I. SIGNIFICANCE

The 2008 *Clinical Practice Guideline for Treating Tobacco Use and Dependence* reviewed over 8,700 research articles, identified conclusive support for the efficacy of pharmacotherapy and counseling on increasing abstinence success, and identified varenicline as the leading single pharmacotherapy for smoking cessation.[1] The *Guideline* identified a paucity of research related to treatment among a) racial and ethnic minority smokers, and b) light smokers, and called for treatment research in these groups. In response, the proposed study will be the first placebo-controlled trial to test the efficacy of varenicline to promote smoking abstinence among African American smokers, including light smokers.

A. Advancing treatment of African American smokers is central to reducing disease burden.

Tobacco use remains the leading preventable cause of morbidity and mortality for all racial/ethnic groups in the United States, responsible for more than 30% of cancer deaths.[2] While having similar smoking prevalence to non-Hispanic Whites, African Americans experience disproportionately greater tobacco-related disease burden, including the highest rates of cancer incidence and mortality.[2-4] For example, African American smokers have a 50% higher relative risk of smoking-attributable lung cancer compared to Whites.[3] Health disparities exist despite the fact African Americans smoke fewer cigarettes per day (cpd). Indeed, over half of all African American smokers use 10 or fewer cigarettes per day (cpd), and are considered light smokers.[5,6]

Additional characteristics differentiate African American and White smokers: African Americans are more likely to smoke high-tar and menthol cigarettes,[7,8] inhale more deeply,[9] have a slower rate of nicotine metabolism,[10] show higher levels of cotinine per cigarette smoked,[11-13] and are less likely to receive tobacco use treatment or to achieve abstinence when making a quit attempt.[14,15] Multiple pharmacotherapy trials have identified poorer treatment outcomes in African American relative to White participants.[16-18] Identification of effective treatment for African American smokers is a critical public health priority.[1,19]

Attention to light smokers. We refer to "light smokers" as those who smoke ≤10 cpd,[20-22] a common definition consistent with our two previous NIH-funded clinical trials of African American light smokers.[23,24] Like heavy smokers, light smokers report nicotine dependence and experience substantial tobacco-related disease.[25-30] Unfortunately, light smokers perceive less risk of disease.[31] Light smokers also differ in variability of daily smoking patterns and cue exposure. Decades research excluded light smokers from treatment studies, limiting evaluation of smoking behavior and treatment outcomes.[1,20] Only four clinical trials have focused on treating light smokers, including two of our *Kick It at Swope* (KIS) trials, and quit rates have been low.[16,23,24,32] While overall rates of smoking in the U.S. remain flat, the proportion of those who are light smokers continues to increase.[28] Advancing tobacco treatment including attention to light smokers is timely and critical.

B. Research is needed to advance treatment for African Americans, including light smokers.

Because so few studies have focused on establishing evidence-based treatment for African American smokers[16,19,24] there is limited data to guide clinical care for 5.6 million African American adult smokers. The proposed study builds on our history of research dedicated to advancing treatment of African American smokers through the *Kick It at Swope* (KIS) studies. KIS-I (NCI R01 CA77856) established the efficacy of bupropion for initial and long-term smoking cessation among African American *moderate to heavy* (≥10 cpd) smokers.[33] KIS-II (NCI R01 CA91912) was the first treatment study for African American light smokers (≤10 cpd), evaluating nicotine gum versus placebo combined with health education (HE) counseling versus motivational interviewing (MI). Results showed no measurable benefit of nicotine gum potentially due to less than optimal adherence, but demonstrated the efficacy of HE counseling, showing a doubling in abstinence compared to MI.[23] HE counseling will be used in the current proposal. KIS-III (NCI R01 CA091912), a placebo-controlled trial of bupropion for light smokers, found bupropion increased abstinence during the medication phase of the study, but did not produce the long-term abstinence seen in KIS-I heavy smokers.[24] KIS-III light smokers reported average use of 8 cpd, showed notably high levels of cotinine (275.8ng/ml), and reported smoking soon after wakening (72% within 30 min), suggesting physical nicotine dependence.[34] Overall, the KIS studies have identified some differences in African American light and heavier smokers (e.g., long-term response to bupropion), but many similarities (e.g., higher cotinine levels compared to Whites, time to first cigarette showing reflecting nicotine dependence, bupropion doubled quit rates relative to placebo at end of treatment, long-term treatment response was related to adherence). To further advance treatment, we propose the first pharmacotherapy trial to include all levels of cpd to examine both shared and differentiating characteristics of African American smokers, and to evaluate how these factors impact treatment outcome.

Given notable cotinine levels, nicotine dependence, and the early impact of bupropion on abstinence, findings support the idea that African American light smokers will benefit from pharmacotherapy to aid smoking cessation. Only two other studies have evaluated pharmacotherapy for light smokers.[16,32] Shiffman

demonstrated efficacy of nicotine lozenge relative to placebo in a largely White sample (1-15 cpd).[32] Gariti[16] compared nicotine patch and bupropion in a racially mixed sample (6-15 cpd; 68% African American), and found lower quit rates among African Americans. Modest quit rates in those studies are consistent with our KIS findings, further supporting the need to improve treatment for African Americans, including light smokers.

C. Evaluating varenicline for African Americans, including light smokers, is responsive to the *Clinical Practice Guidelines*.

The *Guidelines* recommend pharmacotherapy to aid quitting, unless contraindicated.[1] Varenicline, a α4β2 nicotinic acetylcholine receptor partial agonist and antagonist, is a first-line medication for smoking cessation approved by the FDA in 2006. Varenicline demonstrates the highest quit rates of any single medication: average month 6 smoking abstinence rates for varenicline were 33%, compared to 19-27% for bupropion and nicotine replacement therapies and 13% for placebo.[1] Past varenicline trials have included predominantly White samples, with less than 5% African Americans across studies,[35] and have been unable to test efficacy specifically among African Americans. Given varenicline's impact on the α4β2 nicotinic acetylcholine receptor, findings of genetic variability showing differences between African Americans and Whites associated with smoking and dependence[36,37] add support for examining efficacy of varenicline in African Americans.

While trials of varenicline have been conducted among moderate to heavy smokers,[38-47] varenicline is approved for all levels of smokers. Prior studies have not shown differences in efficacy or safety of varenicline based on smoking level (i.e., moderate level smokers have similar rates of abstinence as heavier smokers), but light smokers of any racial/ethnic group have not been included and little is known about the side-effect profile in light smokers. Indeed, as varenicline is a non-nicotine medication and is not dosed based on smoking level, it is not expected that side effect profiles will differ in light smokers relative to heavier smokers. Nonetheless, we will evaluate this along the spectrum of smoking levels. Further, adherence to counseling and pharmacotherapy has been consistently linked to improved smoking cessation outcomes,[48-50] and early adherence is identified as particularly important.[48,51-53] Our pilot study of varenicline for moderate to heavy African American smokers (> 10 cpd) achieved excellent adherence (>86% of doses taken).[48] Because side effects may impact adherence, we will include evaluation of these factors in relation to treatment outcome.

