Study Title: Understanding Disparities in Quitting in African American and White Smokers

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SPECIFIC AIMS

Racial/ethnic differences in smoking are well documented; African Americans (AA) smoke fewer cigarettes per day than Whites but experience disproportionately greater smoking attributable morbidity and mortality. Well documented disparities also exist in smoking cessation with AA consistently quitting at lower rates than Whites. Our experienced, multi-disciplinary team has been working to improve tobacco use treatment outcomes in AA smokers for the last 10 years. Acknowledging the limitations of comparisons across different studies, five of our previous clinical trials enrolling only African Americans have documented lower quit rates for AA with nicotine gum, nicotine patch, and bupropion SR than those achieved for Whites in similar clinical trials. Results of our recently completed pilot study (n=72) of varenicline in AA smokers, considered to be the most effective of currently available medications, mirrors these previous findings. Cotinine-verified abstinence at 12 weeks was 24% in this all AA sample, substantially lower than the 49% week 12 biochemically-verified abstinence rates achieved for White smokers in published clinical trials. These findings highlight questions with regard to disparities in smoking cessation pharmacotherapy among AAs and the reasons for these disparities. To most effectively answer these questions, comparisons must be made between participants enrolled in the same trial. To date, no adequately powered study, stratified on race/ethnicity has been conducted to prospectively examine AA-White differences in smoking cessation and concurrently to examine potential causal pathways explaining AA-White differences in quitting. Such findings have important implications for improving tobacco treatment among AA smokers.

The **long-term** goal of our research is to reduce disparities in tobacco-related morbidity and mortality by evaluating promising interventions for high risk groups. By conducting the first head-to-head AA-White pharmacotherapy study, the **objective of this application** is to examine varenicline for smoking cessation among AA and White smokers, and to better understand racial differences in quitting. We will conduct a prospective cohort intervention study, stratified on race, age (< 40, ≥ 40), and gender, in which 448 participants (224 AA, 224 White) will receive 3 months of varenicline. The **central hypothesis** is that AAs will demonstrate lower 7-day abstinence from smoking at month 6 than Whites. We will also examine smoking, psychosocial, treatment process, and biological mechanisms underlying racial differences in quitting. Our specific aims are:

Aim 1: Describe the differences in smoking cessation among AA and White smokers treated with varenicline. Hypothesis 1. AAs will have significantly lower cotinine-verified 7-day abstinence at month 6 than Whites.

Aim 2: Identify the smoking, psychosocial, treatment process, and biological factors that independently explain the relationship between race/ethnicity and cotinine-verified 7-day abstinence at month 6. Hypothesis 2.1.(Smoking Factors). Menthol smoking will moderate, while cigarettes per day, nicotine intake, and nicotine dependence will mediate the relationship between race/ethnicity and cotinine-verified 7-day abstinence among AA and White smokers. Hypothesis 2.2.(Psychosocial Factors). Socioeconomic status (SES), social support, self-efficacy, barriers, negative affect, and perceived stress will mediate the relationship between race/ethnicity and cotinine-verified 7-day abstinence among AA and White smokers. Hypothesis 2.3.(Treatment Process Factors). Side effects, adherence (medication, counseling), withdrawal, craving, and the reinforcing effects of nicotine will mediate the relationship between race/ethnicity and cotinine-verified 7-day abstinence among AA and White smokers. Hypothesis 2.4. (Biological Factors). Phenotypic (3HC/COT) and genotypic (CYP2A6) markers for nicotine metabolism will moderate the relationship between race/ethnicity and cotinine-verified 7-day abstinence among AA and White smokers.

Aim 3: Examine the side effect profile of varenicline by smoking level. Hypothesis 3: There will be no difference in side effect profiles (number or intensity) by level of smoking [NOTE: Side effects will be examined as a mediator in Aims 2 but have been included as a separate aim here because no known studies have examined varenicline in lower level smokers (3-10 cpd)].

This study is innovative. It will be the first known study to report on the use of varenicline in AAs, the first to examine varenicline in light smokers (<10 cpd) and among a wide range of smoking levels (3-20 cpd), the first head-to-head study, stratified on race, designed to prospectively compare pharmacotherapy in AAs versus Whites, and one of a few to explore mechanisms underlying disparities in quitting between AA and White smokers. The impact of these findings has ramifications for treatment, clinical practice, and policy. Significant knowledge will be gained about AA-White differences in quitting. Findings will improve tobacco use treatment by moving the field away from a generic focus on race/ethnicity toward a targeted focus on modifiable barriers and facilitators to quitting smoking for AAs and Whites.

A. SIGNIFICANCE

A1. Disparities in Tobacco-Related Morbidity and Mortality. Tobacco is responsible for more than 442,000 total deaths and more than 30% of all cancer death annually in the U.S.[1,2] Although African Americans (AA) smokers use fewer cigarettes per day than Whites, they bear a disproportionate share of tobacco attributable morbidity and mortality.[3,4] AAs have the highest incidence rates for all cancers combined, and the highest overall cancer mortality rates compared to other racial/ethnic groups.[3,4] With regard to smoking-attributable lung cancer, specifically, AAs have a strikingly 43-55% higher relative risk compared to Whites.[5]

A2. Disparities in Smoking Cessation. Facilitating cessation among AAs is a national health priority.[6] Although AAs are more likely to attempt to quit smoking in a given year, they are less successful. Recent estimates suggest that 38% of AA ever smokers have quit compared to 50% of White ever smokers.[7]

While many studies have evaluated pharmacotherapy for smoking cessation among Whites, few have assessed efficacy with AA. Our research team has a dedicated line of research to better understand and facilitate smoking cessation among AAs. We have conducted previous NIH-funded trials in AA smokers examining bupropion, nicotine patch, and nicotine gum, in combination with behavioral counseling [8-11] and have consistently found modest quit rates compared to those achieved by White smokers on comparable therapy in similar studies.[6,8-10,12] Results of our recently completed pilot study of varenicline for smoking cessation in AAs mirrors these findings. Cotinine-verified Wk 12 abstinence was 24%. This is substantially lower than 49% Wk 12 abstinence rates found for White smokers in published randomized clinical trials (RCTs) and leads to more questions about disparities between AA and Whites in smoking cessation pharmacotherapy and the reasons for these disparities. It is important to note that we are comparing studies with different methodologies and sample characteristics and, therefore, caution should be used in interpreting the observed racial differences in quitting. In order to draw accurate conclusions about pharmacotherapy for one group relative to another it is necessary to make comparisons of participants enrolled in the same trial. The proposed study moves beyond the traditional approach of evaluating pharmacotherapy separately for each racial/ethnic group to comparing between AA and Whites enrolled in the same trial.

