University of Kansas Medical Center
RESEARCH PROTOCOL INVOLVING HUMAN SUBJECTS
TEMPLATE WITH GUIDANCE

Version date: 5/24/2018

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Study Title: Informing Tobacco Treatment Guidelines for African American Non-Daily Smokers

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(NOTE: not all sections of this template will apply to all projects. "N/A" is an acceptable response.)

I.   PURPOSE, BACKGROUND AND RATIONALE

A. Aim and Hypotheses

Non-daily smokers, i.e., those who smoke on some but not all days, represent a substantial and growing proportion of racial/ethnic minority smokers. 1 out of 4 African Americans (AA) are non-daily smokers. AAs experience disproportionately greater smoking attributable morbidity and mortality at lower levels of smoking and AA non-daily smokers have strikingly higher levels of nicotine and the potent carcinogen, NNAL, than White and Hispanic non-daily smokers, despite a comparable level of smoking. To date, however, no evidence-based treatment guidelines exist for non-daily smokers, leaving health care providers wondering how to treat this high risk and growing subgroup, and **no** fully powered studies have been conducted to explore treatment options for non-daily smokers.

The specific aims of our study are to:

1)   **Compare abstinence rates among AA non-daily smokers receiving either smoking cessation counseling (C) or smoking cessation counseling in combination with NRT (C+NRT).** <u>Hypotheses:</u> Participants randomized to C+NRT will have significantly higher biochemically verified smoking abstinence than participants randomized to C at 12 weeks end of treatment (primary outcome) and at 26 week follow-up.

2)   **To compare patient- and provider-desired outcomes -- e.g., nicotine intake, carcinogen exposure, number of days abstinent, and side effects – among AA non-daily smokers receiving C versus C+NRT and, within the C+NRT group, examine choice and use of NRT during the treatment period.** <u>Hypothesis:</u> Participants 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.

3)   **Identify subgroups of AA non-daily smokers for whom the relative benefits of treatment might differ using novel Classification and Regression Tree (CART) modeling methods that can be directly implemented into clinical practice.**

B. Background and Significance

<u>**Smoking is associated with significant health burden in the US.**</u> Despite tobacco control efforts that have resulted in overall reductions in smoking prevalence, smoking is still the number one cause of

preventable disease and death in the U.S, killing nearly 445,000 Americans each year. Smoking is also a major contributor to chronic disease. For every one adult who dies from smoking, another 20 live with one or more tobacco-related chronic illnesses, including heart disease, cancer, chronic-obstructive lung disease, and stroke. The economic impact of smoking is staggering. Annually, cigarette smoking is responsible for an estimated $96 billion in direct medical costs and $97 billion in lost productivity.[1] At the employer-level each employee who smokes costs nearly $6,000 more each year than their non-smoking counterpart, due mostly to more time off for sickness, frequent smoke breaks/lost productivity, and increased health care costs and pension benefits for smokers.[2] Few conditions impose a more significant health burden on the U.S population.

Smoking imposes a more significant burden on African Americans at lower levels of smoking.
The burden of smoking is not equally distributed across the population.[3] While non-Hispanic African American (subsequently referred to as AA) adults smoke at rates that are slightly lower than non-Hispanic White adults (19.4% versus 20.6%) (subsequently referred to as White),[4] they have disproportionately higher rates of tobacco-related disease and death. AAs have the highest incidence rates for all cancers combined, the highest overall cancer mortality rates compared to all other racial/ethnic groups, and have twice the rates of premature death attributable to cardiovascular disease.[5] In addition, AA smokers have a 43-55% higher relative risk of smoking attributable lung cancer compared to Whites[6] and are at higher risk for nearly all smoking-related chronic diseases.[7,8]

The irony of these data is that AAs disproportionately suffer greater tobacco-related disease and death at notably lower levels of smoking. Among AA smokers, 53% consume 1-10 cigarettes per day (cpd) and are classified as light daily smokers compared to only 26% of Whites.[3] An additional 24%, or 1 out of every 4 AA smokers smoke on some but not all days and are, therefore, classified as non-daily smokers compared to only 16% of Whites.[9] Only one small pilot study (n=52) has looked at cessation treatment, in the form of counseling, for White non-daily smokers.[10] Findings indicate that counseling may be helpful; however smoking cessation pharmacotherapy was not included as a part of treatment and the study was not powered on smoking abstinence. **No** adequately powered randomized clinical trials have been conducted with non-daily smokers despite the fact that they represent 1 in 7 White and 1 in 4 AA smokers. We focus on AA non-daily smokers in the proposed study because of the higher prevalence and notable disparities that exist.

AA smokers are less likely to quit. While smoking cessation is a national health priority for all smokers, it is particularly important for AAs who are more likely to attempt to stop smoking within a given year, but whose attempts are less successful.[11,12] Of AA smokers who have made a quit attempt in the last year, only 32% stay quit for 30 days in contrast to 42%-50% of Whites, Asian American/Pacific Islanders, and Hispanics/Latinos.[3] Furthermore, AAs smokers have a 50% reduced likelihood of quitting smoking for 6 month or more compared with Whites. The decreased likelihood of success for AA smokers may be partly attributed to the fact that they are less likely than Whites to receive advice/assistance from a health care provider to quit [13-16] and to be prescribed smoking cessation pharmacotherapy to aid in their attempts.[12,17,18]

Current tobacco treatment guidelines do not address non-daily smoking. More than 70% of smokers visit a physician each year and current Clinical Practice Guidelines for treating tobacco dependence recommend that health care providers ask each patient about their tobacco use and offer assistance in the form of medication and counseling for those interested in quitting.[11] The problem with these guidelines, however, is that they were developed for **daily** smokers, leaving health care providers wondering how to treat the unique but growing sub-group of non-daily smokers.

Within the medical community there is a perception that non-daily smokers represent only a small proportion of current U.S. smokers, are transitional smokers in the stages of smoking initiation or reduction/cessation, are not at substantial risk from the health effects of smoking, not addicted, and are either not interested in quitting or can quit on their own without the advice of health care providers or smoking cessation pharmacotherapy.[19] These perceptions are not supported by the literature.

Non-daily smokers represent nearly one-quarter of U.S. adult smokers. Non-daily smokers represent 22% of all current smokers and specifically, 24% of AA smokers.[9] These rates are growing significantly each year subsequent to declining rates of daily smoking.[20]

Non-daily smokers are stable smokers. Data from one study indicate that 30% of non-daily smokers had smoked at their current, non-daily rate for >5 years and 45% had been nondaily smokers for at least a year.[21] National prevalence data from another study indicate that 66% of non-daily smokers have smoked at their current non-daily rate for 10 years or more.[22] Together, these data indicate that non-daily smokers are a distinct group who can demonstrate a stable and longstanding pattern of non-daily use.