Because varenicline acts, in part, by saturating the nicotinic receptor and thereby reducing the reinforcing effects of nicotine, i.e., reducing withdrawal and craving, as well as reducing the rewarding effects of smoking,[54] *it may be particularly appropriate for light smokers*. While heavier smokers may titrate levels of nicotine in order to avoid withdrawal,[55] light smokers may be more likely to smoke for the positively rewarding aspects of tobacco use. Utilization of a placebo-controlled design will allow evaluation of expected mechanisms of action, and over the course of treatment we will assess change in withdrawal and craving relative to placebo for all participants, and rewarding effects of nicotine for continued smokers.

<u>The proposed study addresses critical gaps in the literature by conducting the first known placebo-controlled study of varenicline in African American smokers and the first study of light and moderate to heavy smokers within a single trial with the goal of examining efficacy for African American smokers</u>. We will not formally examine equivalence *between* light and heavier smokers (see III.B.5.). Instead, we will focus on the clinically relevant question of whether varenicline is effective for each of these subgroups. This is particularly critical for light smokers, for whom few evidence-based treatments have been established. Our approach will enable evaluation of varenicline efficacy for African American smokers generally (Aim 1) and examine efficacy specifically within light smokers (Aim 2a) and also within moderate to heavy smokers (Aim 2b).

Our proposed research will add vital scientific and clinically meaningful data beyond current NIH varenicline trials. One efficacy study of varenicline examines a predominantly White subset of light smokers (PI: Ebbert; NCT01639560), but that study will not address efficacy for African Americans. Our team is involved in another study to understand *differences* in quitting between African American and White smokers (PI: Nollen; NCT01836276), but that study does not evaluate efficacy of varenicline compared to placebo or any other treatment, does not include the full range of cpd, and will be unable to evaluate the effect of varenicline on side effects or factors that may contribute to treatment efficacy (e.g., withdrawal, craving, reward, medication adherence) compared to placebo, all of which are important contributions of the proposed study.

D. Nicotine intake may inform dependence, treatment response, and disease burden.

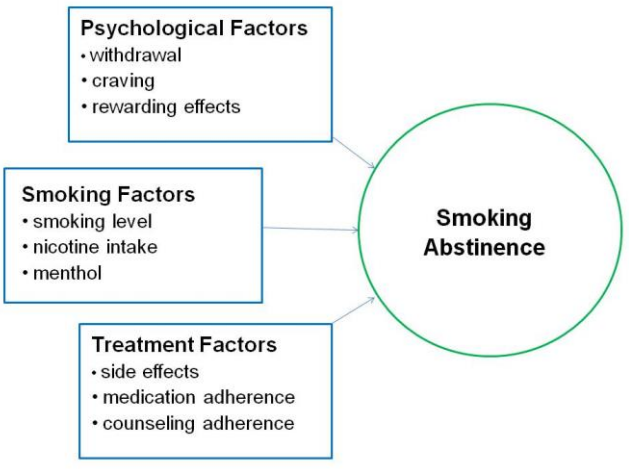
Compared to moderate to heavy smokers, light smokers historically have been thought to be less dependent, less in need of treatment to aid quitting, and excluded from clinical trials.[1,20] Cigarettes per day (cpd) was commonly used as a proxy for dependence, i.e., the more cigarettes smoked, the higher nicotine intake must be, producing a more physically dependent smoker. Thus, it was largely presumed physical dependence was not a concern for light smokers. Many clinical trials with predominantly White samples of

moderate to heavy smokers showed cpd and nicotine dependence predicted treatment outcome, i.e., higher dependence or greater cpd increased risk for continued smoking.[56-59] However, as research has begun to examine light smokers, findings show many light smokers have difficulty quitting, are unable to quit even when motivated and using treatment, and benefit from pharmacotherapy.[24,32] With African American smokers, understanding "light" smokers by only considering cpd may be limited, as low cpd does not clearly translate to low levels of nicotine intake. African American smokers have higher levels of cotinine based on their smoking level compared to White smokers.[12,60] Variation in nicotine metabolism plays some role, as African Americans are more likely to have slower nicotine and cotinine metabolism,[13] such that they smoke fewer cpd but produce higher levels of cotinine.[11] In both KIS-II and KIS-III, baseline cotinine rather than cpd predicted treatment outcome.[51,61] Cotinine is metabolized to 3-hydroxycotinine (3HC). The 3HC:cotinine ratio is a valid, noninvasive marker for nicotine metabolism.[62,63] Use of menthol cigarettes may also contribute to the ability to intake higher levels of nicotine per cigarette smoked.[64,65] Given limited data on African American light smokers (e.g., higher cotinine, similar nicotine intake to heavier smokers of other racial/ethnic groups, challenges in stopping smoking[16]), it will be informative to expand our evaluation, looking beyond cpd by examining *nicotine intake* across all cpd levels. Total nicotine exposure is best estimated by measuring total nicotine equivalents (TNE) (nicotine and all major nicotine metabolites: nicotine, nicotine-glucuronide, cotinine, cotinine-glucuronide, 3-hydroxycotinine, 3HC-glucuronide) in urine.[66] Nicotine intake is a direct measure of the extent of self-administration. Individuals with lower levels of nicotine intake are expected to respond better to less intensive treatment intervention, while those with higher levels might have greater need for pharmacotherapy to aid abstinence. In this study, we will expand evaluation of our sample by evaluating TNE in relation to cotinine, nicotine metabolism (3HC:cotinine), and cpd, and will examine these factors as predictors of abstinence (Aim 3). By moving beyond simple conceptualization of light and heavy smokers based only on cpd, we will advance our understanding of how these factors may influence differential response to treatment.

Further understanding nicotine intake in relation to carcinogen exposure remains important given health disparities experienced by African American smokers. For example, Africans Americans have a higher lung cancer risk than White smokers, with this difference most pronounced at low levels of cigarette consumption.[67] Indeed, while the relative risk at $\geq$30 cpd is not significant (1.22; ns), relative risk is increased at 11-20 cpd (1.75; $p < .001$) and even greater at $\leq$10 cpd (2.22; $p < .01$). While cpd provides some indication of disease risk, it is not an accurate estimate of carcinogen exposure.[68] Assessment of nicotine intake (using TNE) is highly correlated with carcinogen exposure, as measured in 4-(methylnitrosamino)-1-(3)pyridyl-1-butanol (NNAL). NNAL is a specific biomarker for tobacco smoke carcinogenicity.[69,70] NNAL is a pulmonary carcinogen and metabolite of 4-(methylnitrosamino)-1-(3)pyridyl-1-butanone (NNK), a tobacco-specific nitrosamine related to the development of lung cancer.[68] Benowitz and colleagues found NNAL and TNE assessed in urine are highly correlated, independent of race.[68] Prior studies of the relationship between nicotine exposure and NNAL have been limited in terms of analysis specifically of African Americans across the spectrum of cpd: these studies have not been designed to adequately evaluate light smokers within the lower levels of the smoking continuum or heavier African American smokers above 20 cpd.[68,71,72] The proposed research would advance previous findings: examination of nicotine intake (TNE) and carcinogen exposure in African American smokers (Aim 3), *including all levels of cpd*, would expand our understanding of these relationships, thereby elucidating biological factors that may contribute to the disproportionate disease burden faced by this high risk group.[68]

