisted quit attempt in the last 30 days, or are uninterested in quitting smoking, taking NRT, refraining from the use of electronic cigarettes or smoking cessation pharmacotherapy, and completing study-related requirements. Individuals with medical contraindications to NRT, including being pregnant or breastfeeding and having a cardiovascular event (i.e., heart attack, angina, arrhythmia, chest pain) in the past 30 days are also excluded; women must be willing to use birth control to avoid pregnancy while taking NRT. Use of non-cigarette tobacco products (e.g., cigarillos, little cigars) are common among NDS, [8, 22, 23] ; users of these products are included in the study as long as they are not daily users (i.e., ≥ 28 days in the past 30) of non-cigarette tobacco products.

2.4. Screening and Consent.

Interested individuals contact us by telephone and are screened for eligibility by study staff. Those who are provisionally eligible after the phone screening are scheduled for final, in-person eligibility screening, which consists of pregnancy testing and collection of urine for baseline assessment of nicotine biomarkers. Individuals who are eligible following final, in-person screening participate in a consenting interview conducted by study staff. Those providing written informed consent are enrolled into the study, randomized, and immediately participate in baseline (Week 0) activities (described below).

2.5. Intervention

2.5.1. Counseling (C and C+NRT).—Participants receive five smoking cessation counseling sessions in person at Weeks 0 (baseline) and by phone at Weeks 1, 4, 8, and 10. The counseling protocol is evidence-based [24–26], individualized and culturally-specific. It was developed by our team over 20 years in collaboration with an African American community advisory board and African American former study participants [27] and has been found to be superior for African American smokers in head-to-head comparisons with other counseling approaches (i.e., motivational interviewing, brief advice) [28, 29]. The goals of counseling are to increase knowledge, including information particularly relevant to African Americans, develop individualized behavioral and cognitive skills related to cessation, and provide intra-treatment social support. For the current study, counseling is tailored to meet the needs of NDS and, therefore, focuses heavily on managing smoking cues, triggers, and the acute positive reinforcing effects of smoking in addition to dealing with nicotine withdrawal and craving. Skills include strategies to address smoking triggers (e.g., avoidance of social situations that trigger smoking, coping responses to address withdrawal/craving), reduce cue-smoking contingencies (e.g., alcohol, marijuana), manage stress and negative affect, and increase self-efficacy. Our approach is intentionally flexible to match the needs of each participant over the course of behavior change. Counseling goes hand-in-hand with a 40-page culturally-targeted quit smoking guide, used in our previous trials with African American smokers [28, 30, 31]. For the purposes of rapport and continuity of care, participants meet with the same counselor each session. Counseling is delivered by our experienced staffs who are certified tobacco treatment specialists, have extensive experience treating African American smokers within clinical trials, and are active members of the community. The baseline session lasts 30 minutes, on average, with follow-

up sessions averaging 15 minutes. Counseling fidelity is monitored by a licensed psychologist during bimonthly counseling supervision meetings.

2.5.2. Written materials (C and C+NRT).—Participants receive a 40-page stop smoking guide at baseline. The guide has been designed to go hand-in-hand with the counseling and includes information on the health consequences of tobacco use, benefits of quitting, strategies to promote abstinence such as making a quit plan, obtaining social support, identifying reasons for smoking and activities that could take the place of smoking, strategies for dealing with urges, managing withdrawal and craving, coping with a lapse, and relapse prevention. The guide for participants randomized to C+NRT includes an additional section on NRT that addresses choosing the right NRT, adjusting the dose, and managing side effects.

2.5.3. Nicotine replacement therapy (C+NRT).—Participants randomized to C+NRT are given a choice of nicotine gum, patch, or lozenge. To facilitate choice, participants are instructed on the proper use of gum, patch, and lozenge at baseline (Week 0) and sent home with a 3-day trial of each. Participants select their NRT during the Week 1 counseling phone call and a 4-week supply is immediately shipped. The target quit day for both groups is set at 2-weeks post-baseline to allow time for participants in both arms to properly prepare for their quit day and for participants in C+NRT to select, receive, and begin using their NRT. Refills of NRT are provided at Weeks 4 and 8. NRT treatment lasts 12 weeks.

Dosing NRT for NDS.: Current NRT dosing recommendations do not fully capture the needs of NDS whose natural smoking patterns include days of abstinence and variability in the amount of tobacco consumed on the days that they do smoke [24, 32]. To address these unique challenges, 30-day Timeline Follow Back (TLFB) methods are used to dose medication. Participants are asked to recall the amount and type of tobacco consumed each day for the past 30 days [33, 34]. NRT is dosed based on the number of tobacco products used on the highest smoking day using an algorithm that assumes that African Americans extract ~30% more nicotine per cigarette smoked, have higher blood cotinine levels at lower levels of smoking [35, 36], and have been under dosed on NRT in previous studies that used standard dosing guidelines [28, 37].