Non-daily smokers experience significant health effects from their smoking. Smoking at any level is harmful, and nondaily smokers are not immune to these effects. Compared to never smokers, non-daily smokers are at increased risk for mortality, cardiovascular disease, lung and gastrointestinal cancers, respiratory tract infections, cataracts, and compromised reproductive health.[23,24] In addition, non-daily smokers are just as likely as daily smokers to report hypertension, heart disease, and asthma, to have made the same number of visits to the emergency room in the past year, and to have missed an equal number of days of work due to poor health [19]

Non-daily smokers are addicted and want to quit but do not receive support from their health care provider. On the days that they smoke, 60% of non-daily smokers smoke their first cigarette within 30 minutes of waking, a hallmark for nicotine addiction.[25,26] Non-daily smokers also want to quit. They are significantly more likely than daily smokers to have made a quit attempt in the last year (57% versus 43%) and to want to quit in the next 7 days (44% versus 30%).[26,27] Unfortunately, non-daily smokers are much less likely to be asked about their smoking status or be advised to quit by a health care provider.[19] This tendency to be overlooked in care is a major contributor to the low rates of use of behavioral (8%) and pharmacotherapy aids (16%) and high rates of quitting failure (73-82% resume smoking within 90 days) among non-daily smokers.[22]

Nicotine replacement therapies (NRT) could be helpful for non-daily smokers. Current smoking cessation guidelines recommend NRT as a first-line therapy for quitting smoking.[11] Nicotine patch, gum, and lozenge are available without a prescription and have been found to double the rate of quitting relative to placebo or a non-NRT control.[28] Despite the well-established efficacy of these products, NRT has been mostly reserved for daily smokers given concern that low level smokers are not addicted enough to warrant NRT or the amount of nicotine delivered through these products could exceed the levels achieved through non-daily smoking.[29]

AA non-daily smokers may be at increased risk. There are no published papers focusing exclusively on AA non-daily smokers. A handful of existing studies have oversampled AAs because of the increased likelihood that they are non-daily smokers,[25,26,30] but the data are not presented by race/ethnicity and do not allow for comparisons across groups. Our group recently completed a large

cross-sectional survey of 1,201 non-daily smokers -- 401 AA, 400 Hispanic/Latino, and 400 White.[31-34] Findings suggest that AA non-daily smokers are similar to White and Hispanic/Latino non-daily smokers on many factors. AA non-daily smokers are stable smokers, having smoked at their current rate for 11.4 (12.2) years, they are nicotine dependent, with 44% smoking their first cigarette within 30 minutes of waking on the days that they smoke, they suffer health consequences related to their smoking, with 23% rating their current health as fair or poor and 4%-13% living with one or more smoking-related chronic diseases (e.g., heart disease, cancer, asthma, emphysema). They also want to quit -- 62% had quit for one day or longer in the last year and 34% planned to quit in the next 6 months -- but only 24% had been offered assistance to quit by a health care provider and few had used pharmacotherapy (1%-19%) or behavioral approaches (2.2%-4.7%) to aid their attempt. However, there are notable exceptions in our data.[35] AA non-daily smokers were significantly more likely than White (W) and Hispanic/Latino (H/L) non-daily smokers to use menthol cigarettes (84% versus 35% and 59%, respectively, p<0.0001), which may increase the depth of inhalation and optimize the amount of nicotine delivered.[36,37] AA non-daily smokers also had strikingly higher levels of urinary cotinine, the major metabolite of nicotine

Tobacco and Carcinogen Exposure among AA, Hispanic/Latino, and White Non-Daily Smokers[35]		
	AA	H/L	W
Cotinine	807.8 ng/mg	125.2 ng/mg	264.8 ng/mg
NNAL	187.6 pg/mg	64.6 pg/mg	40.7 pg/mg
Participants were equivalent on cpd on days smoked (5.0 cpd on days smoked) and days smoked in the last 30 (13.0 days smoked)		

and an objective marker of daily nicotine exposure, and NNAL, a potent carcinogen that is independently associated with the risk of lung and esophageal cancer in large cohorts of smokers.[38,39] Studies of daily smokers have found median cotinine levels of 1,323 ng/mg and NNAL levels of 230-300 pg/mg.[40,41] In comparing our data (see table) to these studies, AA non-daily smokers (median of 5.0 cpd on days smoked) had an average daily cotinine intake that was 61% that of daily smokers, who smoked substantially more (11.5-17.2 cpd), [46,47] while the average daily intake of H/L and W non-daily smokers was only 9% and 20% that of daily smokers. More striking, however, is that AA non-daily smokers are exposed to substantial amounts of the potent lung and esophageal carcinogen, NNAL, despite their low levels of cigarette consumption. By comparison, AA non-daily smokers in our study averaged 63%-82% of the intake of NNAL of daily smokers, compared to H/L and W non-daily smokers whose intake of NNAL was only 14%-28% that of daily smokers. [35,40,41] These data are consistent with other studies indicating that, while AA smoker fewer cigarettes per day, they smoke cigarettes more intensively, extracting more cotinine and potent carcinogens per cigarette smoked.[42-44] Together, these data suggest that AA non-daily smokers incur significant nicotine and carcinogen exposure at low levels of cigarette consumption and make the treatment of AA non-daily smokers a critical but overlooked area.

Significance

This study addresses each of the funders (PCORI) criteria for significance (noted in italicized and underlined text). Specifically, it *addresses a critical gap in current knowledge, is novel, and responds directly to the call for guideline development efforts*. To date, **no** fully powered randomized clinical trials have been conducted with non-daily smokers despite the fact that they represent 1 in 7 White and 1 in 4 AA smokers. This study will determine if NRT is effective for AA non-daily smokers. The program will be the first to examine treatment options for non-daily smokers and could directly contribute to the first evidence-based guidelines for treating the 9.7 million U.S. adult non-daily smokers for whom no guidelines currently exist. By providing the first-ever data on the efficacy of counseling alone versus counseling plus NRT, efficacy of patch versus gum versus lozenge, and clearer protocols for titrating NRT dose to address the unique smoking patterns of non-daily smokers, the