E. Biopsychosocial factors influence tobacco use and treatment outcomes.

Our research is guided by the Biobehavioral Model of Nicotine Addiction and Tobacco-Related Cancers,[103-104] which conceptualizes tobacco use as resulting from multifaceted relationships between psychological, social, and biological factors in relation to behavioral factors, and in relation to tobacco use, smoking cessation and relapse, and subsequent morbidity. While some factors contributing to African American smoking may be shared risk factors identified in other groups (e.g., gender, dependence, lower socioeconomic status), other factors may be particularly salient for African American smokers (e.g., nicotine intake, menthol use). Because biopsychosocial determinants of smoking may differ by



racial or ethnic group, empirical study focused specifically on African American smokers is needed to advance treatment.[73] We propose to describe key psychological (e.g., withdrawal, craving, reward), smoking (behavioral and biological factors, e.g., smoking level, nicotine intake, menthol use), and treatment factors (side effects, medication adherence, counseling adherence) characterizing African American smokers, in order to learn more about the relationship between these factors and treatment outcome (smoking abstinence) (Aim 4). Measures and analyses are detailed in III.J. and III.K. While we expect interaction between some of these factors (e.g., nicotine intake and smoking level), the proposed analyses will identify critical relationships as a foundation on which to advance this line of research in order to better understand mechanisms of action. Further, as African Americans are a hetero-geneous group, identification of individual differences may shed light on individual protective or risk factors related to tobacco use and treatment response. As novel therapeutics are designed for treating tobacco use and as behavioral interventions recognize key individual differences, elucidation of pertinent biopsychosocial factors will promote tailored treatment and enhance treatment efficacy. Increased treatment efficacy will subsequently reduce tobacco-related health disparities, morbidity and mortality among African Americans.

F. Summary of Impact.

The proposed evaluation of varenicline treatment for African American smokers is responsive to the *Clinical Practice Guidelines'* call for treatment research among minorities and research including light smokers.[1] Experience from our previous KIS trials suggests efficacy of pharmacotherapy established in Whites cannot be applied to efficacy in African Americans, who differ from White smokers in terms of smoking patterns and rates of cessation. A varenicline trial is imperative for improving knowledge about factors that promote and inhibit abstinence in African Americans across the full range of cpd. Given a) the heavy and disproportionate disease burden faced by African American smokers, b) the relatively lower quitting success seen in African American smokers, c) the increasing proportion of light smokers in the general population and among African Americans, and d) the limited study of African American smokers or light smokers, our findings have the potential for major impact on advancing treatment, reducing mortality, and narrowing the health disparities gap.

By being the first placebo-controlled, pharmacotherapy clinical trial to include all levels of smokers, we will be able to evaluate shared or differing responses to varenicline relative to placebo with specific attention to mechanisms of action. In doing so, we will know more about key behavioral and biological features that will provide tangible evidence to direct clinical care and to inform future intervention research. The proposed study will also advance biological characterization of African American smoking, elucidating key relationships between nicotine intake, smoking level and carcinogen exposure. This knowledge is critical to improving treatment for African American smokers, with implications for individualized pharmacotherapy and education about personalized health risks. Establishing efficacy of varenicline for African American smokers with attention to both light and heavier smokers will have significant direct impact on clinical practice guidelines for treatment of this high-risk group. Any advancement in treatment will subsequently reduce tobacco-related morbidity and mortality and will narrow the gap to reduce tobacco-related health disparities.

II. INNOVATION

The proposed research marks the first placebo-controlled study of varenicline among African American smokers and the first to include all smoking levels. Emphasis on the full range of smoking levels is culturally relevant because over half of African American daily smokers are light smokers. This study will also be the first, within the context of treatment, to characterize nicotine intake (using TNE) and carcinogen exposure among African American smokers across the full spectrum of smoking level. Further, while standard design for smoking cessation pharmacotherapy trials includes evaluation at end of treatment (EOT) and long-term (e.g., 6 month) follow-up, such a design does not allow examination of potential early relapse following EOT. KIS-I and –III found significant drug effect during treatment but different long-term medication effects, yet study design did not collect data immediately following EOT. The proposed study design is strengthened by evaluating abstinence during the treatment phase (through Week 12, EOT), adding evaluation at Week 16, and including long-term evaluation (Month 6) to elucidate our understanding of smoking behavior change and relapse. Innovation is enhanced by the application of the *Biobehavioral Model* to the evaluation of African American smoking and treatment response. Using 3:2 randomization will allow more participants to receive active medication which will strengthen evaluation of side effects and medication adherence, and will facilitate examination of relationships between biopsychosocial and smoking factors in relation to treatment variables. We will stratify randomization on cpd ($\leq$10 or >10) and gender, to ensure balance across treatment groups. Proposed measurement offers evaluation of self-reported smoking behavior that may capture variations in daily

patterns which may be more evident in light smokers. Identifying effective pharmacotherapy and elucidating pertinent biopsychosocial factors related to abstinence will advance personalized treatment, thereby enhancing treatment efficacy. Our experienced, multidisciplinary investigative team, established community infrastructure, and history of smoking cessation trials with African Americans make us uniquely qualified to successfully complete this research.

III. APPROACH

A. Overview.

Table 1. Study timeline.

	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5
Development*	■				
Enrollment		■	■		
Follow-up		■	■	■	
Laboratory eval.		■	■	■	■
Data analyses		■	■	■	■

*Includes production of medication & matching placebo.

The proposed research is a randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy of varenicline among African American smokers. Five-hundred African American smokers will be randomized using a 3:2 ratio to receive varenicline (n=300) or placebo (n=200) for 12 weeks. Randomization will be stratified on cpd (≤10 or >10) and gender. All participants will receive a culturally-appropriate smoking cessation guide and individually-tailored, health education counseling. Follow-up assessment will occur at Weeks 16 and 26. Participation will last for 6 months. Self-reported assessment will measure smoking history and key psychosocial constructs, and salivary assessment will provide biological assessment of nicotine intake and verification of self-reported smoking abstinence. Study visits will be located at Swope Health Central (see III.D). Implementation will be supported by our KIS Community Advisory Board and community partners.

B. Design rationale and considerations.

B.1. Why a placebo-controlled trial? Because so few African Americans have been included in previous placebo-controlled trials of varenicline, sub-analyses of efficacy specifically within African American smokers have not been published. A placebo-control design allows evaluation of varenicline i) efficacy (blind to treatment condition), ii) side-effects, iii) effects on factors such as withdrawal, craving, reward, depression and iv) adherence. We considered comparing varenicline to bupropion or nicotine replacement, but identified several concerns. Two studies of nicotine replacement for light smokers[23,32] noted challenges in dosing light smokers and limited treatment response. We considered comparison to bupropion; however, our KIS-III trial of bupropion for African American light smokers did not show a sustained treatment effect.[24] Bupropion also has a greater number of contraindications compared to varenicline, which would result in a higher rate of exclusion of interested smokers. We endorse the need to evaluate all forms of pharmacotherapy for African American smokers, but focused this proposal on varenicline. Finally, we will not have a 'no treatment' condition, as all participants will receive individualized health education (HE) counseling: this practical, strategy and skill focused counseling was found to double quit rates compared to Motivational Interviewing, in our sample of African American smokers in KIS-II.[23] Thus all participants in this study will be provided with an effective counseling intervention, which is well beyond usual care.