For participants selecting nicotine patch, our algorithm results in an initial recommendation of 7 mg patch for those smoking ≤ 5 tobacco products on their highest smoking day, 14 mg patch and ad lib nicotine gum or lozenge for those smoking 6–10 tobacco products, and 21 mg patch and ad lib nicotine gum or lozenge for those smoking ≥ 11 tobacco products. For participants selecting gum or lozenge, we use the general recommendation of 1 piece every 3–4 hours for those smoking ≤ 5 tobacco products on their highest smoking day, 1 piece every 2–3 hours for those smoking 6–10 tobacco products, and 1 piece every 1–2 hours for those smoking ≥ 11 tobacco products on their highest smoking day. Gum and lozenge are provided in 4 mg formulation. Participants who smoke 3–7 days of the week are encouraged to use NRT daily, even on non-smoking days. Those smoking 1–2 days per week are encouraged to use NRT only on the days that they smoked; however, those smoking 1–2 days per week but who report craving or withdrawal on non-smoking days are encouraged to use NRT daily. Response to NRT is monitored at Weeks 4 and 8; dosing recommendations

and/or the medication(s) being used are modified, as needed, based on response to therapy and participant choice.

2.6. Retention.

Study staff contact participants one week prior to each study visit via phone, text, email and postcards. For any missed session, participants receive up to 6 additional contacts to facilitate rescheduling. Participants are compensated $40 at Weeks 0 and 12 and $20 at Weeks 1, 4, 8, 10, and 26 for their time. Remuneration is based on visit attendance and not on smoking status. Participants are eligible to receive an additional $60 for referring up to 3 friends who were eligible and enrolled in the study.

2.7. Outcomes Measures

2.7.1. Smoking abstinence.—The primary outcome is anabasine- and anatabine-verified 30-day PPA from smoking, defined as no tobacco products for the previous 30 days at Week 12. Anabasine and anatabine are tobacco alkaloids that represent the gold standard for confirming abstinence when cotinine measurements are invalid (i.e., detectable levels of cotinine reflect NRT use, smoking, or both) [38]. The recommended cut-off of 2 ng/ml will be used to differentiate smokers from non-smokers (considered a non-smoker if both alkaloids are < 2 ng/ml) [38]. The secondary endpoint is cotinine-verified 30-day PPA from smoking at Week 26. The recommended cut-off of 50 ng/ml will be used to differentiate smokers from non-smokers [39]. The longer 30-day PPA time frame is being used because the more customary 7-day PPA time frame could reflect normal variations in smoking and abstinence for NDS.

2.7.2. Nicotine exposure.—Nicotine exposure is assessed via urinary cotinine levels measured at Weeks 0 and 26 [40].

2.7.3. Carcinogen exposure.—Carcinogen exposure is assessed via urinary levels of the NNK metabolite 4-(methynitrosamino) -1-(3) pyridyle-1-butanol[NNAL] at Weeks 0 and 12. NNK is a tobacco-specific nitrosamine that is widely considered to be one of the most important causative agents in the development of lung cancer [41]. NNK is metabolized into NNAL, which can be measured in the urine and is used to indicate tobacco-specific exposure to this potent lung carcinogen.

2.7.4. Days abstinent.—Participants are asked to recall the number of cigarettes, hand rolled cigarettes, little cigars, cigarillos, full size cigars, blunts, pipes, bidis, smokeless tobacco, and hookah used for each of the past 30 days at Weeks 4, 8, and 12 [33, 34]. The total number of tobacco free days will be summarized from this data.

2.7.5. Treatment-related side effects.—Participants are asked about symptoms commonly associated with quitting smoking and/or NRT (e.g., nausea, trouble sleeping, skin or mouth irritation) at Weeks 0, 4, 8, and 12 using a standardized symptoms checklist [42–45].

2.8. Covariates

Little is known about African American NDS, therefore, an extensive survey battery is being used to adequately characterize and describe demographic characteristics, smoking patterns and behaviors, and comorbid conditions among this population and to examine how these factors impact abstinence.

2.8.1. Demographics.—Baseline demographic measures include participant age, gender, marital/partner status, employment and housing status, educational level, health care coverage [46], income [47], perceived health [48], height, weight, and body mass index [49].

2.8.2. Smoking, tobacco use, and quitting history.—Baseline assessment of smoking history includes amount of cigarettes smoked (days smoked in last 30 and number of cigarettes on days smoked), type of cigarette smoked (menthol versus non-menthol), use of non-cigarette tobacco products [33, 34], NDS type [i.e., formerly a daily smoker (converted) or always a NDS (native)] [8, 50], age when started smoking regularly [51], reasons for smoking some but not all days [21, 52], identity as a smoker [8], smoking triggers [21, 52], time to the first cigarette of the day (a marker of nicotine dependence) [53], dependence motives [54], nicotine withdrawal [55], and craving [56].

2.8.3. Social influences on smoking.—Baseline assessment of social influences on smoking includes the extent to which one smokes socially or alone [20], number of five best friends or family who smoke, number of smokers in the home, and partner smoking status [57].

2.8.4. Quitting history.—Baseline assessment of quitting history includes number of 24 hour quit attempts in the past year, length of the longest quit attempt, and previous use of behavioral and/or pharmacological quitting aids [5, 51].