study will not only inform evidence-based guidelines but also address *the wide variations in practice patterns that suggest clinical uncertainty in treating non-daily smokers*. The proposal has been *identified as important by patient and clinician groups*. Throughout the course of our ongoing smoking cessation programs at Swope Health Central, one of two recruitment sites for this study, a growing number of AA smokers were being excluded because of their non-daily smoking status, and we received countless requests for help from AA non-daily smokers. At the same time, providers expressed concern about the lack of evidence-based recommendations for treating non-daily smokers and the need for a quit smoking program to meet the demands of this growing patient population. The study is directly derived from these requests. Finally, the experience of our group, our previous success using research finding to change policy/practice, and integration of the CART decision tree (Aim 3) into electronic medical records will ensure that the *findings, whether positive or negative, are disseminated quickly and affect changes in current practice*. A distinct advantage of this proposal is that its ability to impact practice is not tied to finding group differences in the hypothesized directions (Aims 1, 2). Rather, independent of whether there is an overall difference between groups in treatment efficacy, our decision tree will identify subgroups for whom treatment efficacy differs. Some patients may benefit most from counseling only, others may benefit from counseling and nicotine patch, and others may benefit from counseling and gum or lozenge. Our decision tree will identify these subgroups, allow patients and providers to estimate an individual's chance of success given their treatment and select patient characteristics (e.g., gender, age, menthol versus non-menthol cigarettes, nicotine dependence, nicotine intake, polytobacco versus cigarette only use), and can be directly implemented into clinical practice.

C. Rationale

To date, no studies have explored treatment options for non-daily smokers and, as a result, treatment guidelines are not available to guide patients or healthcare providers. The study will compare two treatments -- smoking cessation counseling alone versus counseling in combination with patients' choice of nicotine patch, gum, or lozenge -- on their effects on quitting smoking and reducing exposure to nicotine and cancer causing agents. Findings will identify which patients are most likely to benefit from each form of treatment (counseling, nicotine gum, patch, or lozenge) and will allow patients and providers to estimate their chances of success based on personal characteristics – for example, age, gender, level of smoking – and the treatment they chose. This study will determine if NRT is safe and effective for AA non-daily smokers. The program will be the first to examine treatment options for non-daily smokers and could directly contribute to the first evidence-based guidelines for treating the 9.7 million U.S. adult non-daily smokers for whom no guidelines currently exist.
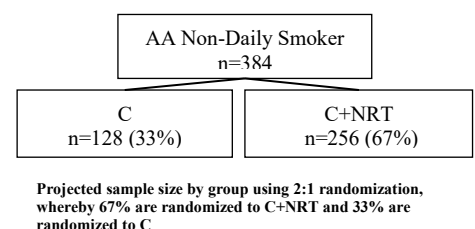
II.   RESEARCH PLAN AND DESIGN

A. Study Objectives

The objective of this study is to examine if NRT is an effective treatment option for AA non-daily smokers. Outcomes will be measured at weeks 12 and 26 and will include biologically confirmed smoking abstinence, nicotine intake, carcinogen exposure, days abstinent, NRT adherence and side effects.

B. Study Type and Design:

The proposed study is a randomized trial of 384 AA non-daily smokers randomized to receive either 5 sessions of smoking

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          AA Non-Daily Smoker
                n=384
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       C                       C+NRT
   n=128 (33%)              n=256 (67%)
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Projected sample size by group using 2:1 randomization, whereby 67% are randomized to C+NRT and 33% are randomized to C

cessation counseling in combination with 12 weeks of nicotine patch, gum, or lozenge (C+NRT) or 5 sessions of smoking cessation counseling alone (C). We will use 2:1 randomization; for every patient randomized to C, two will be randomized to C+NRT (see Figure). The primary outcome is biologically-confirmed 7-day abstinence from smoking at 12 weeks. Patient- and provider-driven secondary outcomes include reductions in nicotine intake and carcinogen exposure, days abstinent, NRT adherence and side effects. Participants will be recruited from the University of Kansas Medical Center (KUMC) and Swope Health Central, a community-based primary care clinic in urban Kansas City that serves a predominately AA clientele.

C. Sample size, statistical methods, and power calculation

384 AA non-daily smokers will be randomized. We will use 2:1 randomization; for every patient randomized to C, two will be randomized to C+NRT (see Figure). Randomization will be determined by computer-generated random numbers generated by Dr. Mayo. Randomization assignments will be placed in sealed envelopes by a member of Dr. Mayo's team with sequential study ID numbers. After baseline date collection has been completed, the research assistant will select the sequential study ID number from the sealed envelope to determine the randomization assignment.

The maximum number of participants enrolled in C will be 128 and the maximum number enrolled in C+NRT will be 256. Our sample size is based on our primary outcome, biochemically confirmed point-prevalence abstinence at Week 12 using an intent-to-treat approach. Based on treatment studies with AA light smokers who have received tobacco treatment guideline-based counseling and no pharmacotherapy, we expect a 10% point prevalence abstinence rate in the C group and a 20-25% point prevalence abstinence rate in the C+NRT group based on recent meta-analyses and studies examining the effectiveness of these medications in AA light smokers.[11,28,45,46] Using the chi-square test, along with the assumptions above, 256 participants in the C+NRT group and 128 participants in the C group (n=384), we will have 95% power to detect an increase from 10% to 25% in cessation at Week 12 between C and C+NRT, 87% power to detect a and increase from 10% to 22.5%, and 71% power to detect an increase from 10% to 20% with a type 1 error rate of 5%.

Analysis Plan for Each Aim
All primary analyses on smoking cessation will be conducted using intent-to-treat and will code those lost to follow-up as smokers. Subsequently we will evaluate the missing data pattern. If there is a differential loss based upon group, multiple imputation techniques will also be used.

Specific Aim 1: To compare abstinence rates among AA non-daily smokers receiving either smoking cessation counseling (C) or smoking cessation counseling in combination with NRT (C+NRT). Hypothesis: Participants randomized to C+NRT will have significantly higher biochemically verified smoking abstinence than participants randomized to C at 12 weeks end of treatment (primary outcome) and at 26 week follow-up. Analytic strategy: The chi-square test will be used to compare the verified abstinence rates at Week 12 (primary cessation endpoint) and Week 26 (secondary cessation endpoint) between C and C+NRT. For our primary comparison, those lost to follow-up will be considered as smokers. Assuming the expected treatment effect, we will descriptively examine the cessation rate within the C+NRT group by choice of NRT. A statistical comparison will not be conducted as we do not know a priori who will choose what and the choice will not be random. We also will look at completers only and will utilize multiple imputation techniques to ensure valid comparisons between the two groups if the loss to follow-up is not random. Secondarily, we will utilize Generalize Estimating Equation methodology to *longitudinally* compare verified abstinence. We will then examine the effects

of the covariates and patient and provider outcomes listed in the measurement table above 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. Given the sample size and expected cessation rate, we anticipate a model that contains at most six covariates. We expect no difference in the distribution of demographic and smoking history covariates between groups and we will not statistically compare those as per CONSORT recommendations for randomized clinical trials. Within the NRT treatment group, we will examine the effect of NRT adherence over the first 12 weeks on verified cessation using logistic regression.