B.2. Why 3:2 randomization? This study will examine African American smokers, an underserved population. Increasing the number of participants who will be receiving active medication strengthens three objectives. First, the increased number will strengthen our ability to describe side effects of active medication. Second, we will enhance our ability to evaluate Treatment Factors (medication adherence). Finally, we expect increased likelihood of receiving active medication to facilitate recruitment and enhance community support for this trial.

B.3. Safety of varenicline in light smokers? Varenicline is FDA approved for use with all smokers. We will use established inclusion/exclusion criteria for use of varenicline in this study. Data from previous trials show no evidence of increased number or greater severity of side effects in lighter (10-15cpd) compared to heavier smokers (>15cpd) (Pfizer, M. Posey, personal communication, May 1, 2010). Data from our varenicline pilot in African American moderate to heavy smokers also showed no correlation between smoking level and number or severity of side effects. However, as varenicline has not been previously evaluated for smokers who use <10cpd, we will routinely monitor side effects and follow protocols for reducing or discontinuing varenicline in the event of severe adverse events (AE), including discontinuation of varenicline in accordance with the most current FDA guidelines. In our varenicline pilot study only 2% of participants required discontinuation due to mood disturbance or neuropsychiatric symptoms: all other AEs were expected and not severe (e.g., nausea).

B.4. Why stratify randomization based on cpd and gender? Randomization will be stratified based on smoking level (≤10 cpd or >10cpd) and gender (female or male) in order to ensure a balanced allocation of light smokers to each treatment, heavier smokers to each treatment, and females and males to each treatment. This approach will ensure there is no confounding between these two variables and treatment allocation. We

are not focusing on cpd and gender as primary moderators, but instead propose to evaluate these and other individual characteristics within the proposed analyses (see III.K.)

B.5. Why not compare light versus heavier smokers? We do not hypothesize varenicline to have significantly greater efficacy in light or heavier smokers due to the partial agonist and antagonist effects which may allow it to both reduce the positively rewarding aspects of smoking as well as the negatively reinforcing effects of withdrawal; indeed, because of these properties, we expect varenicline to demonstrate efficacy in light smokers and in heavier smokers. Our approach does not determine whether varenicline effects are equivalent across light and heavier smokers: to perform a full equivalence test between light and heavier smokers, it would require over 1200 participants, which is well beyond budget constraints for this trial (see also III.K.3.2). Instead, we focus on the most *clinically relevant* questions of not only i) *does varenicline increase abstinence among African American smokers generally?* (Aim 1) but also ii) *does it work for light smokers?* (Aim 2a) and iii) *does it work for heavier smokers?* (Aim 2b) to most directly inform treatment and clinical practice.

B.6. Generalizability. Due to medication contraindications, generalizability of findings will be limited to African American smokers for whom varenicline may be safely considered. Our multi-channel, community-wide recruitment will support diversity of participant enrollment. We anticipate the majority of our sample will be lower SES, but relatively balanced between light smokers and moderate to heavy smokers. Given increasing prevalence of light smoking in the U.S. and high rates in some minority groups, the findings will be meaningful to a growing population. Our careful selection of assessments will aid the characterization of our sample and evaluation of the generalizability of our findings.

C. Preliminary studies.

Our multidisciplinary team has extensive experience conducting tobacco control, health disparities, and smoking cessation research. Dr. Cox has 15 years experience in controlled trials of pharmacotherapy and behavioral treatment of tobacco use, including minority populations, and was the Principal Investigator of the most recent NCI-funded KIS-III trial of African American smokers (CA091912). Dr. Ahluwalia is a leader in tobacco-related health disparities and has led 4 smoking cessation RCTs enrolling over 2,000 African American smokers. Dr. Benowitz is a preeminent expert on the pharmacology of nicotine in humans, including nicotine and carcinogen exposure and metabolism across racial/ethnic groups. Drs. Nollen and Ellerbeck have led three NIH-R01 tobacco treatment clinical trials in underserved populations. Dr. Faseru has expertise in chronic disease prevention in underserved populations and, through an NIH-funded minority supplement, was a co-I on the KIS-III trial. Dr. Mayo has expertise in biostatistics and led the analytical components of all three KIS trials. Our consultant, Dr. Tyndale, is an internationally recognized expert in drug metabolism related to tobacco use. Detailed description of the expertise of this team is found in the budget justification. Overall, this team has an established history of collaboration and successful completion of NIH-funded research.

The selected research highlighted below supports the current proposal demonstrating 1) successful recruitment and retention of African American smokers in pharmacotherapy clinical trials involving biological data collection, 2) our success in conducting community-based research in collaboration with Swope Health Central, 3) support for health education (HE) counseling, 4) feasibility of varenicline, protocols for medication management, and adverse event reporting, 5) use of pill boxes, adherence counseling and assessment, 6) our ability to maintain the integrity and fidelity of interventions, 7) existing protocols for training, supervision, and data management, and 8) our success with multidisciplinary, inter-institutional collaboration. Our KIS trials and varenicline pilot study have produced 45 publications to date, making substantial contributions to the literature on African American smoking behavior and treatment.

C.1. Kick It at Swope (KIS-I): (NCI R01 CA77856; Ahluwalia (PI), Mayo), KIS-I demonstrated efficacy of standard bupropion for 600 African American moderate to heavy smokers (≥10 cpd) showing significant treatment effect of bupropion compared to placebo at Week 7 end of treatment (36% vs. 19%) and at Month 6 follow-up (21% vs. 13%).[33] Greater reduction in depression was seen in the bupropion group compared to placebo, but there was no treatment effect on withdrawal reduction. 84% of the sample returned at 6 months.

C.2. Kick It at Swope II (KIS-II): (NCI R01 CA91912; Ahluwalia (PI), Nollen, Mayo, Benowitz, Cox). The first treatment study of AA light smokers (≤10cpd) demonstrated the efficacy of health education (HE) counseling compared to motivational interviewing (MI) (16.7% vs. 8.5% abstinence at Month 6 follow-up) but found no significant effect of nicotine gum relative to placebo.[23] 84.4% completed 6 month follow-up. Because health education doubled quit rates relative to MI, we used HE in KIS-III and will use HE in the proposed study.