Quitting disparities have been reported by others. Posthoc analyses of clinical trials enrolling both AA and Whites have still found racial differences in quitting. A secondary data analysis from varenicline trials [13,14] found Wk 12 smoking abstinence rates of 27% among AAs (n=26/97) compared to abstinence rates of 49% for Whites (n=381/782) (M. Posey, personal communication, May 1, 2010). AAs in the Lung Heart Study were significantly less likely than Whites to quit smoking at year 1 (23% versus 34%), despite receiving nicotine gum and the same intensive cognitive-behavioral therapy for smoking cessation.[15] AAs in a randomized trial of counseling in combination with either bupropion or the nicotine patch were significantly less likely than White participants to be abstinent at year 1 ($Z=-2.21$, $p=0.03$)[16] Similarly, minority smokers, of whom 80.2% were AA, enrolled in a large multi-center randomized clinical trial of nicotine inhaler, bupropion, or both, were 44% less likely to quit smoking at Wk 12 (OR=0.56, $p<0.01$) compared to Whites, with 16% of minority and 26% of White smokers ($p<0.01$) demonstrating abstinence.[17] These studies have limitations, most notably, none were designed to empirically study the question about quit rates between AA and White smokers. Additionally, none were stratified by race, and most grouped all minorities together, limiting the ability to draw conclusions about AA-White differences in pharmacotherapy efficacy or smoking abstinence. Finally, and importantly, little attempt was made to explore possible mechanisms (e.g., income, adherence, menthol, etc.) for the observed disparities in quitting. Our proposal will address these key issues.

We anticipate that our study will demonstrate similar disparities and our unique study design will then allow us to examine the factors that underlie these disparities. If, however, we don't demonstrate these disparities, this study will still be equally significant – demonstrating that equal access to treatment with varenicline can eliminate disparities in outcomes. In the unlikely event that we don't see disparities in outcomes of this study, a modified analytic plan would still allow us to test for racial differences in mediators/moderators of smoking cessation (see C8). The resulting race specific models would explore factors associated with quitting for AA and for Whites and would have significant implications for identifying and developing interventions that address unique barriers and facilitators to abstinence in each group.

Reasons for Disparities. An understanding of possible reasons underlying AA-White differences in quitting smoking is guided by the Biobehavioral Model of Nicotine Addiction, which posits that tobacco use results from multifaceted relationships between biopsychosocial factors.[18,19] Our conceptual model of smoking, psychosocial, treatment, and biological factors linking race to quitting (Fig.1) is grounded in the biobehavioral model and factors speculated to explain lower quit rates in AAs relative to Whites, although existing empirical evidence is based on post-hoc analyses of trials that were not designed to examine AA-W differences. To maximize the potential of our findings to inform future practice we have selected factors that can be addressed

through intervention. Of the 14 proposed mediators most are modifiable, with evidence suggesting that attention to these factors improves treatment outcome. Of the factors selected, some should make it easier for AA to quit smoking (e.g., cpd), while others should make it more difficult (e.g., menthol). A rationale for the possible role of each factor in accounting for racial differences is summarized below.

Smoking Factors. AA smoke fewer **cigarettes per day** than Whites but prefer mentholated cigarettes; [20,21] 82% of AA smoke menthol cigarettes compared to 23% of Whites.[22] Smoking fewer cigarettes per day should translate into lower nicotine dependence, lower nicotine intake, and improved quit rates for AAs relative to Whites, but evidence suggests this is not the case. AA light smokers have comparable blood nicotine levels and dependence and experience the same difficulty quitting as Whites. [6,23-25] It is possible that any positive benefit of smoking fewer cigarettes per day is overwhelmed by AAs preference for menthol cigarettes. **Menthol cigarettes** have higher tar and nicotine content, have been shown to lead to greater **nicotine dependence** and **nicotine intake** per cigarette smoked, possibly because of the cooling effect that leads to greater depth of inhalation,[26,27] and facilitate the absorption of tobacco specific carcinogens.[28-30] Literature on the effect of menthol smoking on cessation is mixed, with some studies finding lower cessation rates in menthol versus non-menthol smokers[29,31,32] and others finding no association.[33-36] Examination of the interrelationships between race/ethnicity, menthol, and cessation is limited but, in two existing studies, both found that menthol was associated with poorer cessation outcomes for non-White smokers only.[31,37] The former, a population-based study, found that AA and Hispanic menthol smokers were significantly less likely to quit smoking (AOR=0.55, $p<0.01$) than AA and Hispanic non-menthol smokers. [37] In contrast, White menthol smokers were more likely to quit than White non-menthol smokers (AOR=1.17, $p<0.01$). The second, a treatment study, found that AA menthol smokers had half the odds of quitting compared with AA non-menthol smokers (AOR=0.48, $p<0.05$) while no difference was found in the odds of quitting for White menthol and non-menthol smokers.[31] These findings point to a possible moderating effect – i.e., menthol has a different effect on cessation in AAs and Whites – but to-date, only one treatment study has looked at these relationships. We will extend the existing research by examining the hypothesized moderating effect of menthol on cessation in the proposed study. Identifying smoking factors that underlie racial disparities in cessation outcomes is critical to improving treatment of smoking cessation in AAs. As FDA considers potential regulatory action, our study will inform this ongoing debate by being one of only a few treatment studies (the majority of evidence is based in population surveys) to examine if menthol reduces the rate of quitting success in AA relative to Whites, and if so, to examine the interrelationship of menthol, cpd, nicotine intake and dependence in explaining this disparity.

Psychosocial Factors. Smokers of a low **socioeconomic status** (SES) are less likely to quit than high SES smokers.[38-41] This may be due to a variety of factors. Low SES individuals encounter more stress than high SES individuals,[42] including stressors from daily hassles and discrimination. In addition, they often have less social support and resources for quitting.[43,44] During a quit attempt, low SES smokers experience greater stress, negative affect, and craving, receive less benefit from the buffering effect of social support, and are at greater risk of relapse than high SES smokers.[45-47] **Social support** has been found to have a positive influence on smoking cessation by increasing **quitting self-efficacy**, decreasing **perceived barriers**, and reducing **negative affect/stress**.[48-50] Because, on average, AAs have a lower SES than Whites,[51] these factors may partly explain lower quit rates for AA relative to Whites. A recent path model found a negative effect of daily stress on quitting among low-income, predominately AA women,[46] while another study found significant positive associations between social support during a quit attempt and cessation for low income AA women (OR=1.41, CI=1.11-1.78) and AA men (OR=1.50, CI=1.05-2.15).[52] A similar study found that stress, social support, and negative affect mediated the relationship between SES and quitting equally for low income AA, White, and Latino smokers.[53] The proposed study builds on the limited body of literature by examining these relationships in AA and White smokers and by examining psychosocial factors relative to smoking, treatment process, and biological factors in explaining the relationship between race and quitting. Identifying psychosocial factors that underlie racial disparities in cessation outcomes is critical to improving treatment of smoking cessation in AAs. We may find, for example, that AAs receive less support for quitting than Whites and that this difference predicts cessation. This could have major implications for clinical practice guidelines that address partner support interventions and skills training for support personnel.[54-57] Similarly, we may find that racial disparities is quitting are mediated by stress and/or negative affect. This could have major implications for clinical practice guidelines that address the role of stress and mood management techniques in supporting quitting.[58-60]