2.8.5. Comorbid mental health and substance use.—Baseline assessment of comorbid mental health and substance use includes symptoms of depression [58], alcohol misuse [59], and past 30 day use of marijuana and prescription pain relievers (mostly opioids) [60].

2.8.6. Treatment process.—The number of counseling sessions completed will be summarized for participants in both groups. For those in C+NRT, data on the medication(s) dispensed is captured at Weeks 1, 4, and 8 and participants are asked about the amount of NRT used each day for the past 30 days at Weeks 4, 8, and 12.

2.9. Data analysis

2.9.1. Sample size justification.—The primary outcome is biochemically-confirmed 30-day PPA at Week 12. Because this is the first smoking cessation intervention study with AA NDS, our sample size estimates are based on data from randomized trials of AA low level DS [24, 31, 61, 62]. Based on these studies we postulate a 10% PPA rate in the C group and a 25% PPA in the C+NRT group. The current sample size of 93 in C and 185 in C+NRT provides 91% power to detect a difference in cessation with a type I error rate of 0.05 using

a two-sample, two-tailed Chi-square test. If the difference between treatment and control groups is smaller than hypothesized (e.g., 10% abstinence in the control group versus 22% abstinence in the treatment group), we will have 78% power to detect these differences with a sample size of 278.

2.9.2. Missing Data.—All primary analyses on smoking cessation will be conducted using intent-to-treat and will code those lost to follow-up as smokers per the Russell Standard [63]. Subsequently we will evaluate the missing data pattern. If there is a differential loss based upon group, multiple imputation techniques will also be used. All 278 participants will be included in analyses of smoking outcomes. We also will look at completers only.

2.9.3. Statistical analyses for Aim 1: Smoking abstinence.—The chi-square test will be used to compare the verified abstinence rates at Week 12 (primary endpoint) and Week 26 (secondary endpoint) between C and C+NRT. For our primary comparison, those lost to follow-up will be considered as smokers. We also will look at completers only and will utilize multiple imputation techniques to ensure valid comparisons between the C and C +NRT if the loss to follow-up is related to treatment. Secondarily, we will utilize Generalize Estimating Equation methodology to longitudinally compare verified abstinence over time.

2.9.4. Statistical analyses for Aim 2: Nicotine and carcinogen exposure, days abstinent, and treatment-related side effects.—We will utilize linear mixed models to longitudinally compare nicotine (Week 0 to 26) and carcinogen exposure (Week 0 to 12) between C and C+NRT and then subsequently examine the effects of the covariates (Table 2) using a best subsets selection method for both nicotine and carcinogen exposure independently. A generalized linear mixed model approach will be used to model days abstinent, controlling for number of days in study, to assess the effect of treatment on this endpoint. We will compare the prevalence of any side effect as well as each specific side effect, from baseline to week 12, between the two groups using the chi-square test. If there is a global difference, we will examine, within the NRT group, if type of NRT impacts the side effect profile. Within the NRT group, we will descriptively summarize the number and percent of subjects who choose each type of NRT. Subsequently, we will describe and descriptively compare the percent of subjects within each of these subgroups who use the NRT of choice during the treatment period (i.e., percent of patients within the patch, gum, and lozenge groups who used the medication) and the relationship between adherence to NRT and initial NRT choice.

2.9.5. Statistical analysis for Aim 3: Identify predictors of abstinence.—Assuming the expected treatment effect, we will descriptively examine the cessation rate within the C+NRT group by choice of NRT. Within the C+NRT treatment group, we will examine the effect of C+NRT use over the first 12 weeks on verified cessation using logistic regression. We will then examine the effects of the covariates on this endpoint by utilizing best subsets selection techniques. Our goal is to identify a final model utilizing the smallest subset of covariates that describes cessation over the length of the study. Our analysis for this study will be limited to main effect predictors of abstinence due to the 2:1

randomization schema and the hypothesized cessation rates by group (i.e., limited number of quitters), which make it implausible to examine the interaction of factors with treatment.

2.9.6. Analyses for the current paper.—In this paper we provide descriptive summaries of baseline (Week 0) demographic, smoking, and comorbid mental health and substance use characteristics using frequencies and percentages for categorical variables and means and standard deviations for quantitative variables. Future manuscripts will present findings on primary and secondary outcomes.

3. Results

3.1. Recruitment flow.

The flow of participants into the study is shown in Figure 1. Six-hundred and twenty-five African Americans initially identified as NDS out of 2,528 African American smokers (24.7%) who were pre-screened as part of enrollment for this study and another ongoing study of African American *daily* smokers (data not shown). Of these, 63 (10.0%) were excluded after more in-depth screening indicated that they did not meet study criteria for non-daily smoking (smoked cigarettes on 4–27 days per month for ≥ 3 months). In total, 22.2% (562/2,528) of African American smokers who were screened met our criteria for non-daily smoking. Of these, 553 met the other phone screen eligibility criteria but 249 (45.1%) did not keep their appointment to complete final, in-person, eligibility screening. Of the 304 who completed in-person eligibility screening, 279 were randomized, 185 to C +NRT and 94 to C. A protocol violation (i.e., randomized not according to code) resulted in one participant being removed, bringing the final sample size to 185 C+NRT and 93 C.