C.3. Kick It at Swope III (KIS-III): Enhancing tobacco use treatment among African American light smokers. (NCI R01 CA091912) Cox (PI), Ahluwalia, Benowitz, Faseru, Mayo, Nollen. Dr. Cox (PI) led KIS-III, a double-blind, placebo-controlled, randomized trial evaluating the efficacy of bupropion versus placebo for smoking

cessation among 540 African American light smokers (≤10 cpd) who all received HE counseling. Participants smoked an average 8.0 cpd, had a mean serum cotinine of 275.8ng/ml, had 3.7 quit attempts in the past year, and 72% smoked within 30 minutes of waking.[74] At Week 26 follow-up, cotinine-confirmed abstinence rates were 13.3% and 10.0% in the bupropion and placebo groups, respectively, showing no significant group difference in long-term abstinence.[24] However, at Week 7 end of treatment, confirmed abstinence rates were 23.7% in the bupropion group and 9.6% in the placebo group ($p < 0.0001$) showing a significant drug effect during the medication phase.[24] The initial treatment effect could not be attributed to reduction in withdrawal or depression, completion of study visits, or adverse events.[24] Use of non-menthol cigarettes, lower baseline cotinine, medication use, and counseling session attendance predicted abstinence at Week 7.[51] Drug adherence was limited and early adherence significantly increased abstinence.[75] Lack of long-term efficacy in KIS-III light smokers was in contrast to significant long-term benefit of bupropion in KIS-I moderate to heavy smokers. KIS-III findings highlight the initial effect of bupropion treatment on supporting quitting in African American light smokers and the clear challenge of abstinence for light smokers not using pharmacotherapy.

C.4. Does Varenicline Help African American Smokers Quit: (Kansas Masonic Cancer Research Institute Pilot Study; Nollen (PI), Cox, Ahluwalia, Ellerbeck, Benowitz). This pilot study of varenicline among 72 African American moderate to heavy smokers (>10 cpd) included emphasis on medication adherence within counseling, pill-boxes to support medication adherence, and a combination of medication monitoring and self-report to assess medication adherence. This pilot demonstrated feasibility and safety, but included a limited sample, no placebo, and was not designed or powered to evaluate efficacy. Cotinine-verified abstinence was 24% at Week 12 end of treatment: while this rate was modest compared to varenicline efficacy trials (with predominantly White samples),[38-47] it is promising relative to other pharmacotherapy trials in African Americans.[16,23,24,33,76] This pilot achieved excellent adherence (86% of doses were taken at Week 12) and retention (85% returned at Week 12).[48] We examined side effects by smoking level and found no significant difference in mean number of total or severe side effects between moderate (11-15 cpd) and heavier (>15cpd) smokers.[48] Protocols to be used in the proposed study include i) varenicline distribution and adherence assessment, ii) assessment of adverse events and counseling strategies for managing varenicline side-effects, and iii) monitoring mood per FDA guidelines.

D. Study site.

Swope Health Central is a community clinic located in urban Kansas City. Swope and the University of Kansas Medical Center have had a collaborative relationship for over 14 years, and Swope has been the home of our three previous NIH R01 KIS trials and our varenicline pilot. Swope has over 51,000 unique patients who complete over 174,000 yearly visits; 75% of patients are African American.

E. Community Advisory Board (CAB).

Our existing CAB (community leaders, healthcare providers, clergy, media experts, former smokers, some of whom have served on our CAB since KIS-I) will meet twice annually to review materials/recruitment, act as a local sponsor for the project, and facilitate dissemination of findings.

F. Recruitment.

We will enroll 500 eligible adult African American smokers. Prior KIS trials support our considerable knowledge of recruitment, in coordination with Swope,[74,77] enrolling over 2,000 African American smokers to date. While recruiting solely from Swope is feasible (Table 2), limited recruitment would reduce generalizability of study findings. Thus, as in our previous studies, recruitment will extend to the greater Kansas City area (population 2.1 million, 11.9% African American). Participants will be recruited using a combination of our most successful methods (described elsewhere[35,76]) through multiple clinic and community-based strategies running concurrently. We will also add new methods taking advantage of electronic medical records within KUMC (identifying 1,900 African American smokers from outpatient clinics in past 6 months) and of our membership in the Midwest Cancer Alliance to further enhance enrollment.

Table 2. Example of potential for clinic-based recruitment from Swope Health Central.

Annual Adult Visits	Unique patients per year	Adjust for 75% AA at Swope	Adjust for smoking prevalence*	Adjust down for 50% light smokers	Adjust down 50% for ineligible and refusals	Adjust down 40% for no-show to enrollment	Targeted enrollment
174,128	51,868	38,901	10,892	4,901	2,450 eligible	1,470	610

*Adjustment for smoking prevalence by gender = 28%

G. Participants.

Eligibility criteria are outlined in Table 3. To minimize risk, exclusion criteria are consistent with contraindications for varenicline.

An authorized provider, which includes the study physician, Dr. Ed Ellerbeck, authorized providers at KUMC, or the patient's primary care provider must approve use of varenicline for each participant, in writing, prior to enrollment. Individuals not receiving authorization will not be enrolled into the study. Inclusion criteria identify daily smokers (the focus of this study), and exclude intermittent smokers (smoking fewer than 5 days/week), and those transitioning in behavior (smoked current pattern < 12 months). Those ineligible for the study will be offered self-help materials and referral to local cessation resources.

Table 3. Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
• Self-identified African American • ≥ 18 years of age • Smokes ≥1cpd • Smoke on ≥25 days of the past 30 days • Functioning telephone • Interested in quitting smoking • Interested in taking 3 months of varenicline • Willing to complete all study visits • Medication approval from their own physician	• Renal impairment • Evidence or history of clinically significant allergic reactions to varenicline • A cardiovascular event in the past month • History of alcohol or drug dependence in the past year • Major depressive disorder in the last year requiring treatment • History of panic disorder, psychosis, bipolar disorder, or eating disorders • Use of tobacco products other than cigarettes in past 30 days • Use of pharmacotherapy in the month prior to enrollment, including prior use of varenicline • Pregnant, contemplating getting pregnant, or breastfeeding • Plans to move from KC during the treatment and follow-up phase • Another household member enrolled in the study

H. Intervention.

H.1. Kick It at Swope Guide.

The *Kick It at Swope: Stop Smoking Guide* is a 36-page health education guide used in our KIS-II and KIS-III studies. The guide will be revised and updated to include information on varenicline, importance of medication adherence and strategies to support adherence.

H.2. Health Education (HE) Counseling. Our work and others have documented the efficacy of directive, health education (HE) counseling including information, cognitive and behavioral components.[16,23,78] Specific content for HE counseling (outlined in Table 4) is consistent with treatment guidelines, incorporating cognitive and behavioral strategies and skill building based on personal needs to individualize treatment. The Information-Motivation-Behavioral Skills (IMB) model of adherence behavior change, will support medication use.[79-85] Sessions will incorporate use of the *Kick It at Swope: Stop Smoking Guide*. Quality of counseling is critical to study integrity. Drs. Cox and Nollen will lead training along with Dr. Faseru (Co-I) and Project Director Tricia Snow, MPH. Counseling sessions will be audio-taped for weekly supervision provided by Dr. Nollen. Counselors will also complete training in human subjects protection, management of adverse events, suicide assessment/referral, and data management, with ongoing fidelity monitoring per established protocols.