Treatment Process Factors. Adherence to medication and counseling is also linked to quitting. In a randomized, placebo-controlled trial, Shiffman found that the odds of quitting increased by 10% for each

additional nicotine lozenge used per day[61] and, in a separate study, found significant improvement in abstinence outcomes among subjects receiving active nicotine patch in adherent compared with nonadherent subjects.[62] Pooled results from two randomized controlled trials found a positive correlation between adherence to pharmacotherapy and smoking abstinence[63] and our varenicline pilot study found a significant positive relationship between medication adherence and quitting.[64] Counseling attendance and use of treatment self-help materials is also positively related to quitting smoking.[10,65]

Data about racial differences in adherence to tobacco treatment programs is limited. Nonetheless, there is some evidence that AAs may be less likely to complete treatment than Whites. Two recent studies found that AAs were 23%-40% less likely to use nicotine replacement therapy than Whites, controlling for income.[66,67] AAs in the Lung Heart Study were significantly less likely to return for follow-up (91% versus 96%, $p<0.05$) after the first year, which may partially explain the lower quit rates found for AAs relative to Whites (23% versus 34%), despite equal access to nicotine gum and counseling.[15] Smoking cessation medications reduce **withdrawal, craving**, and the **reinforcing effects of nicotine**, with greater reductions linked to abstinence,[13,14,68,69] but adherence to the prescribed dose and treatment length is necessary to achieve these effects. If AAs are less likely to follow treatment they may not get the full benefit – e.g., reductions in withdrawal and craving, acquisition of behavioral strategies for preventing relapse --relative to Whites. Given that withdrawal and craving predict relapse,[70,71] it is plausible that racial differences in these factors could help explain quitting disparities in AA versus Whites, directly and indirectly through adherence. Identifying treatment process factors that underlie racial disparities in cessation outcomes is critical to improving treatment of smoking cessation in AAs. We may find, for example, that adherence to treatment is lower among AAs than Whites and that this difference predicts cessation, alone, or through treatment response pathways – i.e., less reduction in withdrawal, craving, nicotine reinforcement in AAs relative to Whites. This could have major implications for clinical practice guidelines that address the role of adherence and the importance of adherence-based interventions for maximizing treatment outcomes.[64,72-75]

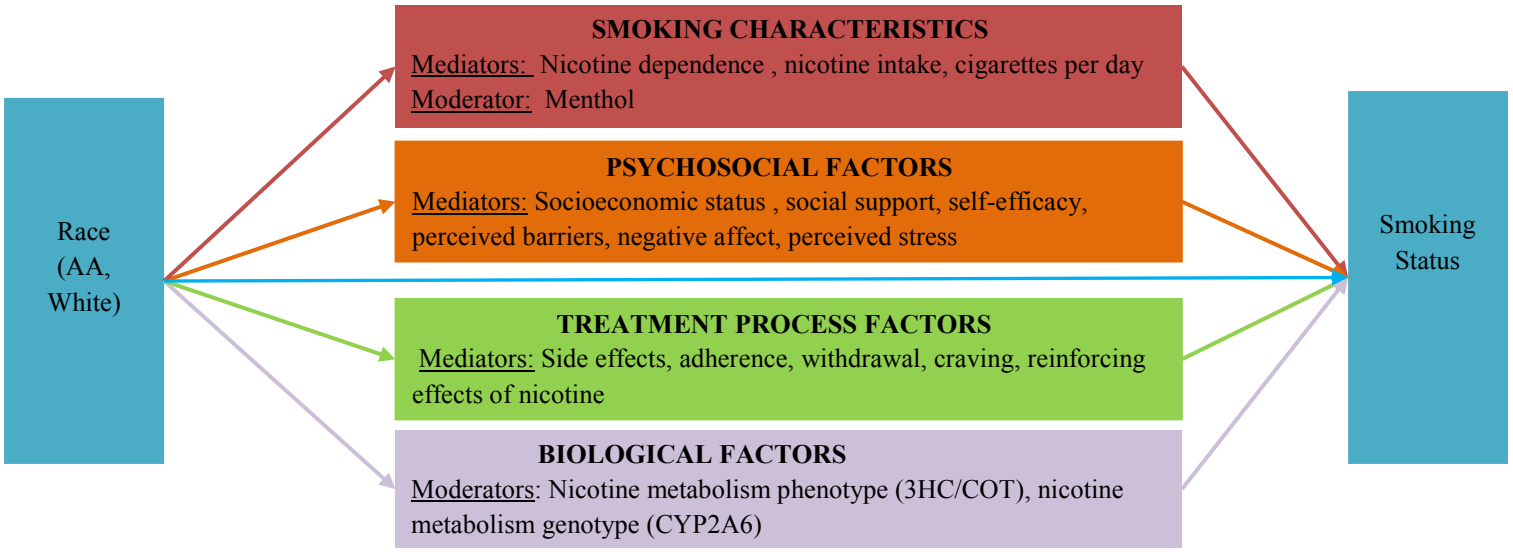
Biological Factors. Nicotine is metabolically inactivated to cotinine, and cotinine is metabolized to 3'hydroxycotinine, primarily by CYP2A6.[76] **CYP2A6 (genetic)** and **3HC/COT (phenotypic)** are both well-established markers of **nicotine metabolism**. Slower nicotine metabolism is consistently linked to higher quit rates, including for AA in our varenicline pilot study where Wk 12 abstinence by CYP2A6 activity was 27% for slow metabolizers, 20% for intermediate metabolizers, and 15% for normal metabolizers.[77-83] Large inter-ethnic variations in CYP2A6 activity have been reported.[78,84-86] Specifically, AAs have slower rates of nicotine metabolism than Whites,[87] and Tyndale (co-I) has identified novel CYP2A6 variants (*17,*20,*23-28,*31,*35) occurring at a higher frequency in AAs that contribute to these slower rates.[88-91] While both AA and White slow metabolizers have better quit rates than normal metabolizers, it is still not understood why AAs have lower quit rates relative to Whites if their overall nicotine metabolism is slower. This study address this issue by providing the first direct comparison of quit rates while looking at nicotine metabolism (phenotype and genotype) in AA and Whites enrolled in the same study and by looking at nicotine metabolism as it relates to psychosocial and treatment factors. Identifying biological factors that underlie racial disparities in cessation outcomes is critical to improving treatment of smoking cessation in AAs. It could be that any positive benefit of slower nicotine metabolism in AAs relative to Whites is attenuated by psychosocial (e.g., stress, support) and/or treatment (e.g., adherence) factors. This could inform the ongoing debate about ways in which pretreatment biological markers of nicotine metabolism rate (CYP2A6, 3HC/COT) could be used to estimate a smoker's response to therapy and have significant implications in the movement toward personalized medicine.[92]