3.2. Baseline characteristics.

Baseline characteristics overall and by study group are displayed in Table 3. Per CONSORT guidelines for the reporting of RCT, baseline differences between groups are not statistically compared [64] but, as can be seen, groups are comparable on most factors. A nearly equal proportion of men and women enrolled. The majority of participants are of lower socioeconomic status, as indicated by income, poverty level, employment status, and home ownership, and of good to fair perceived health. Participants smoke cigarettes an average of 10.6 (3.9) days per month, use 4.7 (3.5) cigarettes on the days smoked, and have been NDS for an average of 7.0 (9.9) years. The majority are former DS and indicate trying to cut back or quit as one of the primary reasons for smoking non-daily. Participants have tried to quit an average of 6.8 times (SD=24.7) in the past year; 56.5% have used quitting aids. Other non-cigarette tobacco products are used by about one-third of participants; although use is infrequent (1.9 products used an average of 4.7 days per month). Almost half smoke their first cigarette of the day after 30 minutes of waking, indicating less nicotine dependence, and have withdrawal and craving scores in the low to moderate range. They are more likely to smoke because of primary (e.g., to relieve withdrawal, craving, and because of tolerance) versus secondary (e.g., social cues/contexts, weight control, mood enhancement) dependence motives. One-third smoke mainly with others versus alone and most have a social network comprised of smokers. Use of other substances is high; nearly 50% meet criteria for alcohol misuse, 28.4% used marijuana in the past month, and almost 40% used

prescription pain relievers in the past month. Finally, almost one-quarter screened positive for depressive symptoms.

4. Discussion

A number of observations from the current study are worth noting to inform future cessation intervention studies with NDS. Nearly one-quarter of individuals screened met our NDS criteria. This is consistent with national prevalence data and reinforces the need for ongoing treatment studies with this growing subpopulation of smokers [1]. However, almost half of NDS who met our initial screening criteria did not keep their in-person appointment, possibly reflecting lower identity as a smoker and ambivalence about quitting smoking among this group [65]. As a result, we screened 2,528 people in order to randomize 278 NDS. We conservatively estimated accruing 20 participants per month into the study but our actual accrual rate was slower, averaging 11–12 participants per month. The large numbers of participants needing to be screened to meet recruitment goals (i.e., percent screened to enrolled ratio was 10.9% in the current study) and potentially slow accrual are factors that should be considered when designing and implementing cessation trials with NDS.

Characteristics of the current sample influence how abstinence is operationalized among NDS, as well as targets for intervention. Participants smoked an average of 10 of the last 30 days, which is within the range reported in other NDS studies [7, 8]. Cessation trials commonly use self-reported 7-day PPA from smoking as the standard for taking samples for biochemical verification of smoking status [39]. However, because NDS often abstain for seven days or more as part of their regular smoking pattern [7, 8, 12], longer periods of PPA should be used to confirm a NDS as quit; we used 30-day PPA in the current study. Similarly, one-third of NDS in the current study used non-cigarette tobacco products in the past 30 days. Use of non-cigarette tobacco products has grown exponentially in the US over the last two decades [66, 67] and is higher among NDS than DS [22]. Investigators working with NDS must decide if the goal is to achieve abstinence from all tobacco products or only cigarettes. All tobacco products are associated with harmful health effects [68, 69 , 70–73] and, therefore, we opted to achieve abstinence from all tobacco products, although it is a more conservative approach that may result in fewer quitters [74]. Alternatively, investigators could exclude poly-tobacco users but this limits generalizability to the larger population of NDS. The high rates of alcohol, marijuana, and prescription pain reliever use in this study are also striking but reflect growing national trends among smokers of all levels [3, 8, 75–78]. Other substance use often serves as triggers/cues to smoke, are commonly used in conjunction with tobacco to enhance the experience [79, 80] and may make quitting tobacco more difficult [75]. Our examination of these factors as predictors of abstinence will provide important information about how depression and co-use of alcohol, marijuana, and prescription pain relievers increase or decrease the odds of cessation among NDS; however, future studies with NDS should consider these factors as important targets for intervention.