Table 4. Overview of Health Education Counseling Sessions

Session	Goal	Topic
Wk 0	Establish rapport, emphasize willingness to help, encourage motivation/confidence to quit.	Health risks for AA smokers, benefits of quitting, learning from quit attempts; develop quit day plan; instructions of medication use, emphasizing adherence; identifying triggers, managing withdrawal.
Wk 1 *via phone*	Reinforce quit day plan, address medication use, identify concerns, barriers, and strategies for success.	**If quit:** Rewarding yourself, recovering from slip, review medication use/adherence, managing stress, alternatives to smoking, identify barriers/strategies, living smoke-free.
Wks 4, 8, 12, 16 *in person*	Reinforce/encourage abstinence efforts. Identify concerns, barriers, and strategies for successes.	**If still smoking:** Review reasons for not quitting, reasons for quitting, discuss specific problems that lead to relapse, problem solve primary barriers, and attempt to set a new quit plan.

H.3. Varenicline. Dosing will be 1mg of varenicline twice daily, with titration following standard dosing guidelines (0.5 mg once daily for 3 days, 0.5 mg twice daily for 4 days, then 1 mg twice daily for the remaining 11 weeks of treatment). Varenicline is an FDA approved medication for smoking cessation. Common side effects are nausea, insomnia, vivid dreams, dry mouth, flatulence, constipation, irritability, headaches, dizziness, fatigue. We are sensitive to the FDA warnings regarding neuropsychiatric complications (depressed mood, suicidal behavior) and cardiovascular symptoms reported in some patients. We will protect participants and minimize risks by using strict exclusion criteria and careful monitoring of Adverse Events (AE). Varenicline use will be under supervision of study physician Dr. Ellerbeck and clinical psychologists Drs. Cox and Nollen. Participants will be prompted to report side effects at each visit and given the study phone number to report AEs at interim time points. Issues needing medical attention will be referred to Dr. Ellerbeck. We will follow NIH guidelines for reporting AEs to

the Human Subjects Committee. Further we will be supported by the University of Kansas Cancer Center's Data Safety Monitoring Board (DSMB).

Varenicline will be discontinued for those who become pregnant or develop a contraindication that requires discontinuation (e.g., persistent vomiting, neuropsychiatric complications). Per package insert, dose reduction from 2 mg to 1 mg per day may be recommended for other moderate to severe symptoms (e.g., headache) that have not diminished with side-effect management techniques. Active or identical placebo medication will be dispensed in pill boxes: participants will receive one month of study medication at Weeks 0, 4, and 8. Pill boxes will include one week of extra medication to ensure adequate time to obtain the next medication refill. Participants will be asked to begin medication the day after randomization and to set a quit date for Day 8.

I. Study procedures.

I.1. Initial screening. Interviews by phone or in person will review inclusion/ exclusion criteria and provide detailed information about study participation. Those eligible and interested will be scheduled for final, in person, eligibility screening within 25 days at Swope Health Central.

I.2. Final screening, consent, enrollment, randomization (Week 0). Final eligibility will be in person at Swope or at the KUMC CRU to minimize attrition. It will include a pregnancy test for women of childbearing age. For those eligible, staff will review consent forms describing study goals, procedures, medication risks, and confidentiality. Staff will emphasize voluntary participation; participants may withdraw at any time without affecting their relationships with Swope or the University. Staff will answer questions, obtain verbal and written informed consent, and distribute a copy of the consent form. Those completing consent will be enrolled and assigned a unique identification number.

I.3. Medication dispensing (Weeks 0,4,8). Medication will be dispensed in pill boxes in one month increments (received at Weeks 0,4,8, returned at Week 12). We tested feasibility of pill boxes and monthly refill visits in our varenicline pilot and achieved excellent adherence (90% of doses taken at Week 4; 86% at Week 12).[48]

Table 5. Overview of Major Study Events

		Pharmacotherapy Phase					Follow-up		
	Screen	Enroll	Quit Date			EOT		Primary Outcome	
Week/Month		Wk 0	Wk 1	Wk 4	Wk 8	Wk 12	Wk 16	Mo 6	
Remuneration		$30		$30	$20	$40	$20	$50	
Intervention									
Counseling		x	x*	x	x	x	x		
Dispense meds.		x		x	x				
Measures									
Screening	x*	x							
Consent		x							
Assessments		x		x	x	x	x	x	
Biological Sample Collection									
Urine		x							
Blood		x		x					
Saliva				x		x	x	x	

*Phone visit; all other visits in-person.

I.4. Health education counseling (Weeks 0,1,4,8,12,16). Counseling sessions (described above) will be completed in person at Weeks 0, 4, 8, 12, 16, and by telephone at Week 1. The number of sessions is consistent with previous KIS studies. Sessions will last approximately 30 minutes.

I.5. Self-report assessment (Weeks 0,4,8,12,16, and Month 6). Trained staff will administer self-report assessments at each in person visit. Time to complete surveys will be approximately 30-40 minutes at Week 0, 15 minutes at Weeks 4, 8, 12, 16, and Month 6 . Compared to our previous clinical trials, we have increased the number of assessment time-points in order to gather additional information about smoking behavior change, relapse, and medication adherence.

I.6. Biological sample collection. Urine collection (Week 0) will assess total nicotine exposure (TNE), measuring levels of nicotine, cotinine, 3-hydroxycotinine (3HC), and their respective glucuronide metabolites. The molar sum of all metabolites normalized for urine creatinine will be computed (called nicotine equivalents) as the estimate of daily nicotine intake from smoking. Week 0 urine will also be used to assess total NNAL (free plus glucuronide) as an indicator of carcinogen exposure. Blood will be collected at Week 0 and will be used for analysis of nicotine metabolism genotype (CYP2A6 and associated markers) and phenotype (3HC:cotinine nicotine metabolism ratio). Blood collected at Week 4 will measure varenicline levels to assess medication adherence early in treatment. Saliva will be collected at all in-person visits beyond baseline from those reporting 7-day point-prevalence abstinence, to provide biological verification of smoking status, using the cut-point of 15ng/mL to differentiate smokers from nonsmokers.[86] Only among participants who self-report abstinence but also report use of nicotine replacement therapy (NRT) (contrary to study protocol), we will

collect urine samples for assessment of anabasine and anatabine (tobacco alkaloids) as biomarkers of tobacco use, to distinguish from NRT.[87] Standard procedures will be used for urine nicotine, cotinine, 3HC, urine NNAL, blood nicotine metabolism and varenicline, and salivary cotinine samples. Dr. Benowitz and Dr. Tyndale's labs will use standard quality control measures.

I.7. Stratified randomization based on smoking level (cpd) and gender. Randomization will be stratified based on smoking level (≤10 cpd or >10cpd) and gender (female or male) in order to ensure similar numbers of lighter and heavier smokers in each treatment condition and similar numbers of females and males in each treatment condition. Producing treatment groups balanced on these factors will strengthen proposed analyses.

I.8. Retention. KIS trials have had successful retention, using a system of reminders and compensation. Participants will provide contact information (address, email, two telephone numbers, alternate contact) to facilitate follow-up. Post cards and multiple calls will be used to remind all follow-up visits.