A3. Why Varenicline? The prevalence of cigarette smoking increased among US adults for the first time in nearly 40 years, from 19.7% in 2007 to 20.6% in 2010.[93] In 2008, 45% of US adult smokers made a quit attempt yet only 9% were abstinent at 6 months.[94,95] Varenicline, a first-line, non-nicotine medication, is a α4β2 nicotinic acetylcholine receptor partial agonist approved by the FDA for tobacco use treatment in 2006. Because of its mixed agonist-antagonist effects, varenicline reduces the reward associated with smoking while also relieving nicotine craving and withdrawal. Ten post-approval RCTs have been conducted to date. A meta-analysis from these trials found varenicline to be more effective than other available therapies.[6] Average month 6 quits rates for varenicline were 33%, compared to 27% for nicotine nasal spray, 25% for nicotine inhaler, 24% for bupropion, 23% for nicotine patch, and 19% for nicotine gum. While these findings are promising, post-approval RCTs were conducted among predominately White, heavy smokers. Of the nearly 8,000 smokers enrolled, 6% (475) were AA or 'other'. The mean number of cigarettes smoked per day at baseline was 22.[13,14,96-103] Therefore, we know relatively little about varenicline in AA or lower level smokers. The proposed study addresses a critical gap in the literature by conducting the first known study, beyond our pilot, of varenicline in AAs.

A4. Why Include Lighter Smokers? Clinical trials have focused on moderate to heavy smokers (> 15 cpd) although recent data indicate a decline in moderate-heavy smoking subsequent to an increase in light smoking.[104] Data from the 2009 National Health Interview Survey indicate that the majority (80%) of US adult smokers consume ≤20 cpd, with average daily consumption being 12.7 cpd.[104] Given the trend toward decreasing cigarette consumption[105] and data suggesting that lighter smokers experience the same health risks as heavier smokers,[106,107] Clinical Practice Guidelines call for the inclusion of all smokers in research.[6] Of the few RCTs that have been conducted,[9,16,108] light smokers experienced the same difficulty quitting as moderate to heavy smokers,[6,23-25] strengthening our rationale for including light smokers in the proposed study. We have chosen to exclude very light smokers (1-2 cpd) because they represent a small sample of smokers (less than 5% of the general population and 1% in our previous clinical trials) and because evidence regarding nicotine dependence and pharmacotherapy treatment in this subgroup is lacking. [9,109,110] Varenicline is approved for all smokers but has not been examined in those smoking ≤ 10 cpd. Existing studies show no evidence of a greater number or more severe side effects by smoking level.[64] Nonetheless, we will routinely monitor side effects and will follow treatment protocols for reducing or discontinuing varenicline in the event of severe adverse events (AE). In our pilot study, only 2 participants required discontinuation due to severe AE: all others were expected and not severe (e.g., nausea).

A6. Conceptual Framework. Our conceptual model linking race to quitting (Fig 1) is guided by the Biobehavioral Model of Nicotine Addiction.[18,19] [18,19]The majority of factors will be assessed at multiple time points. We will take full advantage of these longitudinal data by comparing the change in factors over time for AA and Whites and examining how differences are related to cessation. The model has identified 4 pathways, each modeled independently, which might underlie AA-White differences in quitting. If multiple mediators and/or moderators are identified, our analytic plan will allow for examination of the interrelationship of factors across smoking, biological, psychosocial, and treatment domains (C8). Following standard definitions,[111] mediator variables are those that operate the same in both groups and explain how a predictor influences an outcome. Moderator variables are those that operate differently in groups and influence the strength or direction of the association between the predictor and dependent variable. Menthol and nicotine metabolism are hypothesized as moderators because of literature documenting 1) that menthol is associated with poorer cessation outcomes for non-White smokers only,[31,37] and 2) slower nicotine metabolism in AA relative to Whites despite evidence that AA have lower quit rates [78,84-86] All other factors have been hypothesized as mediators because literature suggests they adversely impact quitting, irrespective of race, although some may be more true for AA (e.g., adherence) and others more true for Whites (e.g., nicotine dependence).

Figure 1. Conceptual Model of Smoking, Psychosocial, Treatment Process, and Biological Pathways Explaining Hypothesized Relationships between Race and Smoking Abstinence



A7.Summary of Impact. This study addresses an important public health problem – health disparities in relation to smoking – and through a prospective stratified cohort design will move the field beyond descriptive, post-hoc analyses. Findings from this study will not only address if disparities in quitting exist but, more importantly, will examine modifiable mechanisms underlying the difference, including probable interrelationships of factors across domains. Identification of mechanisms that underlie racial disparities in

cessation is critical to improving treatment of smoking cessation in AAs. The selection of variables across biological, psychological, and social/environmental domains offers a comprehensive approach and is strongly grounded in the literature. Attention to proximal, modifiable factors (e.g., adherence, stress, social support) further maximizes the potential of our findings to inform practice by moving the field away from a generic focus on race toward an empirically derived approach that will guide researchers in identifying specific factors to address to improve cessation outcomes and reduce tobacco-related morbidity and mortality in future studies with AAs.

B. INNOVATION

There has been much speculation about the mechanisms underlying racial disparities in quitting, but these mechanisms have not been tested in a **prospective** study and comparisons within existing studies are hampered by low recruitment of AAs and by inclusion of only a select group of AA that smoke > 10 cpd. Our study is innovative and improves upon the existing literature by being the first adequately powered prospective study, stratified on race, to provide a direct comparison of smoking cessation pharmacotherapy in AA and Whites and concurrently explore mechanisms underlying the expected disparity. By assessing factors over time, we will be able to examine how factors differ at baseline and change over time for AA and Whites and how these differences are related to cessation. Longitudinal comparisons of this kind have not, to our knowledge, been conducted between AA and Whites and will provide among the first evidence of differences in factors that facilitate quitting for AA and for Whites. Innovation is further enhanced by being the first known to examine varenicline in AAs, light smokers (<10 cpd) and among a wide range of smoking levels (3-20 cpd).

C. APPROACH

C1. Overview. The proposed research is a prospective cohort intervention study, stratified on race, age (< 40, > 40), and gender, to evaluate varenicline for smoking cessation in 448 AA versus White smokers (224 AA, 224 White). All participants will receive varenicline for 12 weeks and 6 sessions of health education counseling. Participation will last for 6 months. Participants will be enrolled from Swope Health Central, a community-based primary care clinic in Kansas City and from the surrounding urban community. 448 smokers (224 AA, 224 White) will be required at baseline to detect the proposed treatment main effects.