Finally, the use of pharmacotherapy for NDS is an area of ongoing debate. NDS are currently conceptualized as ‘peak seekers’ who smoke because of external cues or acute positive reinforcing effects of nicotine (e.g., enhanced cognitive function, improved mood) and, therefore, behavioral counseling focused on management of external stimuli may be

ideally suited to address the primary cessation needs of these smokers [81]. This may not be true for African American NDS. African American non-daily smokers take in *more* cotinine per cigarette and have nicotine blood levels in the range of White daily smokers [16, 17], suggesting that African American NDS may be in need of nicotine replacement to succeed in quitting. NDS in this study noted more primary versus secondary dependence motives. Primary dependence motives reflect traditional reasons for smoking (i.e., to relieve withdrawal, craving, and replace nicotine) [54, 82, 83], supporting our hypothesis that NRT may lead to higher rates of quitting in this population relative to counseling alone. However, periods of routine abstinence and within-smoker variability in the amount of tobacco consumed on smoking days make the dosing of NRT complicated. Nicotine patch provides steady nicotine throughout the day at levels that might exceed what some NDS get from tobacco and, therefore, might be considered inappropriate for NDS. Ad libitum nicotine gum and lozenge provide nicotine replacement only when needed and may be better suited to the natural smoking patterns of NDS; however compliance with ad libitum products is an issue [28, 37]. For these reasons, we provide a choice of nicotine patch, gum, and lozenge among participants randomized to C+NRT and the opportunity to switch medications in order to better manage side effects, withdrawal, craving, or compliance issues. Within the C+NRT group we will examine the cessation rate by choice of NRT as well as how type of NRT impacts side effects and medication use. These data will inform the debate about how to dose NRT for NDS.

5. Summary

Non-daily smoking is an increasing pattern of tobacco consumption in the US [1], yet a paucity of information exists on effective treatments for this growing subgroup of smokers. The current study will answer important questions about the comparative effectiveness of counseling only versus counseling in combination with NRT for smoking abstinence in African American NDS. Regardless of whether our hypothesis that counseling plus NRT will be more effective than counseling alone is supported, the current study addresses concerns among providers about lack of evidence-based recommendations, particularly related to use of smoking cessation pharmacotherapy, and concerns among NDS who indicate a strong desire to quit through use of behavioral and pharmacological strategies, and will inform treatment-guidelines for NDS.

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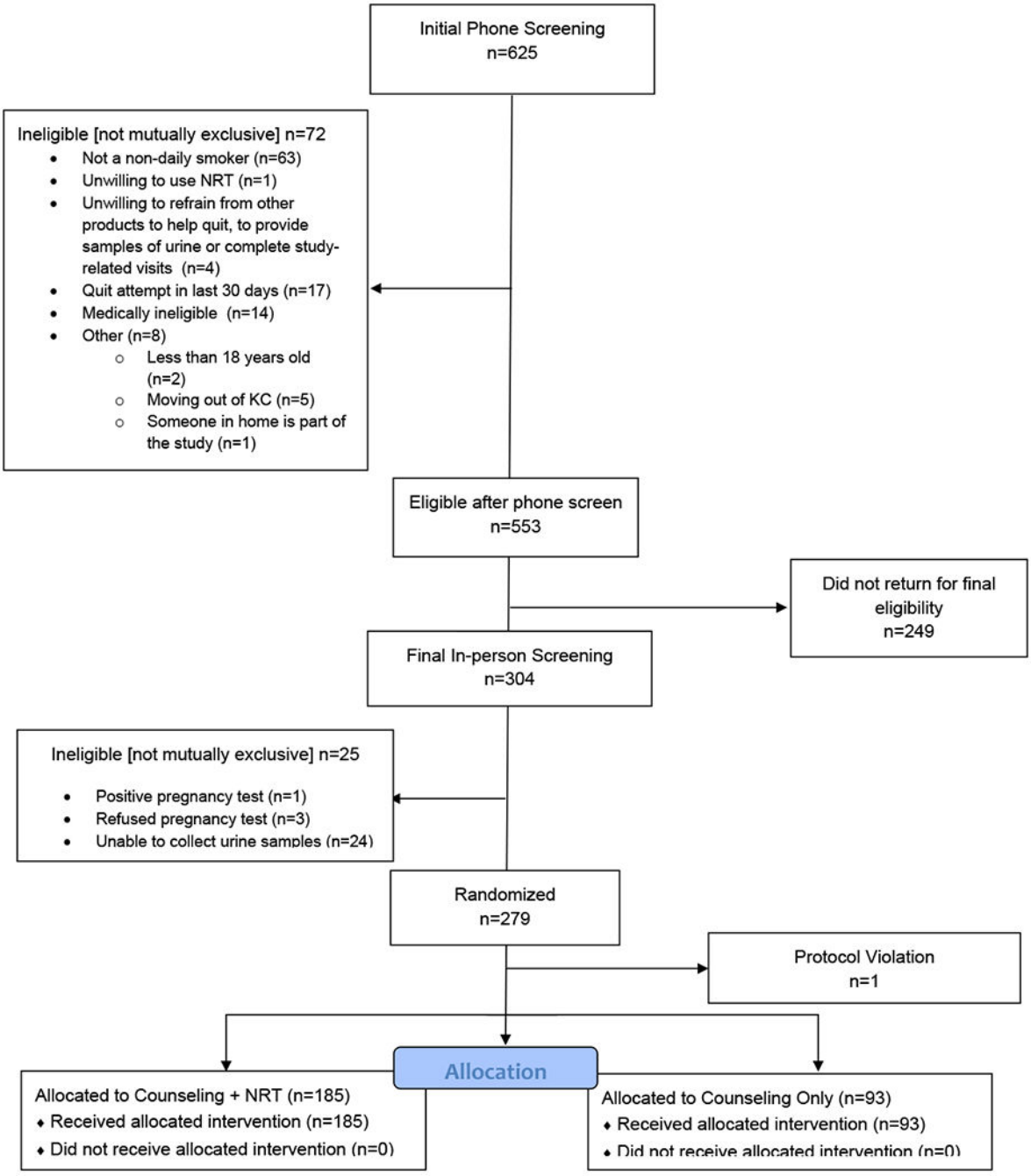

Figure 1.
Study Flow Daigram.