Specific Aim 2: To compare patient- and provider-desired outcomes -- e.g., nicotine intake, carcinogen exposure, number of days abstinent, and side effects – among AA non-daily smokers receiving C versus C+NRT and, within the C+NRT group, examine the choice of NRT and use during the treatment period. Hypothesis: Participants 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. Analytic strategy: We will utilize linear mixed models to longitudinally (week 12 and 26) compare nicotine and carcinogen exposure between the two groups, then subsequently examine the effects of the covariates listed in the measurement table above 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 and best subsets selection will be used to examine the effects of covariates on this endpoint. For each of these models, based upon the sample size, we anticipate that ten to twelve covariates could be included in a final model. 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).

Specific Aim 3: Identify subgroups of AA non-daily smokers for whom the relative benefits of treatment might differ. We will employ a Classification and Regression Tree decision tree modeling on Week 12 verified smoking status (quit versus not quit) to identify subgroups of participants whose personal characteristics might impact the benefit of treatment. The resulting decision tree will allow smokers and their providers to estimate their individual chances of success given their choice of treatment. To maximize the utility of the decision tree, we solicited input from our Stakeholder Advisory Committee and Patient Advisory Panel and included the demographic, smoking, and treatment-related variables identified by them (see Measures and Time Points Table) for possible inclusion in the predictive model. The candidate variables, along with treatment assignment (C, C+NRT) will be entered into a recursive partitioning model as described by Brieman and Freidman using the RPART package in the R statistical software.[47] Specific methods related to building the tree (using appropriate splitting criteria and loss incorporation using the altered priors method), pruning the tree and handling missing data (using surrogate variables) will be deployed using the techniques described by Therneau et al.[48] Given the cessation rate expected and overall sample size, a validation subsampling scheme will not be feasible, thus we will utilize 10-fold cross-validation on the regression tree to assess its properties. Additionally, we will account for the uncertainty in tree classification by

generating a bootstrap sampling distribution of the predictive as described by Shalizi.[49] Modeling cessation was of greatest interest for our initial Patient and Stakeholder Advisory Panels, but other outcomes (reduction in nicotine or carcinogen exposure) could be modeled if our patients and stakeholders think that these additional models might be useful.

D. Subject Criteria (See Vulnerable Populations appendix, if applicable)

Participants will be AA adults over the age of 18 who smoked on 4-27 days out of the past 30 at enrollment and have smoked at this non-daily rate for $\geq$ 3 months. The study will be open to both men and women. We have chosen to focus on AAs only because their unique smoking profile places them at greater risk for tobacco-related disease and death [44,45,50-52] Importantly, this study represents a starting point for future work that can be expanded to other ethnic groups with high rates of non-daily smoking.

Inclusion Criteria
Inclusion criteria are displayed in the adjoining table. Participants must have smoked 100 cigarettes or little cigars in their lifetime to ensure that they are smokers and to have smoked at their current rate for $\geq$ 3 months to avoid enrolling smokers who are in the transitory stages of smoking initiation or reduction/cessation. Participants also cannot be daily users of other tobacco products, not including e-cigarettes. Other racial groups will be excluded as our primary aim is to evaluate NRT in AA smokers.

Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
- African American $\geq$ 18 years of age - Smoke 100 lifetime cigarettes - Smoke cigarettes or little cigars on 4-27 days of the past 30 days - Smoke cigarettes or little cigars at current rate for $\geq$ 3 months - Use of any tobacco product, not including e-cigs, on 4-27 days in last 30 - Functioning telephone - Interested in quitting smoking - Willing to take NRT for 12 weeks and complete all study procedures	- Unstable cardiac condition (e.g., unstable angina or AMI in the past 4 weeks) - Plans to move from KC during the treatment and follow-up phase - Use of pharmacotherapy, including e-cigs, in the month prior to enrollment - Pregnant or breastfeeding - Another household member enrolled in the study - Unstable housing (e.g., homeless, drug/alcohol treatment center)

Exclusion Criteria
Exclusion criteria are also displayed in the adjoining table. Exclusion criteria are consistent with contra-indications for nicotine gum, patch, and lozenge.[11]

Withdrawal/Termination Criteria
There are no expected circumstances in which the subject's participation will be terminated by the investigator.

Clarify whether a study subject may participate in another research study while participating in this research study
Subjects are not able to participate in another smoking cessation research study while they are enrolled in the current study.

E. Specific methods and techniques used throughout the study

Laboratory Tests

Not more than 30 ml of urine will be collected three times throughout the study for biochemical verification of **cessation** at Wk 12 (via urine anabasine and anatabine, with the recommended cut-off of 2 ng/ml to differentiate smokers from non-smokers[50]) and Wk 26 (via cotinine, the proximate metabolite of nicotine, with the recommended cut-off of 50 ng/ml used to differentiate smokers from non-smokers[51]), **nicotine intake** at Wks 0, 12, 26 [quantified by examining the sum of four of the major nicotine metabolites (cotinine + cotinine-glucuronide + trans-3'-hydroxycotinine + 3HC-glucuronide) to creatinine ratio using procedures described by Benowitz (consultant)[51]], and **carcinogen exposure** at Wks 0, 12, and 26 [quantified by examining *NNAL* (4-(methylnitrosamino)-1-(3)pyridyl-1-butanol) and polycyclic aromatic hydrocarbons (PAH) and specifically, *1-hydroxypyrene (1-HOP),* using procedures described by Benowitz (consultant)[40]]. All bioanalytical operations will be performed in a GLP-compliant Bioanalytical Laboratory at the Fairway Clinical Research Center under the direction of Greg Reed, PhD. This state-of-the-art laboratory is a dedicated facility for the support of clinical and translational studies. The new facility is equipped for accurate and efficient preparation of samples and standards, and contains two Waters UPLC-Xevo TQ-S LC-MS/MS systems. A refrigerator and both -20º and -80º freezers are available for sample storage, and they are monitored. Analytical and microbalances are available for preparing standards and reagents, and mixers, vortexers, centrifuges, and evaporators/concentrators for sample preparation are all in the lab. All general and study-specific procedures are performed according to Bioanalytical Lab SOPs, and all aspects of the work are fully documented in accordance with GLP.

Study Procedures

Intervention
All eligible participants who provide written informed consent and complete the baseline survey will be randomized in a 2:1 fashion to either counseling plus NRT (C+NRT) or counseling only (C).