Prospective Stratified Cohort Design

AA (224)			White (224)		
	<40	≥40		<40	≥40
Male	n=56	n=56	Male	n=56	n=56
Female	n=56	n=56	Female	n=56	n=56

C1a. Design Considerations.

Stratification. Women and younger smokers are less likely to quit smoking than their male or older counterparts.[104,112] To minimize threats to internal validity and to ensure a comparable sample of AA and Whites, we have decided to stratify our recruitment on these factors and enroll equal numbers of subjects into the 8 race, age, gender sub-cohorts.

Study Timeline

	Y1	Y2	Y3	Y4	Y5
Development					
Stratified Cohort Study *Enrollment (~15/month)* *Follow-up*	90	180	178		
Data Cleaning					
Data Analyses					

Development (Year 1): Medication preparation, staff training, assessment and database development, recruitment preparation. *Cohort Study (Years 1-4):* Recruitment, screening, enrollment, intervention, assessment, follow-up, abstinence verification, data management. *Data Analysis and Dissemination (Years 4-5):* Data analysis, interpretation, research presentations, manuscript preparation.

Other Racial/Ethnic Groups. This proposal capitalizes on the strengths of our team, including our experience with AA smokers and the strong body of literature documenting quitting disparities between AA and Whites, and broadens our research to understanding possible underlying mechanisms. Importantly, this study represents a starting point for future work where we can expand to other ethnic groups (e.g., Native Americans, Latinos) that experience high rates of smoking-related morbidity and mortality.

Placebo. This is not an efficacy study, and therefore we do not have a placebo group. We are providing the best known treatment to examine AA-White differences in response to pharmacotherapy and to understand mechanisms that account for differential quit rates.

Secondary data analysis. A secondary data analysis of existing varenicline RCTs would not accomplish our secondary aims. Limited data was collected on factors associated with quitting in these trials – e.g., menthol status was not asked; nicotine metabolism phenotype or genotype was not assessed; psychosocial variables were not collected; and no attention was given to treatment adherence. Most importantly, to address our primary aim and hypothesis, a study with the proper design needs to be conducted.

Smoking level. We have specified a lower and upper limit of cigarettes per day (3-20 cpd) to minimize possible confounds in treatment response while still representing the majority of AA and White smokers. Although we expect that our sample of AA will smoke fewer cigarettes per day, on average, than our sample of Whites, they will have comparable blood nicotine levels[9,21,113,114] and will experience the same difficulty quitting as Whites. [6,98-100] The lower limit was selected because very light smokers (1-2 cpd) represent only 5% of

smokers in the general population and 1% in our previous clinical trials and because evidence regarding nicotine dependence and pharmacotherapy treatment in this subgroup is lacking. [9,109,110] The upper limit was selected because 80% of US adult smokers consume ≤20 cpd, with average daily consumption being 12 cpd.[104]

Other pharmacotherapy. Providing the same medication to everyone limits any confounding effects of treatment, allowing us to minimize noise and effectively examine mechanisms underlying AA-White differences in quitting. We chose varenicline over other pharmacotherapy because it is the best available medication and allows for the objective measure of adherence via plasma drug levels.

C2. Preliminary Studies. Our group has extensive experience conducting tobacco control research. Dr. Nollen has been conducting smoking cessation studies for 10 years, and has worked with AAs in three RCTs. Dr. Cox has been the PI on 4 smoking cessation trials conducted in urban, community clinics serving low income minority smokers. Dr. Ahluwalia is nationally known for his work for the past 18 years in work with AA smokers, and has been the PI of 4 large smoking cessation RCTs enrolling more than 2,000 smokers. Drs. Benowitz and Tyndale have collaborated with Drs. Nollen, Cox, Ahluwalia, and Mayo for 10 years, and are nationally known for their work in pharmacokinetics and pharmacogenetics.

1) Does Varenicline Help AA Smokers Quit [Kansas Masonic Cancer Research Institute; Nollen (PI) Cox, Ahluwalia, Benowitz, Tyndale]: [64] We completed a pilot study of varenicline for cessation among 72 AA smokers. COT-verified quitting at Wk 12 was low (24%). In preparation for this application we examined quitting by nicotine metabolism, finding that COT-verified abstinence was higher among slow metabolizers (see A.2 Biological Factors). In preparation for this application we also examined side effects by smoking level. No significant differences were found in the mean number of total (3.1 versus 2.9) or severe side effects (0.9 versus 1.3) experienced by moderate (≤ 15cpd) versus heavy (>15cpd) smokers, providing preliminary evidence of the safety of varenicline among lower level smokers. Our pilot is the first study to examine varenicline in AA smokers; it informs the current proposal in a number of ways: 1) COT-verified quit rates in this sample of AAs were lower than expected compared to published studies of White smokers. 2) Associations were found between phenotypic (3HC/COT) and genotypic (CYP2A6) markers of slow nicotine metabolism and quitting. The nature of these relationships will be examined in more depth in the proposed study, including the unique interplay between race, nicotine metabolism, and quitting. The proposed study will be the first known to make direct comparisons of quit rates while looking at metabolism in AA and Whites enrolled in the same study. 3) Varenicline was safe in lower level smokers, providing preliminary evidence of tolerability, although the nature of these relationships will be examined in more depth in the proposed study.

2) Kick It at Swope I [NCI R01 CA77856; Ahluwalia (PI), Mayo]: [8,34,115] In 2001, we completed the first in our series of Kick It at Swope (KIS) projects that have, to date, enrolled 1,895 AA smokers from Swope Health Central. KIS I randomized 600 AA smokers (>10 cpd) to counseling plus bupropion SR (150mg bid) or placebo. Main outcomes, published in *JAMA*, found COT-validated abstinence rates at 26 weeks of 21.0% in the bupropion and 13.7% in the placebo groups (p=0.02). 84% of the sample returned at 6 months. This study demonstrates: 1) our team's capacity to conduct research with AA smokers in Kansas City,2) established Swope as an excellent partner for recruiting AAs, 3) quit rates are lower than whites in comparable RCTs, and 4) our extensive follow-up procedures are successful in retaining participants.