Table 1.

Schedule of enrollment, intervention, and assessment activities

	STUDY PERIOD							
	Screening	Enroll-ment	Follow-up Visits in Weeks					
TIMEPOINT	*-14 to -1 days prior to Wk 0*	Wk 0	*1*	*4*	*8*	*10*	*12* *End of drug*	*26* *End of Study*
ENROLLMENT:								
Eligibility phone screen	X							
Final in-person eligibility screening		X						
Informed consent		X						
Allocation[a]		X						
INTERVENTIONS:								
NRT dispensed[b]		●—	X	X	X	——	—●	
Counseling[c]		X	X	X	X	X		
ASSESSMENTS:								
Surveys[d]		X		X	X		X	X
Outcome Variable								
Anatabine/anabasine-verified quitting							X primary endpoint	
Cotinine-verified quitting								X secondary endpoint
Biological Samples								
Cotinine **(reduction in nicotine exposure)**		X						X
NNAL **(reduction in carcinogen exposure)**		X					X	

[a] Participants were randomized in a 2:1 fashion to counseling plus nicotine replacement therapy (C+NRT, n=185) or counseling only (C, n=93)

[b] A 4-week supply of participants choice of nicotine gum, patch, or lozenge was dispensed by mail at Week 1 and in-person at Weeks 4 and 8 to those randomized to C+NRT.

[c] Counseling sessions were conducted in person at Week 0 and by phone at Weeks 1, 4, 8, and 10

[d] See measures section and Table 2 for a description of each measure and the time point it was administered

Table 2.

Measures at Each Time Point[a] and Covariates to be Examined as Predictors of Outcomes

	Eligibility	Baseline Week 0	Week 1	Week 4	Week 8	Week 10	Week 12	Week 26
Smoking Abstinence Outcomes								
Anatabine/anabasine (primary)							x	
Cotinine (secondary)								x
Patient- and Provider-Centered Outcomes								
Reduction in nicotine exposure (cotinine)		x						x
Reduction in carcinogen exposure (NNAL)		x					x	
Days abstinent				x	x		x	x
Treatment-related side effects		x		x	x		x	
Demographics								
Demographics (e.g., age, gender, education, income)	x	x						
Perceived health		x						
Body mass index		x						
Smoking and Tobacco Use History								
Past 30 day use of all tobacco products		x		x	x		x	x
Menthol/Non-Menthol		x						
Age first used cigarettes		x						
Identity as smoker		x						
Reasons for non-daily smoking		x						
Non-daily type (i.e., native, converted)		x						
Triggers for smoking		x						
Social smoking		x						
Withdrawal (Minnesota Withdrawal Questionnaire)		x		x				
Craving (Questionnaire of Brief Smoking Urges)		x		x				
Nicotine dependence (Time to First Cigarette)		x						
Dependence motives (Wisconsin Inventory of Smoking Dependence Motives)		x						
Social Influences on Smoking								
Smoking status of partner/spouse		x						
Number of smokers in household		x						
Home smoking restrictions		x						
Number of friends/family who smoke		x						

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	Eligibility	Baseline Week 0	Week 1	Week 4	Week 8	Week 10	Week 12	Week 26
Quitting History								
Past year quitting (# of times and longest period)		x						
Use of pharmacological and behavioral aids to quit	x							
Alcohol, Other Drugs, and Depressive Symptoms								
Depressive symptoms (Patient Health Questionnaire-2)		x						
Alcohol use (AUDIT-C)		x		x	x		x	x
Marijuana use		x		x	x		x	x
Use of prescription pain relievers		x						
Treatment Process								
Counseling completion		x	x	x	x	x		
NRT use (C+NRT only)				x	x		x	x

[a]Assessments were completed in-person at Weeks 0, 4, 8, 12, and 26 and by phone at Weeks 1 and10.

Table 3.