Missed sessions will be followed by 6 calls to the participant or alternate contact in effort to complete the session in the protocol window (see Appendix).

I.9. Remuneration. Participants will be given a ClinCard and the following amounts will be loaded on the card after completion of specific study visits: $30 at Wks 0 and 4, $20 at Wks 8 and 16, $40 at Week 12, and $50 at Wk 26. If participants complete all study visits, they will be compensated a total of $190 for their time/travel and in appreciation for their participation. Compensation will not be contingent on smoking status. 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.

J. Measures.

Measure selection was guided by our theoretical model and factors related to cessation. Measures are widely used, validated, and demonstrate adequate psychometric properties in our studies with African Americans. Due to varied participant literacy levels, questions will be read to or along with participants by study staff.

J.1. Primary Outcome. *Smoking Abstinence:* The primary endpoint is biochemically verified 7-day point prevalence abstinence defined as no cigarettes (not even a puff) for the previous 7 days at Month 6, as defined in consensus statements.[88] Secondary endpoints will be verified 7-day point prevalence abstinence at Week 12 (EOT). Saliva will be collected from participants who self-report 7-day point prevalence abstinence at post-baseline visits (Weeks 4,,12,16, and Month 6) to evaluate abstinence over the course of the study. Cotinine is the measure of choice because of its superior sensitivity and specificity.[12,88] We will use the recommended cut-point of 15ng/mL to differentiate smokers from nonsmokers. *Note: Cotinine levels from even excessive secondhand smoke (SHS) exposure (5-6 ng/ml) are far lower than our cut-point for abstinence verification (15 ng/ml),[89]thus we will not risk misclassification due to SES exposure. Further, to differentiate abstinent individuals who may have used nicotine replacement (contrary to study protocol), among those who report abstinence but also self-report NRT, we will collect urine to evaluate tobacco alkaloids anabasine and anatabine to distinguish tobacco use from NRT and thereby validate tobacco abstinence.[87]*

J.2. Demographics. We will assess age, gender, marital status, education, income, employment at Week 0.

J.3 Smoking Variables. Items from the *COMMIT Smoking Prevalence Survey* will assess *Smoking History*: tobacco use, age when first smoked, age when started smoking regularly, quitting/relapse history, use of menthol, brand smoked, home smoking restrictions, and social influence on smoking. Baseline assessment of *Nicotine Dependence* will use the *Fagerström Test for Nicotine Dependence (FTND)*[90] which includes "time to first cigarette" of the day, increasingly considered a proxy for individual level of nicotine dependence for even light smokers, and the multidimensional *Brief Wisconsin Inventory of Smoking Dependence Motives*.[91] At all timepoints, we will assess *Daily Smoking Patterns* using the *Timeline Follow-Back (TLFB)*[92,93] which measures estimated daily number of cigarettes and variation in smoking patterns over time, to examine initial abstinence, smoking reduction, lapses, time to relapse, and behavior transitions recommended for assessment of treatment mechanisms.[94] Standardized PROMIS items (Patient-Reported Outcomes Measurement Information System) will be used to assess baseline (Week 0) *Dependence*, *Smoking Motivation*, and *Health Expectancies*. For participants who report a quit attempt and subsequent relapse, we will assess reasons for relapse at Weeks 4, 12, 16, and 26.

J.4. Social and Psychological Variables. Baseline assessment (Week 0) will include standard survey items of use of alcohol (AUDIT), marijuana and prescription pain relievers (SAMSHA National Survey on Drug Use). We will measure *Social Isolation* at Week 0 using Cohen's Social Network Index. To evaluate potential changes over the course of treatment, we will evaluate nicotine withdrawal, craving, and negative affect at Weeks 0,4,7,12. We will assess *Nicotine Withdrawal* using the *Minnesota Withdrawal Scale (MNWS)*[98]; *Craving* using the *Brief Questionnaire of Smoking Urges (QSU-Brief),*[99] a multidimensional measure of craving;

and symptoms of ***Depression*** using the *Center for Epidemiological Studies Depression Scale (CES-D)*, short form, a 10-item measure of psychological distress, assessing cognitive, behavioral, and physical symptoms of depression.[100] Finally, we will assess ***Reinforcing Effects of Smoking*** (e.g., satisfaction, reward) using the 11-item *modified Cigarette Evaluation Questionnaire (mCEQ)*[101,102] at Week 0 for all participants and at Weeks 4,7,12 for continuing smokers. We will also examine ***Stress*** (*Perceived Stress Scale*, 4-item) and ***Anxiety*** (*Generalized Anxiety Disorder scale*, 7-item) at Weeks 0, 4, 12, 26.

J.5. Biological Variables. Baseline urine samples will be used to evaluate ***nicotine intake*** as total nicotine equivalents (TNE) (defined in I.6), the gold standard which has the strongest correlation with nicotine (and carcinogen) dose in laboratory studies.[66] Blood will be used to measure nicotine metabolism genotype (CYP2A6 and related metabolites) and phenotype (the 3HC:cotinine ratio).[62,63] Baseline urine will be used to assess total NNAL (free plus glucuronide) as a measure of ***carcinogen exposure***.[103,104] Height (Week 0) and weight (Week 0, 12, Month 6) will also be measured.

J.6. Treatment Adherence. *Early medication adherence* will be biologically evaluated using Week 4 blood samples to assess varenicline levels. *Medication adherence over the course of treatment* will be assessed at Weeks 4, 8, and 12 by participant self-reported recollection of pill use for the prior 5 days (5-day recall); we found strong correlations between drug levels, in-person recall, and telephone pill counts[105] and data support the validity of this approach.[106,107] We will examine *counseling adherence* as number of counseling sessions completed to examine percentage of total sessions completed.

J.7. Side effects. We will assess side effects using an adapted version of a 26-item medication symptoms checklist[108] at Weeks 0 (pre-drug), 1, 4, 8, and 12 to assess common symptoms (e.g., nausea, sleep disturbance, irritability) experienced in the past week, perception of the cause of each symptom (e.g., study medication versus other cause), and severity of the symptom ('does not bother at all' to 'bothers a lot'). We will use NCI's Common Toxicity Criteria (CTC) version 4.0 to assess individual adverse events at Weeks 1, 4, 8, and 12 (EOT) and Week 16 (30 days post EOT). We will also assess any pressure a person feels to be in the study. This will be tracked in order to monitor and report as an adverse event.

K. Analytical plan.

K.1. Sample size and power.

Aim 1: The primary endpoint will be cotinine verified 7-day point prevalence abstinence at Month 6. Based on data from our varenicline pilot study of African American smokers, we expect overall abstinence of 24% at the end of treatment (Week 12) and 17% at Month 6 follow-up (Primary Outcome) for participants in the varenicline group. Based on placebo conditions from KIS trials, we anticipate abstinence of 10% at the end of treatment (Week 12) and 8% at Month 6 follow-up (Primary Outcome) for participants in the placebo group. Using the chi-square test, along with the assumptions above, 300 participants in the varenicline group and 200 participants in the placebo group will give us 80% power to detect expected differences at Month 6 with a type 1 error rate of 5%; we will also have 97% power to examine Week 12 abstinence.