***3) Kick It at Swope II [NCI R01 CA91912; Ahluwalia (PI) Nollen, Mayo, Benowitz, Tyndale]*:** [9,11,116] This randomized trial examined the efficacy of nicotine gum (active versus placebo) and counseling [motivational interviewing (MI) versus health education (HE)] for smoking cessation among 755 AA smokers (≤10 cpd). 637 (84.4%) were followed-up at Wk 26. COT-verified quit rates for nicotine gum were no better than for the placebo (14.2% vs 11.1%, p=0.23). However, HE performed significantly better than MI (16.7% vs 8.5%, p<0.001). This study continued to demonstrate our ability to recruit and retain AA smokers and has informed development of the current proposal in three ways: 1) Participants who completed the protocol were significantly more likely to quit smoking than those who did not (OR=0.48, CI=0.27-0.84), leading to the inclusion of treatment adherence (medication, counseling) as a factor of interest in the proposed study, 2) Participants receiving HE counseling were more than twice as likely to quit smoking as participants receiving MI, justifying our rationale for HE counseling in the proposed study.

4) Kick It at Swope III [NCI R01 CA091912; Cox (PI), Nollen, Ahluwalia, Mayo, Benowitz, Tyndale]: [109] We have successfully enrolled 540 AA smokers in a randomized trial to examine the efficacy of bupropion (active versus placebo) in combination with HE counseling for smoking cessation in African American light smokers. Verified abstinence rates at Wk 26 were 13.3% in the bupropion group versus 10.0% in the placebo group (p=0.23). These quit rates are, again, quite modest compared to those found among Whites. This study highlights our ongoing work with AAs and our ongoing recruitment resources available to support this study.

C3. Study Site. This study will be conducted at Swope Health Central, a community-based clinic located in urban Kansas City. Swope has been the site for our three previous trials and has a longstanding relationship with the University of Kansas Medical Center. Dr. Nollen (PI) has secured commitment from Swope for this study (see letter of support). Dr. Ahluwalia (co-I) secured research office space at Swope in 1997, and we have maintained it for the past 13 years. Swope has over 51,000 unique patients who complete 174,000 yearly visits; 75% (38,901) of patients are AA, 20% (10,374) are White, and 90% are below poverty.

C4. Participants and Recruitment. We will recruit 448 eligible (224 AA, 224 White) smokers for this study. Our previous research in KIS –I, -II, and –III has provided us considerable knowledge of recruitment of smokers within this urban community in coordination with Swope. All recruitment documents will be identical in content and will be designed to attract the interest of our target population by featuring images, graphics, and success stories of both AA and White smokers. We will use both clinic- and community-based recruitment strategies. **Clinic-based recruitment.** Swope clinic staff will be fully informed about the study, the eligibility criteria, and the enrollment process and will be able to refer smokers to the project office. Posters and flyers will be distributed throughout the health center. Finally, letters from Swope physicians will be mailed directly to clinic patients to inform them of the study. While it is feasible to recruit all participants from Swope (see Table), we will recruit from a partnering health center, Truman Medical Center (TMC), as needed. TMC served 95,000 unique patients in 2009. Patients are demographically similar to those seen at Swope (see C3.) TMC served as a recruitment site in KIS-III. To recruit patients at TMC, a TMC employee will query their electronic medical records to identify potential subjects. The TMC employee will mail letters signed by a sponsoring TMC physician on Truman letterhead to potential subjects to inform them of the study. No PHI will be disclosed to KUMC study staff and identities of potential subjects will only be known when they call our study line to find out if they are eligible. The sponsoring TMC physician and TMC employee will not query their records until they have received an approval of waiver of privacy authorization from the TMC Privacy Board. **Community-based recruitment.** We will use additional community-based strategies (word of mouth, radio and television ads, print materials) as needed, to reach our targeted enrollment of 224 AA and 224 White smokers. **Accrual.** We have conservatively estimated accruing 15 participants per month. Accrual in KIS II and III has averaged 26 per month; however accrual in this study may be slower because of our stratified design. Participants will be recruited until the targeted 56 persons per cell have been reached. It is possible that recruitment into some cells may take longer than others.

Projected enrollment from Swope Health Services

	African Americans					
Unique patients per year: 51,868	75% AA at Swope	Adjust down for 32% smoking prevalence[a]	Adjust down for 70% motivated to quit[b]	Adjust down 40% for ineligible and refusals	Adjust down 40% for no-show to enrollment visit (Wk 0)	Targeted enrollment
	38,901	12,448	8714	5228	3137	224 AA
	Whites					
	20% Whites at Swope	Adjust down for 32% smoking prevalence[a]	Adjust down for 70% motivated to quit[b]	Adjust down 40% for ineligible and refusals	Adjust down 40% for no-show to enrollment visit (Wk 0)	Targeted enrollment
	10,374	3,320	2324	1394	837	224 Whites

[a]Smoking prevalence based on rates for low income adult smokers; these rates are as high as 50% among urban smokers but we have used a more conservative estimate of 32% derived from national surveillance surveys. [b]Based on national prevalence data indicating interest in quitting among current smokers.[41]

Eligibility Criteria

Inclusion Criteria	Exclusion Criteria

• Non-Hispanic African American or non-Hispanic White
• ≥ 18 years of age
• *Smoke 3-20 cpd*
• 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
	• Renal impairment
	• Evidence or history of clinically significant allergic reactions to varenicline
	• Hospitalization in the past 2 months for any cardiovascular disease, including but not limited to:
	  ○ Angina
	  ○ Myocardial infarction
	  ○ Peripheral vascular disease
	  ○ Stroke
	• New onset of chest pain or arrhythmia in the past 2 months
	• History of alcohol or drug dependency 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

Eligibility Criteria and Rationale for Participant Selection. Eligibility criteria are displayed in the adjoining table. An authorized provider, which includes the study physician, Dr. Ed Ellerbeck, authorized providers at the KUMC CRU, 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. Exclusion criteria are consistent with documented contra-indications for varenicline and the criteria used in previous

RCTs. [13,14,86-93] Individuals with stable cardiovascular disease will not be excluded, however a specific plan is in place to assess and intervene in the event of a cardiovascular problem. This plan is detailed in Protection of Human Subjects, Protection of Risks. Participants must smoke 3-20 cpd to minimize possible confounds in treatment response and must smoke on ≥ 25 days of the past 30 to avoid enrolling smokers who are in the transitory phase between daily smoking and quitting. Other ethnic groups will be excluded as our primary aim is to evaluate varenicline in non-Hispanic AA and non-Hispanic White smokers.

C5. Intervention

Kick It At Swope Guide. The *Kick It at Swope: Stop Smoking Guide* was developed for our KIS-II and –III studies and goes hand-in-hand with HE counseling. The 36-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, using medication, 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 to include specific discussion of varenicline for smoking cessation and also be modified for use with both AA and White smokers.