Baseline participant characteristics

	Range for Scale Scores	Summary Statistics		
		C+NRT (n=185)	Counseling (n=93)	All (n=278)
DEMOGRAPHIC CHARACTERISTICS				
Age, mean(SD)		48.6 (11.6)	49.0 (11.8)	48.7 (11.7)
Gender, n (%)				
Female		94 (50.8)	47 (50.5)	141 (50.7)
Male		91 (49.2)	46 (49.5)	137 (49.3)
Cohabitation Status, n (%)				
Married or living with a partner		48 (26.0)	17 (18.3)	65 (23.4)
Employment Status, n (%)				
Employed full-time		45 (24.3)	29 (31.2)	74 (26.6)
Employed part-time or seasonally		37 (20.0)	20 (21.5)	57 (20.5)
Not currently employed		63 (34.1)	34 (36.6)	97 (34.9)
Retired		27 (14.6)	4 (4.3)	31 (11.2)
Student/Homemaker		13 (7.0)	6 (6.5)	19 (6.8)
Education Level, n (%)				
Less than high school (HS) graduate		27 (14.6)	13 (14.0)	40 (14.4)
HS graduate or HS equivalent (GED)		53 (28.7)	23 (24.7)	76 (27.3)
Some college or tech school		75 (40.5)	45 (48.4)	120 (43.2)
College graduate or higher		30 (16.2)	12 (12.9)	42 (15.1)
Health Insurance that Pays for Most Medical Care, n (%)				
No		39 (21.1)	26 (28.0)	65 (23.4)
Yes		146 (78.9)	67 (72.0)	213 (76.6)
Household Income in Thousands, mean (SD)		26.9 (24.3)	28.8 (31.7)	27.5 (2.7)
Refused/Don’t Know		18 (9.7)	14 (15.1)	32 (11.5)
Number of people in household, including self, mean (SD)		2.3 (1.6)	2.5 (1.7)	2.4 (1.7)
Poverty level, n (%)				
Missing		18 (9.7)	14 (15.1)	32 (11.5)
≤100		79 (42.7)	38 (40.9)	117 (42.1)
101–200		41 (22.2)	20 (21.5)	61 (21.9)
201–250		17 (9.2)	8 (8.6)	25 (9.0)
251–300		8 (4.3)	4 (4.3)	12 (4.3)
301–400		10 (5.4)	2 (2.2)	12 (4.3)
> 400%		12 (6.4)	7 (7.5)	19 (6.8)
Housing, n (%)				
Own a home		25 (13.5)	7 (7.5)	32 (11.5)
Rent or stay with others		160 (86.5)	86 (92.5)	246 (88.5)
Perceived Health, n (%)				
Good, Fair, or Poor		142 (76.8)	71 (76.3)	213 (76.6)

	Range for Scale Scores	Summary Statistics		
		C+NRT (n=185)	Counseling (n=93)	All (n=278)
Very good/Excellent		43 (23.2)	22 (23.7)	65 (23.4)
Height in inches, mean(SD)		67.6 (3.9)	67.1 (3.6)	67.4 (3.8)
Weight in pounds, mean(SD)		203.5 (57.7)	202.0 (58.4)	203.0 (57.8)
BMI, mean(SD)		31.3 (8.7)	31.7 (9.8)	31.5 (9.1)
TOBACCO USE CHARACTERISTICS				
Age when you started smoking regularly, mean (SD)		21.0 (8.2)	22.5 (9.9)	21.5 (8.8)
Days smoked cigarettes in last 30, mean (SD)		10.6 (3.9)	10.4 (3.9)	10.6 (3.9)
Number of cigarettes used on days smoked, mean (SD)		4.8 (3.6)	4.4 (3.2)	4.7 (3.5)
Non-daily smoker type, n (%)				
Native (i.e., always been a non-daily smoker)		55 (29.7)	24 (25.8)	79 (28.4)
Converted (i.e., formerly a daily smoker)		130 (70.3)	69 (74.2)	199 (71.6)
Length of time as a non-daily smokers in years, mean (SD)		6.9 (9.7)	7.1 (10.4)	7.0 (9.9)
Length of time as a non-daily smoker by category, n (%)				
3–6 months		26 (14.1)	7 (7.5)	33 (11.9)
7–11 months		28 (15.1)	11 (11.8)	39 (14.0)
12 months or greater		131 (70.8)	75 (80.7)	206 (74.1)
Reasons for smoking some but not all days, n (%) [check all that apply]				
Health		96 (51.9)	41 (44.1)	137 (49.3)
Trying to cut back or quit		158 (85.4)	74 (80.0)	232 (83.5)
Cost/can't afford to smoke more		84 (45.4)	51 (54.8)	135 (48.6)
Don't have strong cravings or urges to smoke more		113 (61.1)	49 (52.7)	162 (58.3)
Have control over smoking; can chose when and when not to smoke		107 (57.8)	47 (50.5)	154 (55.4)
Only smoke in certain situations		154 (83.2)	81 (87.1)	235 (84.5)
Because those around you disapprove		67 (36.2)	34 (36.6)	101 (36.3)
Use of other tobacco products in the past 30 days, n (%) yes[a]		58 (31.3)	36 (38.7)	94 (33.8)
Number of days used other tobacco products		4.9 (4.5)	4.4 (4.6)	4.7 (4.5)
Average amount used per day		2.1 (1.6)	1.6 (1.0)	1.9 (1.5)
Menthol smoker, n (%)				
Non-Menthol		35 (18.9)	14 (15.1)	49 (17.6)
Menthol		150 (81.1)	79 (85.0)	229 (82.4)
Nicotine Dependence, "How soon after waking do you first smoke," n (%)				
After 30 minutes		100 (54.1)	51 (54.8)	151 (54.3)
Within 30 minutes		85 (46.0)	42 (45.2)	127 (45.7)
Withdrawal, mean(SD)	0–32	10.3 (7.0)	11.7 (7.5)	10.8 (7.2)
Craving, mean(SD)	10–70	24.5 (15.2)	25.7 (14.9)	24.9 (15.1)
Dependence Motives (WISDM Brief)[b], mean (SD)				
Total	11–77	32.6 (12.3)	33.3 (12.5)	32.8 (12.4)