Counseling (C and C+NRT). Both groups will receive 5 sessions of smoking cessation counseling that is consistent with the current tobacco treatment guidelines.[11] The guidelines recommend the importance of counseling alone or in combination with smoking cessation pharmacotherapy. All sessions will be delivered by a trained, certified Tobacco Treatment Specialist. Dr. Cox, a licensed clinical psychologist, will be responsible for counselor training and supervision. Sessions will use semi-structured scripts to incorporate counseling with use of the *Kick It at Swope: Stop Smoking Guide*.

Sessions are tailored to the quit status of participants. For those who are quit, sessions will focus on strategies for preventing relapse, including alternatives to smoking and identifying and managing stressors that could lead to relapse. For those who are not quit, sessions will focus on motivating them to make another quit attempt, discuss problems that led to relapse/continued smoking, and encourage them to continuing using NRT (C+NRT only) and set another quit day. Counseling will be

Overview of Guideline-Based Counseling Sessions

Session	Goal	Topic
Wk 0* (30 min)	Establish rapport with participant- emphasizing willingness to help them quit and encouraging their motivation/confidence to quit smoking.	Health risks, benefits of quitting, learning from past quit attempts; and developing a plan for quit day; education/empowerment on medication use and tailoring dose to be consistent with smoking patterns, side effects, and experiences of withdrawal and craving *(C+NRT only)*; identifying triggers and managing withdrawal
Wk 1 (15 min)	Reinforce quit day plan, address medication use *(C+NRT only)*, identify concerns, barriers, and strategies for success	**If Quit:** Rewarding yourself, recovering from slip, review medication use (i.e., tailoring dose to be consistent with smoking patterns, side effects, and experiences of withdrawal and craving) or ending medication at Wk 10 *(C+NRT only)*, managing stress, alternatives to smoking, identify barriers, and living smoke-free
Wks 4, 8, 10 (15 min)	Reinforce and encourage abstinence efforts. Identify concerns, barriers, and strategies for successes	**If still smoking:** Review reasons for not quitting, review reasons for quitting, discuss specific problems that lead to relapse, and attempt to set a new quit plan

*Conducted in person. All other sessions will be conducted by telephone.

identical across groups except that medication use will only be discussed in the NRT group.

Written Materials (C and C+NRT). Both groups will receive the *Kick It at Swope: Stop Smoking Guide* that was developed and used for our three previous AA smoking cessation studies (conducted by Drs. Nollen, Cox, and Ahluwalia) to go hand-in-hand with counseling. The 50-page guide includes information about health consequences of tobacco use, benefits of quitting, and specific strategies to promote abstinence (e.g., making a quit plan, obtaining social support, managing withdrawal and craving, coping with a lapse, relapse prevention). The guide will be revised and updated for use in this study with input from our Patient and Stakeholder Advisory Panels to include specific discussion of the health risks of non-daily smoking.

NRT (C+NRT). Participants randomized to C+NRT will be given their choice of nicotine gum, patch, or lozenge to try for 3 days each. After the 3 to 9-day trial period, they will select and receive a 12 week supply of the medication of their choice. Similar NRT choice trials have been used successfully by others.[52] This patient-centered approach was informed by our Patient Advisory Panel, who preferred these medications because of cost and over the counter availability, and our Stakeholder Advisory Panel, who felt that this patient-centered approach emulated clinical practice and would broaden the implications of our study for informing evidence-based guidelines for treating tobacco dependence in AA non-daily smokers. Nicotine gum, patch, and lozenge are all highly effective first-line medications approved for the treatment of tobacco dependence that have been shown to double the rate of quitting compared to placebo.[11,28] _NRT dosing._ One of the clinical implications of this study is to inform the development of NRT dosing guidelines for non-daily smokers. We will work hand-in-hand with our providers and quitline experts to ensure that the counseling and NRT dosing protocols can be easily implemented with non-daily smokers in clinical practice and through the national quitline, Alere. We draw on our decades of experience treating AA smokers, the well-established literature on nicotine metabolism among AA smokers, and expert consensus to derive NRT dosing guidelines. Urine cotinine levels from AA daily smokers are consistent with taking in the equivalent of 8-10 mg of nicotine per day.[40] Urinary cotinine data from our NDS pilot study indicate that AA non-daily smokers have an average daily intake of cotinine that is 61% that of daily smokers or equivalent to 5.5 mg of nicotine per day.[35] The goal of treatment with NRT is to replace most or all of the nicotine that would have been obtained from tobacco with nicotine from the replacement product. However, not all nicotine from NRT is absorbed into the system. For a 7 mg patch, approximately 5 mg of nicotine is absorbed.[53] Likewise, for each 2 mg gum or lozenge, only 1 mg of nicotine is absorbed.[54] Following from the absorption rates of these products and our preliminary data indicating that AA non-daily smokers are in need of at least 5.5 mg of replacement nicotine per day, participants choosing the patch will be started on one 7 mg patch/day and those choosing gum/lozenge will be started on six 2 mg pieces/day.

These doses represent a starting point. To enhance the ability of our findings to be translated into practice, counselors will educate participants about the relationship between cpd and NRT dosing and empower them to tailor use to be consistent with their smoking patterns, intensity of withdrawal and craving, and level of side effects. Participants will be taught that, if the NRT dose is adequate, they may still have urges during the day, but most of the time they will not feel strong physical cravings or discomfort. They will also be educated about side effects that may indicate a nicotine overdose (nausea, vomiting, cramps, dizziness) and the need for a dose reduction (i.e., fewer pieces of gum/lozenge per day, reduction from 24 to 16 or 12 hours per day that the patch is worn), as well as symptoms of withdrawal (e.g., irritability, restlessness, anxiety) and strong physical craving that may indicate the need for a dose increase (i.e., more pieces of gum/lozenge per day, increase to longer wear or a higher dose patch). Counselors will probe for smoking level, use of NRT (days used, amount used per day), side effects, symptoms of withdrawal and craving, and general experiences with the

medication during the week 1, 4, 6, 8, and 10 sessions and will provide guidance, as necessary, to ensure that the medication is working optimally for each participant. The PI and study physician will provide oversight on questions and issues that arise related to side effects, dose reductions and/or increases.

Procedures and Methods

An overview of major study events is provided in the adjoining table.

Overview of Major Study Events

		Enroll./ Baseline					EOT	Final Follow-Up
		Wk 0*	Wk 1	Wk 4	Wk 8	Wk 10	Wk 12*	Wk 26*
Screening/ Assessments	X	X		X	X		X	X
Intervention								
Counseling		X	X	X	X	X		
Medication Dispensing (C+NRT only)		X (3 to 9-day trial period)	X	X	X		X	

*in person; all other visits are by telephone; EOT=end of treatment

Initial Screening. The initial screen will review inclusion/exclusion criteria. Those eligible will be scheduled to complete final eligibility screening within 14 days. All ineligible smokers will be referred to local resources.