Varenicline. All participants will receive 1 mg of varenicline twice daily after titration to full strength in the first week following standard dosing guidelines. Participants will initiate varenicline and set a target quit date one week later (i.e., Day 8). Medication will be dispensed in 30-day pill boxes at Wks 0, 4, 8. Varenicline is approved by the FDA for smoking cessation. Common side effects are nausea, insomnia, vivid dreams, dry mouth, flatulence, constipation, irritability, headaches, dizziness, and fatigue. In July 2009, the FDA introduced a black box warning about neuropsychiatric complications (depressed mood, suicidal behavior) reported in patients attempting to quit smoking with varenicline. We will minimize these risks by using strict exclusion criteria. Use of varenicline will be under the supervision of Drs. Nollen (PI) and Ellerbeck (study physician). Participants will be prompted to discuss side effects at each visit and given the study phone number to report adverse events at interim time points. NIH guidelines for reporting adverse events will be followed. Any problems needing medical attention will be referred to Dr. Ellerbeck who will carry a study pager and has played this role on previous RCTs. Treatment protocols will be followed for reducing or discontinuing varenicline in the event of severe adverse events. In our pilot only 2% of participants required discontinuation due to severe AEs; all others were expected and not severe (e.g., nausea).

Health Education (HE) Counseling.

The current *Tobacco Use and Dependence Clinical Practice Guideline* recommends the importance of counseling in combination with pharmacotherapy for smoking cessation.[117] Our work and others have documented the efficacy of directive, health education (HE) counseling for smoking cessation.[16,118] Specific content for HE counseling by session are outlined in the adjoining table and are consistent with current tobacco treatment guidelines. HE 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 taking varenicline and set another quit day.

Overview of Health Education Counseling Sessions

Session	Goal	Topic
Wk 0	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; instructions of medication use ; identifying triggers and managing withdrawal
Wk 1*	Reinforce quit day plan, address medication use, identify concerns, barriers, and strategies for success	**If Quit:** Rewarding yourself, recovering from slip, review medication use or ending medication (Wk 12), managing stress, alternatives to smoking, identify barriers, and living smoke-free **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
Wks 4, 8, 12, 16*	Reinforce and encourage abstinence efforts. Identify concerns, barriers, and strategies for successes	

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

Counselor training and treatment fidelity. Drs. Nollen (PI) and Cox (Co-I) are psychologists who have trained and supervised over 90 tobacco cessation counselors. Dr. Cox, a licensed psychologist, will lead the counselor training activities. All counselors will be Master's level and will receive extensive training with Dr. Cox. Mock sessions will be videotaped so that Dr. Cox can provide guidance and feedback to the counselors on their performance. When Dr. Cox believes the counselor has a high level of proficiency they will be certified to conduct HE counseling. Sessions will be recorded and listened to by Dr. Cox during weekly supervision to monitor fidelity to the counseling protocol and assure equivalent delivery of counseling across race. **Missed sessions.** Participants missing a session will be sent a letter and called/emailed up to 6 times. To maximize our potential to reach participants, we will update addresses at each visit and obtain names, addresses, and

phone numbers of up to three friends/relatives who can provide information on the participant's whereabouts. These methods have consistently achieved high rates of follow-up. Follow-up in our varenicline pilot was 85%.

C6. Study Procedures and Methods.

Initial Screening. The initial screen will review inclusion/exclusion criteria. Those eligible will be scheduled to complete final eligibility screening within 14 days. Given our stratified design, it is possible that an individual who meets the eligibility criteria may not be included in the study if enrollment for their cell has closed. All ineligible smokers will be referred to local resources.

Overview of Major Study Events

	Screening *	Enroll.				End of Drug		Final Follow-Up
		Wk 0	Wk 1*	Wk 4	Wk 8	Wk 12	Wk 16*	Wk 26
Intervention								
HE Counseling		X	X	X	X	X	X	
Medication Dispensing		X		X	X			
Measures								
Screening	X	X						
Assessments		X		X	X	X		X
Biological Sample Collection								
3HC/COT		X						
Genotype		X						
Nicotine intake		X						
Drug levels				X				
COT-verified quitting				X		X		X
Cortisol		X						

*phone visit; all other visits are in-person

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

Health Education Counseling Visits (Wks 0, 1, 4, 8, 12, 16). Counseling sessions, each lasting approximately 20 minutes, will be completed in person at Wks 0, 4, 8, 12 and by telephone at Wks 1 and 16. The number of sessions is consistent with our previous studies where we have achieved visit completion rates of around 80%. Counseling sessions will be audio taped for clinical purposes only. Specifically, to ensure that participants are receiving the highest quality of care and that counseling fits their unique needs. No data will be drawn from the audiotapes.

Medication Dispensing (Wk 0). Medication will be dispensed under the medical supervision of Dr. Ellerbeck (study physician), Kansas License # 04-20890 in 30-day pill boxes at Wks 0, 4, 8 to facilitate appropriate use of varenicline. Pill boxes led to good medication adherence (86% overall) in our pilot study.

Assessment Visits (Wks 0, 4, 8, 12, 26). Assessments will be completed at all in-person visits.

Biological Sample Collection (Wks 0, 4). There will be two blood draws. The first will occur at Wk 0 to be used for analysis of nicotine metabolism phenotype (3HC/COT) (Benowitz),genotype (*CYP2A6*) (Tyndale), exosomes and Neutrophi Extracellular Traps (NETs), biomarkers that results from exposure to nicotine and the other chemicals in cigarettes. This assessment occurs when we expect smokers to be using tobacco at their regular levels, prior to quitting. The second blood draw will occur at Wk 4 for analysis of varenicline drug levels (Benowitz). Wk 4 was selected to maximize the number of participants still adhering to the protocol and because participants will have reached steady-state blood levels, providing the best estimate of medication adherence. We do not anticipate the collection of biological samples will impact recruitment; only 4% refused blood draws in KIS-III. A small (approximately 1-3 cm) hair sample will be taken from participants at Wk 0 and at Wk 4. This will be used to measure cortisol, an indicator of stress in the past 1-3 months and is optional to participants. Melanin will also be assessed at Wks 0 and 26 using a skin reflectometer.

Retention. We have developed a system of reminders and compensation that have resulted in impressive retention rates in our previous clinical trials. ***Reminders.*** 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. ***Compensation.*** 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 Wk 8, $40 at Week 12, and $60 at Wk 26. If subjects complete all study visits, they will be compensated a total of $180 as compensation for their time/travel and in appreciation for their participation. Subjects will also be given a t-shirt following their Wk 1 phone call and a water bottle following their Wk 16 phone call. These items will be distributed at the in-person visits following the phone calls.

C7. Measures. Due to varied literacy levels of the target population, all questionnaire items will be read to participants. Factors that are stable over time (e.g., demographics) will be assessed at Wk 0; all others will be assessed at multiple time points. All measures are widely used, well-validated, and have been previously used

by our team, demonstrating adequate psychometric properties in the target groups. The length of assessment is consistent with our previous RCTs and has not led to responder/participant burden.