	Range for Scale Scores	Summary Statistics		
		C+NRT (n=185)	Counseling (n=93)	All (n=278)
Primary dependence motives	1–7	3.2 (1.4)	3.2 (1.4)	3.2 (1.4)
Secondary dependence motives	1–7	2.8 (1.1)	2.9 (1.1)	2.9 (1.1)
SOCIAL INFLUENCES ON SMOKING				
Social Smoking, "In the past 30 days, did you smoke…" n (%)				
Mainly when with others		53 (28.7)	22 (23.7)	75 (27.0)
Mainly when alone		65 (35.1)	38 (40.9)	103 (37.1)
As often alone as with others		67 (36.2)	33 (35.5)	100 (36.0)
Number of your five best friends smoke, mean(SD)	0–5	3.0 (1.6)	2.9 (1.7)	3.0 (1.6)
Number of smokers in the home (including self), mean(SD)		1.9 (7.2)	1.8 (3.1)	1.9 (6.1)
Partner smoking status, n (%)				
No partner/spouse		79 (42.7)	46 (49.5)	125 (45.0)
Partner/spouse is a non-smoker		42 (22.7)	22 (23.7)	64 (23.0)
Partner/spouse is a smoker		64 (34.6)	25 (26.9)	89 (32.0)
QUITTING HISTORY				
Number of 24 hour quit attempts in past year, mean (SD)		7.3 (28.2)	5.7 (15.6)	6.8 (24.7)
Longest quit attempt in the past year, mean (SD) in months		1.1 (1.7)	1.3 (1.8)	1.1 (1.7)
Use of quitting aids (i.e., behavioral or pharmacological), n (%) ever		103 (55.7)	54 (58.1)	157 (56.5)
DEPRESSIVE SYMPTOMOLOGY, ALCOHOL, MARIJUANA, AND PRESCRIPTION PAIN USE				
Depressive symptoms (PHQ-2 ≥ 3), n (%)	0–6	39 (21.1)	23 (24.7)	62 (22.3)
Alcohol misuse (AUDIT-C ≥ 3 for women and ≥ 4 for men), n (%)		91(49.2)	47 (50.5)	138 (49.6)
Marijuana, n (%) of participants who used in the past 30 days		56 (30.3)	23 (24.7)	79 (28.4)
Refused		0 (0.0)	1 (1.1)	1 (0.4)
Prescription pain relievers, n (%) of participants who used in the past 30 days		75 (40.5)	33 (35.5)	108 (38.9)

[a] Daily users of non-cigarette other tobacco products, not including electronic cigarettes, were excluded at eligibility screening

[b] Primary dependence motives include automaticity, craving, loss of control, and tolerance. Secondary dependence motives include affective enhancement, affiliative attachment, cognitive enhancement, cue exposure, social/environmental goads, taste, and weight control. Total dependence motives are a sum of all 11 subscales.

Table 4:

Reasons for Ineligibility

Reason	*n*
Ineligible based on initial phone screening (n=72/625)	72
< 18 years of age	2
Daily user of tobacco products (>27 days in last 30)	14
Smoked cigarettes and/or little cigars on <4 or >27 days in last 30	23
Non-daily smoker for < 3 months (only among non-daily smokers)	18
Smoked < 100 cigarettes/little cigars in lifetime (i.e., non-smoker)	8
Unwilling to use choice of nicotine patch, gum, or lozenge as part of the study for the next 3 months	1
Unwilling to refrain from use of other smoking cessation pharmacotherapies, including e-cigarettes for the next 6 months	1
Unwilling to provide urine for biomarker analyses	2
Unable to make study-related visits	1
Another household member enrolled in study	1
Moving out of area in next 6 months	5
Pharmacotherapy- or electronic cigarette-assisted quit attempt in the past 30 days	17
Medical ineligibility	
Hospitalized for heart attack or irregular heart beat in past 30 days	2
Experienced angina or heart-related chest pain in past 30 days	5
Pregnant, planning to get pregnant, or breastfeeding (females only)	2
Unwilling to use birth control methods to avoid pregnancy (pre-menopausal or unsterilized females only)	1
Did not return for final, in-person eligibility screening (n=249/553)	249
Ineligible based on final in-person eligibility screening (n=25/304)	**25**
Unable to provide enough urine for biomarker analyses	24
Medical ineligibility	
Refused or positive pregnancy test (only among pre-menopausal or unsterilized females)	4