Final Screening and Enrollment (Wk 0). Final eligibility screening will be conducted in person and will consist of a pregnancy test on women of childbearing age and obtaining informed consent.

Counseling Visits (Wks 0,1,4,8,10). Counseling sessions will be completed by phone at Wks 1,4, 8,10, and in person at Wk 0. The number of sessions is consistent with our previous studies where we have achieved visit completion rates of around 80%.[45,55,56]

NRT Dispensing (Wks 0-1). Participants randomized to C+NRT will be given a trial supply of nicotine gum, patch, and lozenge and be instructed to try each for 3-days. After the 3 to 9-day trial period, they will select and be mailed a 4 week supply of the medication of their choice. They will receive refills of their selected medication at the Weeks 4 and 8 study visits.

Biological Sample Collection (Wk 0,12,26). Urine will be collected three times throughout the study for biochemical verification of cessation at Wk 12 and Wk 26, nicotine intake at Wks 0, 12, 26, and carcinogen exposure at Wks 0, 12, and 26. Additional details regarding each assay are provided in the Measures and Assessment Time Points table.

Retention. We have developed a system of reminders and compensation that have resulted in impressive retention rates in our previous clinical trials. <u>Reminders.</u> One week prior to each scheduled visit a reminder postcard noting the scheduled appointment date and time will be mailed to participants. In addition, participants will be called up to 6 times to remind them of their upcoming visit. A detailed tracking database, with an automated reminder system, will notify counselors of when to send postcards and complete reminder phone calls. <u>Compensation.</u> Participants will be given a $40 electronically loaded gift card at Wks 0, 12 and a $20 electronically loaded gift card at Wks 1, 4, 8, 10, 26 in appreciation for their time and participation.

Measures

Our selection of measures (see table) and the measurement time points have been driven by our patient and stakeholder advisory panels.

Measure and Assessment Time Points

Primary Scientific Outcome (Aim 1)
Smoking abstinence at Wk 12 (primary cessation outcome) and Wk 26 (secondary cessation outcome). Biochemically confirmed at Wk 12 using urine anabasine and anatabine, with the recommended cut-off of 2 ng/ml to differentiate smokers from non-smokers.[50] These tobacco alkaloids are considered the gold standard for confirming abstinence when cotinine measurements are not valid – i.e., detectable levels of cotinine could reflect NRT use or smoking.[50] Biochemically confirmed at Wk 26 using urinary cotinine, the proximate metabolite of nicotine, with the recommended cut-off of 50 ng/ml used to differentiate smokers from non-smokers.[51] **Time Points: Wk 12, 26**
Secondary Patient- and Provider-Derived Outcomes (Aim 2)
Nicotine intake (total nicotine equivalents/creatinine). Assessed by urine; quantified by examining the sum of four of the major nicotine metabolites (cotinine + cotinine-glucuronide + trans-3'-hydroxycotinine + 3HC-glucuronide) to creatinine ratio using procedures described by Benowitz (consultant).[51] Total nicotine equivalents/creatinine represents the current gold standard for estimating nicotine intake/exposure from tobacco.[57] To ensure that nicotine metabolites detected at Wk 12 are a result of tobacco exposure and not NRT use, we will schedule the urine collection for 7 days after the last dose of NRT. This 7-day time frame is more than adequate given the 15-20 hour (3-4 day) elimination half-life of cotinine and accounts for the substantial individual variability in the rate of elimination of nicotine.[58] **Time Points: Wks 0,12,26**
Carcinogen exposure [NNAL, PAH]. Assessed by urine; quantified by examining *NNAL* (4-(methylnitrosamino)-1-(3)pyridyl-1-butanol) and polycyclic aromatic hydrocarbons (PAH) and specifically, *1-hydroxypyrene (1-HOP),* using procedures described by Benowitz (consultant).[40] While there are >70 established carcinogens in tobacco, *NNAL* and *PAH* are widely considered to be among the most important causative agents in the development of lung and esophageal cancer[38,39,59] and reflect the current gold standard for estimating carcinogen exposure from tobacco products. **Time Points: Wks 0,12,26**
Days Abstinent. Cumulative number of days abstinent **Tim Points: Wks 1,4,8,10,12**
NRT adherence. 3-day recall of *NRT use* (C+NRT only) -- i.e., pieces of gum, lozenge, or number of patches used in the last 3 **Time Points: Wks 4,8,12**
Side effects. Participants will be asked about symptoms commonly associated with quitting smoking and/or NRT (i.e., difficulty concentrating, irritability, skin rash, mouth/throat irritation, nausea, sleep disturbance, heart burn) **Time Points: Wks 4,8,12**
Covariates (Aims 1, 2 & 3)
Demographics. Includes gender, age, income, education level, marital status, and use of alcohol **Time Point: Wk 0**
Smoking history. Includes type of cigarette (menthol, non-menthol), days smoked per month, number of cigarettes smoked per day on days smoked, length of time smoking at current non-daily rate, age of smoking initiation, time to first cigarette of the day (nicotine dependence), use of cigarettes only or cigarettes in combination with alternative forms of tobacco (ATP; e.g., cigars, cigarillos), presence of other smokers in the home, and home smoking restrictions **Time Point: Wk 0**
Treatment. Includes treatment assignment (C, C+NRT) and, for those randomized to C+NRT, their choice of nicotine gum, lozenge, or patch.

Clearly indicate which procedures, tests, visits, etc., are parts of usual standard therapy and which are performed solely for research purposes.

All tests, procedures, and visits are being performed solely for research purposes and are not billable to insurance companies.

Describe the fate of any body component (blood, CSF, bone marrow, etc.) used in the study, emphasizing confidentiality of labeling of the sample and the sample's destruction or storage.

Samples will be labeled only with a unique study identification number and only members of Dr. Nollen and Reed's team will have access to the samples. Samples will be disposed of one month after the final report is sent out to the Principal Investigator, unless participants agree to have their urine stored for future testing.

F. Risk/benefit assessment:

Physical risk

Risks for participating in the study are primarily those related to the use of NRT for participants randomized to the C+NRT arm. The safety of NRT has been demonstrated in hundreds of studies spanning over 30 years of research, including studies of patients who are very low level smokers and nonsmokers. To minimize any possible risk, we will exclude any patients with unstable heart disease (i.e., unstable angina or AMI in the past 4 weeks) per the medical contraindications for NRT. Nevertheless, NRT, particularly in continuing smokers, can be associated with nausea, jitteriness,

insomnia, and vivid dreams. To address these concerns, participants will receive written information and information from their counselor about how to manage any of these symptoms. They will be given advice on when they might need to reduce their nicotine dose (whether through decreasing smoking or decreasing NRT). We will track adverse events and review adverse events regularly (see data safety and monitoring plan below).