Analyses for all aims will be done in an intent to treat manner. Those lost to follow-up will be imputed as smokers and all participants will remain in randomized group assignment regardless of adherence. If there is a significant difference in the loss between the two groups multiple imputation will be utilized.

Aim 2: Given national estimates and prior KIS trials, we anticipate enrolling approximately 50-60% light smokers (1-10cpd). Using the assumptions described above, with the expectation that cessation rates will be similar for light smokers (1-10cpd) and heavier smokers (>10cpd), and assuming we have similar enrollment of light and heavier smokers (≈250 light smokers, ≈250 heavy smokers), we will be able to examine efficacy of varenicline versus placebo independently in light smokers (Aim 2a), and examine efficacy of varenicline versus placebo separately in moderate-heavy smokers (Aim 2b), with 76% power to detect expected differences between varenicline and placebo in each subgroup at Week 12 end of treatment. If we enroll more light than heavier smokers, we would maintain 65% power even if 60% of participants are light smokers.

K.2. Baseline characteristics. Quantitative variables will be summarized by means and standard deviations globally and by treatment group. Categorical variables will be summarized by frequencies and percents globally and by treatment group.

K.3. Evaluation of study aims.

1. Primary Aim: To evaluate the efficacy of varenicline versus placebo for tobacco use treatment among African American smokers: The chi-square test will be used to compare the 7-day point prevalence abstinence at Month 6 (primary outcome) between the two groups. Then we will use multiple logistic regression to assess the effects of gender, age, baseline level of smoking, time to first cigarette, and type of tobacco, along with treatment on 7-day point prevalence abstinence at 6 months. These variables have consistently shown impact in our studies in African American smokers. [61,109] Subsequently, we will use identical methods for secondary outcome, Week 12 (end of treatment). We will also look at continuous and prolonged abstinence in a similar manner.

In addition, we will longitudinally compare verified abstinence across 6 months between the treatment groups using generalized estimating equations (GEE), and will examine the measures defined above as additional covariates in the GEE model while controlling for treatment. This allows us to have information at specific clinically relevant time points as well as over the entire course of study.

Further, we expect treatment may impact certain psychological variables related to smoking and treatment response (withdrawal, craving, depression, and smoking reward, as described in J.4.) which are measured and scored at multiple time points during the medication phase of treatment. For these measures we will compare them between the two treatment groups controlling for baseline level longitudinally, during the treatment phase, using a linear mixed model assuming an autoregressive correlation structure for these measures over time within an individual.

Secondary aims:

2. To examine the effects of varenicline independently in light smokers and independently in moderate to heavy smokers. *Hypothesis 2a:* Light smokers (1-10cpd) receiving varenicline will have higher verified abstinence than light smokers receiving placebo. *Hypothesis 2b:* Moderate to heavy smokers (>10cpd) receiving varenicline will have higher abstinence than moderate to heavy smokers receiving placebo, at end of treatment.

We will utilize the same statistical methodologies on these a priori subsets as proposed for the full cohort as stated above (K.3.1). These are two separate sets of analyses, conducted independently for each subgroup based upon smoking level at baseline.

We do not hypothesize a significant difference in abstinence success rates between these groups, given limited data and given properties of varenicline which may make it well suited for light smokers as well as heavier smokers. The sample size of this study does not have the power to test for equivalence, assuming

equal numbers of light and moderate to heavy smokers, we would have only 21% power to determine equivalence assuming a 3% equivalent level difference or 48% power to detect a 5% equivalent level difference. Instead, our intention is to aid clinical decision making in both light smokers (addressing whether varenicline demonstrates efficacy for light smokers) and in moderate to heavy smokers (addressing whether varenicline demonstrates efficacy for moderate to heavy smoker).

In addition, within Aims 3 and 4 (below) we will evaluate further the relationship between smoking level (cpd as well as other related factors, e.g., cotinine, nicotine intake, nicotine metabolism, dependence) and treatment outcome (abstinence) controlling for treatment, in order to better understand risk and protective factors that influence treatment outcome.

3. To examine the relationship between baseline intake of nicotine and smoking level, and in relation to carcinogen exposure and abstinence in African American smokers.

3a.) To biochemically characterize exposure, we will examine the relationship among baseline nicotine intake (total nicotine equivalents, TNE), cotinine, nicotine metabolism ratio (3HC/cotinine), smoking level (cpd), and carcinogen exposure (NNAL). We will run a correlation analysis examining the pairwise correlations between each of these variables. We will also compare NNAL and nicotine intake at baseline between those defined as light and heavy smokers using a two-sample t-test.

3b.) To examine impact on treatment outcome, we will examine the relationship among baseline nicotine intake (total nicotine equivalents), cotinine, nicotine metabolism ratio (3HC:cotinine), and smoking level (cpd) by examining the correlation between these variables. Subsequently, we will examine these as predictors of end of treatment abstinence, controlling for treatment and demographic factors found associated with cessation from the primary aim.

4. To describe psychological, smoking, and treatment-related characteristics of African American smokers and evaluate these in association with abstinence: We will assess psychological (withdrawal, craving, reinforcing effects of smoking), smoking (nicotine intake (TNE), cpd, menthol), and treatment (side effects, medication and counseling adherence) factors independently. We will examine how these variables are associated with one another; a) two continuous variables will be examined by correlations, b) two categorical measure will be examine by chi-square tests and odds ratios, and c) one continuous and one categorical (dichotomous) will be examine by a t-test. We will also determine if these variables differ between treatment group. We will then evaluate these factors individually in their relationship to cessation and in a model to explore the association with end of treatment abstinence, controlling for treatment and any variables found in the previous aims. Given the expected number of events, we expect to identify at most 7 other factors (which includes potential interactions of factors) beyond treatment that could impact cessation in a multiple logistic regression model.

L. Limitations.

Limits to generalizability exist related to inclusion/exclusion criteria, such that findings may not pertain to all African American smokers. However, our sample will largely reflect the group for whom varenicline would be most appropriate, i.e., medically eligible smokers interested in treatment. The study will be limited to a single site within a mid-western metropolitan area. We will use a broad, multi-method approach to recruitment providing a diverse sample from this Kansas City region. We expect the overall findings will be meaningful in respect to African American smokers across the U.S. Further, while findings may not be directly generalizable to other racial/ethnic groups, evaluation of efficacy of varenicline among light smokers in this study will inform clinical considerations that may impact treatment of the growing number of light smokers of other racial/ethnic groups. At the end of the study, we expect to see significant differences in abstinence rates between treatment groups, demonstrating the efficacy of varenicline for treatment of African American smokers. However, if we do not see a significant drug effect for the whole spectrum of African American smokers in our sample (Aim 1), we will still be able to examine subsets of smokers for whom varenicline is effective (Aims 2a and 2b) and to identify individual factors related to treatment efficacy (Aims 3 and 4) in order to advance the state of science on individualized tobacco use treatment.