Psychological risk
Risks for participants in both treatment arms (C, C+NRT) also include those associated with the inconvenience of participation including answering surveys, providing urine, and participating in follow-up visits and assessments. To minimize the inconveniences associated with study participation we will review all data collection instruments and study procedures with our Patient Advisory Panel and our Stakeholder Advisory Committee. We will use their input to minimize the number of items in our instruments and improve the accessibility and convenience of our study procedures. We anticipate using several methods to enhance convenience to participants, including offering study visits in the evening and on weekends and offering patients a choice of where they will be seen (KUMC or Swope). Another risk is feeling pressured to be in the study, which we will track in order to monitor and will report this as an adverse event.

Social risk
None

Economic risk
None

Potential benefit of participating in the study
There are also no direct benefits to participating in this study except that researchers hope that the information from this research study may be useful in improving treatment for non-daily smokers.

G. Location where study will be performed:

The study will take place at Swope Health Central, 3801 Blue Parkway, in Kansas, Missouri or at the KUMC CRU in Fairway, Kansas based on the preference of each participant. All data will be directly entered into an electronic data capture system (i.e., RedCap or CRIS), therefore minimizing the use of paper records. If paper records are generated, they will be stored in locked file cabinets at Swope. Only study staff will have access to the locked records at Swope and the secure online electronic data capture system.

H. Collaboration (with another institution, if applicable):

Jasjit S. Ahluwalia, M.D., M.P.H., M.S. will serve as a co-investigator, and PI of the subcontract to the University of Minnesota. He is a nationally recognized investigator who was the first to conduct clinical trials with ethnic minority smokers. Dr. Ahluwalia's work has now extended to working with nondaily smokers and those concurrently using other forms of tobacco. He will participate on the design, execution and analysis of the study and relevant protocols. He will participate in weekly team meetings by conference calls and periodic site meetings (a minimum of two a year). He will review documents by email and provide feedback accordingly. He will also be available by email and phone as needed. Dr. Ahluwalia will not interact with participants and any data that he sees during the execution and analysis phases will be deidentified.

Dr. Neal Benowitz, M.D, University of California-San Francisco is a preeminent expert on the pharmacology of nicotine in humans, and has published extensively in understanding nicotine and carcinogen exposure across racial/ethnic groups. He will serve as a consultant on the project and will oversee interpretation of all biological outcomes (i.e., point-prevalence abstinence, markers of nicotine and carcinogen exposure) and will participate in writing up the study findings for publication. Any data that Dr. Benowitz sees will be deidentifed.

I. Personnel:

Indicate, by title, who will be present during study procedure(s)
Personnel on the project include: Nikki L. Nollen (PI), Lisa Cox (co-I), Ed Ellerbeck (co-I and study physician), Matt Mayo (co-I, lead biostatistician), Tricia Snow (project director), Lexi Brown (senior research analyst), Genevieve Casey (research assistant), Brian Hernandez (research assistant), Terri Tapp (research assistant), and Jessica Wearing (research assistant).

Primary responsibility for the following activities, for example:
  a. *Determining eligibility:* Ed Ellerbeck, Nikki Nollen, Tricia Snow, Genevieve Casey, Brian Hernandez, Terri Tapp, Jessica Wearing

  b. *Obtaining informed consent:* Tricia Snow, Genevieve Casey, Brian Hernandez, Terri Tapp, Jessica Wearing

  c. *Providing on-going information to the study sponsor and the IRB:* Nikki Nollen, Tricia Snow, Caroline Murray

  d. *Maintaining participant's research records:* Tricia Snow, Genevieve Casey, Brian Hernandez, Terri Tapp, Jessica Wearing, Lexi Brown, Dinesh Mudaranthakam, Matt Mayo

  e. *Completing physical examination:* Not applicable

  f. *Taking vital signs, height, weight:* Height and weight will be the only vital signs taken. They will be performed by Tricia Snow, Genevieve Casey, Brian Hernandez, Terri Tapp, Jessica Wearing

  g. *Drawing / collecting laboratory specimens:* Tricia Snow, Genevieve Casey, Brian Hernandez, Terri Tapp, Jessica Wearing

  h. *Performing / conducting tests, procedures, interventions, questionnaires:* Tricia Snow, Genevieve Casey, Brian Hernandez, Terri Tapp, Jessica Wearing

  i. *Completing study data forms:* Tricia Snow, Genevieve Casey, Brian Hernandez, Terri Tapp, Jessica Wearing, Lexi Brown

  j. *Managing study database:* Matt Mayo, Lexi Brown, Dinesh Mudaranthakam

J. Assessment of Subject Safety and Development of a Data and Safety Monitoring Plan
This study does not involve more than minimal risk. Specifically, we are using over-the-counter products that have been available on the market for over 30 years. The safety of NRT has been documented in low level smokers[46,55,60,61] and even in non-smokers. [62-64] In addition, the FDA has made labeling changes to over-the-counter NRT to emphasize their safety even when used long-term or in combination with cigarettes and other nicotine-containing products and the limited likelihood of dependence or overdosing on these products.[65] To minimize any possible risk, we will exclude any

patients with unstable heart disease (i.e., unstable angina or AMI in the past 4 weeks) per the medical contraindications for NRT. Some participants may experience nausea, jitteriness, insomnia, and vivid dreams. To address these concerns, participants will receive written information and information from their counselor about how to manage any of these symptoms. They will be given advice on when they might need to reduce their nicotine dose (whether through decreasing smoking or decreasing NRT). Discontinuation of NRT may be recommended for participants whose symptoms cannot be otherwise controlled through a dose reduction and/or decreasing smoking. We will track adverse events during regularly scheduled study visits and through spontaneous reports made by participants. Dr. Ellerbeck and Nollen will be made aware of unexpected or serious AEs within 24 hours of the first report by participants; all other AEs will be reviewed weekly by Dr. Nollen and discussed at regular meetings with Dr. Ellerbeck. SAEs will be reported to the KUMC HSC and to the FDA with 24 hours of first awareness of the event. Unexpected adverse events that are related to the study medication will be reported to KUMC HSC and to the FDA within 5 working days of first awareness of the event if the event is not serious fatal and within 24 hours of first awareness if the event is serious. Unexpected adverse events that are unrelated to the study medication will be reported to the KUMC HSC during yearly routine event reporting. Dr. Ellerbeck will determine relatedness for each reported AE. SAEs will be defined as any event experienced by a study subject while on the study medication that is fatal, life-threatening (subject was at risk of death from the event as it occurred), disabling or incapacitating, requires inpatient hospitalization or prolongs a current hospitalization, is a congenital anomaly in the offspring of a subject who received the study medication, or required intervention to prevent permanent impairment or damage.

III.   SUBJECT PARTICIPATION

A.   Recruitment

Participants will be recruited through clinic and community-based efforts. Flyers will be placed around Swope and KUMC for patients to take and providers will be asked to refer patients by providing them with the study line information. We will use the KUMC HERON database to identify AA nondaily smokers and will ask their physician to send their patient a letter informing them of the study. We will also use the Frontiers registry to identify AA adult smokers who have agreed to be contacted for research. A brief text message will be sent from the KUMC Pediatric Clinic to caregivers of AA children exposed to secondhand smoke. The message will come from the pediatric clinic and no non-Pediatric providers or staff will have access to the patients protected information. The Pediatric Clinic will use a text message company to deliver the text campaign. These individuals will be sent a letter informing them of the study. Only those who contact our study lines or present in person will be screened (i.e., we will not proactively call them). We will also use radio, TV, bus and Facebook ads and word of mouth, as needed, to recruit participants. Finally, AA smokers are currently being screened for other research studies being conducted by our team (i.e., active studies being conducted Dr. Nollen, Ellerbeck, or Cox). Those who are found to be ineligible for these studies will be informed about the current study and offered the opportunity to be screened. Recruitment letters, advertisements, and flyers are in the process of being developed. They will be submitted to the IRB for approval before any participants are enrolled.

B.   Screening Interview/questionnaire

The screening interview will take place over the phone or in person at Swope or the CRU and be conducted by a member of the study team. The screening questionnaire will address the general inclusion/exclusion criteria listed under D. Subject Criteria above. We are in the process of developing the exact questions now and will submit the full screening questionnaire to the IRB for approval before

any participants are enrolled. Only participants who have proactively contacted us (either by presenting in person or contacting our study line) will be screened.

C.   Informed consent process and timing of obtaining of consent
Consent will be obtained prior to participant involvement. Individuals interested in the proposed study will meet the research assistant at Swope or the CRU. Each individual will be given a copy of the consent form and as much time as they need to review its contents. After the consent form is read, both the individual and the research assistant will review the consent form together and the potential participant will be encouraged to ask questions. Each individual will be reminded that participation in the study is completely voluntary and their decision to participate will not affect their current or future medical care at the treating facility. The consenting process will take place in a private location.

D.   Alternatives to Participation
Alternatives to participating in the study are to quit "cold turkey" (without assistance), use other smoking cessation programs, purchase other NRT from their pharmacy, obtain a prescription for varenicline, bupropion or other smoking cessation products from their physician, or continue to smoke.

E.   Costs to Subjects
There are no costs to subjects. All tests, procedures, and visits are being performed solely for research purposes and are not billable to insurance companies.

F.   How new information will be conveyed to the study subject and how it will be documented
We have plans to publish data from this study in aggregate but will not provide any individualized feedback to participants.

G.   Payment, including a prorated plan for payment
Participants will be given a $40 electronically loaded gift card at Wks 0, 12 and a $20 electronically loaded gift card at Wks 1, 4, 8, 10, 26 in appreciation for their time and participation. Participants must complete the visit to receive the reimbursement associated with that time point. Travel costs will not be reimbursed. Participants will also be given $20 for each referral who is eligible and enrolls in the study. Each participant may refer up to 3 total referrals.

H.   Payment for a research-related injury
Not applicable

IV.   DATA COLLECTION AND PROTECTION

A.   Data Management and Security
Confidentiality will be maintained by assigning each participant a study identification number and numerically coding all data. The association of the ID-code and the participant's name will be kept by Tricia Snow in a locked file cabinet. The screening questionnaire and all survey data will be directly entered into RedCap or CRIS and accessible only by study staff. Any paper copies of records will be kept in a locked filing cabinet in offices that are kept locked when unoccupied. Only summaries of group data will be reported in any publications or presentations, with no identification of individuals. Because identifiable information will be collected, participant privacy will be maintained throughout the duration of the study by adhering to the regulations set forth by the HIPAA Privacy Rule. More specifically, identifiable information will not be released without written authorization of the participant.

Mobile devices will not be used for data collection or storage. Identifiable data will not be sent outside of KUMC.

B.   Sample / Specimen Collection

No more than 30 ml of urine will be collected at Weeks 0, 12, and 26. Urine will be de-identified, labeled with a study identification number, and stored at the Bioanalytical Laboratory at the Fairway Clinical Research Center under the direction of Greg Reed, PhD. Samples will be accessible only to members the study team. Results from biomarker analyses will be de-identified and shared only with members of the research team. Any resulting publications will present the data in aggregate; individual participants will not be identified. Samples will be disposed of one month after the final report is sent out to the Principal Investigator, unless participants agree to have their urine stored for future testing. For participants who agree to future testing, samples of their urine will be stored indefinitely.

C.   Tissue Banking Considerations

For participants who agree to future testing, samples of their urine will be stored indefinitely. New markers of nicotine and carcinogen exposure are being discovered and the stored urine samples would be used for analysis of these new markers. All samples stored for future biomarker analyses will be de-identified and accessible only to members of the study team. Results from these analyses will be de-identified and shared only with members of the research team. Any resulting publications will present the data in aggregate; individual participants will not be identified.

D.   Procedures to protect subject confidentiality

Confidentiality will be maintained by assigning each participant a study identification number and numerically coding all data. All urine samples and survey data will be labeled with the study identification number and never with the participants name or other identifiable information. The association of the ID-code and the participant's name will be kept by Tricia Snow in a locked file cabinet and will only be accessible to members of the study team.

E.   Quality Assurance / Monitoring

All data will be directly entered into our electronic data capture system (i.e., RedCap or CRIS) that contains edit checks to control the quality and completeness of data entry. Completeness of data entry will be automatically verified before each assessment is completed. The electronic data capture system is behind the KUMC secure firewall with role-based access that is HIPAA and human subjects compliant. There are no plans for ongoing third party monitoring.

V.   DATA ANALYSIS AND REPORTING

A. Statistical and Data Analysis

See II.C. above (Sample Size, Statistical Methods, and Power Calculations)

B. Outcome

See II.C. above (Sample Size, Statistical Methods, and Power Calculations)

C. Study results to participants

Study results will not be shared with participants.

D. Publication Plan

We plan to publish results in appropriate tobacco journals – e.g., JAMA, JNCI, Journal of General Internal Medicine, Addiction, Annals of Behavioral Medicine, Nicotine & Tobacco Research, Cancer Epidemiology, Biomarkers, & Prevention.

E. Bibliography / References / Literature Cited

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APPENDIX I: VULNERABLE POPULATIONS

Not applicable