Primary Outcome: Abstinence (Wk 12,26). The primary endpoint will be cotinine-verified 7-day point prevalence smoking abstinence, defined as no cigarettes for the previous 7 days at Wk 26. This method is consistent with recommended guidelines.[119] The recommended cut-off of 15ng/ml for salivary cotinine will be used to differentiate smokers from non-smokers[119] and will be conducted by the lab of Dr. Neal Benowitz.[120] Secondary endpoint will be cotinine verified-7 day point prevalence abstinence at Wk 12 (end of drug).

Stratification Variables: Race (Wk 0). Participants will self-identify as non-Hispanic AA or non-Hispanic White and complete the Pharmacogenetics Questionnaire where they note the racial/ethnic background of their grandparents.[121] **Age and Gender (Wk 0).** Participants will provide their date of birth and self-identified gender.

Demographics: Smoking history (Wk 0) will include standard items, including age when first smoked, age when started smoking regularly, and quitting/relapse history.[122] **Cigarettes per day (Wks 0,4 8,12,26).** Timeline Followback asks participants to recall the number of cigarettes smoked per day over a designated time period and provides a more accurate estimation of smoking level than other measures.[123-125]

Smoking Factors: Menthol (Wk 0). Participants will also be asked to bring their cigarettes with them to Wk 0. Research assistants will record the brand, the strength (e.g., regular, mild, light), and type (menthol, non-menthol) of cigarette. **Nicotine dependence (Wks 0,4,8,12,26).** The Wisconsin Inventory of Smoking Dependence Motives will be used to measure nicotine dependence.[126] **Nicotine intake (Wk 0)** will be assessed by a 24-hour urine sample taken and will be quantified by examining the sum of four (cotinine + cotinine-glucuronide + trans-3'-hydroxycotinine + 3HC-glucuronide) of the major nicotine metabolites using procedures described by Benowitz (co-I).[127] This measure of total nicotine equivalents (TNE) has the strongest correlation with nicotine dose in lab-based studies and represents the current gold standard for estimating nicotine dose.[127] Another marker of nicotine intake is the nicotine-derived nitrosamine, NNAL (4-(methylnitrosamino)-1-(3)pyridyl-1-butanol), which will be measured using the same 24-hour urine sample collected for TNE. Exosomes, a tertiary marker of exposure to nicotine and the other chemicals in cigarettes, will be also assessed through the Wk 0 blood draw. Exosomes have been previously characterized in smokers and provide an understanding, beyond TNE or NNAL, of the ways in which nicotine and the other chemicals in cigarettes are harmful to a smoker's health. Exosomes will be examined in relationship to smoking level, TNE, NNAL, cigarette type (menthol, non-menthol), and race. **Psychosocial Factors:** [NOTE: Psychosocial factors beyond those identified here may be related to race and quitting. This study represents a starting point. We have identified factors with strong supporting literature and well-validated measures. Future work will examine the relationship between other factors (e.g., motivation to quit), race, and quitting.]

Socioeconomic status (Wk 0). Standardized questions will be used to assess for income, education, employment, insurance status, and subjective social status.[43,128] **Support (variable timing, see below).** Three support factors known to be associated with cessation will be assessed: general support, support related to quitting, and presence of smokers in the social network.[129] The Interpersonal Support Evaluation List (Wks 0,4,8,12,26) will be used to measure general support across three domains of appraisal, belonging, and tangible support.[130] The Partner Interaction Questionnaire (Wks 0, 4,8,12,26) will be used to assess positive ('compliments you on not smoking') and negative behaviors ('criticized your smoking') performed by the identified support person (partner, friend, relative) during the quit attempt.[54] Social Influence (Wk 0). Participants will be asked to identify the smoking status of their partner, the number of smokers in the home, and the number of family members and friends who smoke.[129,131] **Self-Efficacy (Wks 0,4,8,12,26).** The Smoking Self-Efficacy Questionnaire will be used to assess participant's belief in their ability to refrain from smoking when facing internal (feeling depressed) and external (being with smokers) stimuli.[132] **Perceived Barriers (Wks 0,4,8,12,26).** The Barriers to Cessation Scale will be used to assess barriers in 3 domains: addiction ('feeling lost without a cigarette'), external ('lack of support from family/friends'), and internal ('feeling less in control of mood').[133] **Negative Affect (Wks 0,4,8,12,26).** The Center for Epidemiological Studies Depression Scale (CES-D) is a symptom checklist that measures depressive symptoms during the past 7 days.[134] The Positive and Negative Affect Scale measures feelings of enjoyment (positive affect subscale) and distress/hostility (negative affect subscale) in the past week.[135] **Stress (variable timing, see below).** Stress is a multidimensional construct. For this study we focus on stressors known to influence smoking and health in low income populations. The Perceived Stress Scale (CSS) (Wks 0,4,8,12,26) will be used to assess acute stress in the past month ('something happened unexpectedly,' 'unable to control important things,' 'felt things were going your way)'.[130] The Major Experiences and Everyday Discrimination Scales (Wk 0) includes items about chronic experiences of interpersonal mistreatment and discrimination and attributions of the reason for the discrimination, e.g., race, education/income, gender.[136]

Treatment Process Factors: Treatment compliance (variable, see below). Adherence will be assessed by analysis of varenicline drug levels at Wk 4, monthly pill counts at Wks 4, 8, 12, and the number of HE sessions completed. Pill count was significantly related to drug levels in our pilot study[137] and will provide a secondary measure of medication adherence in this study. **Withdrawal (Wks 0,4,8,12,26).** The Minnesota Withdrawal Scale is used to determine the degree of withdrawal symptoms related to smoking cessation.[138] **Craving (Wks 0,4,8,12,26).** The Brief Questionnaire of Smoking Urges[139] is a measure of self-reported craving.[139] **Reinforcing effects of nicotine (Wks 0,4,8,12,26).** The Cigarette Evaluation Questionnaire assesses reinforcing effects of smoking, including satisfaction, psychological reward, enjoyment, craving relief, and aversion.[140] **Side effects (Wks 4,8,12):** Participants will be asked about symptoms commonly associated with quitting smoking and/or smoking cessation pharmacotherapy (i.e., nausea, sleep disturbance, irritability) and perception of the severity of the symptom ('does not bother at all' to 'bothers a lot'). A similar checklist has been used in varenicline RCTs.[13,14,96-103]

Biological Factors: Genotype (Wk 0). All DNA samples will be extracted from whole blood using established assays previously described by Tyndale (Co-I).[141-144] CYP2A6*1B,*2,*4,*9 and *12 will be genotyped in all subjects; 10 additional alleles (*17,*20, *23-28,*31,*35) will be assessed in AA. These alleles are chosen as they are prevalent in this population, they alter nicotine pharmacokinetics and nicotine metabolism, and have been studied for associations with various smoking behaviors.[78,89-91,141,145] Based on the data from whites and from our KIS I-II AA data we can group variants into normal (no variants), intermediate (one decreased activity *9 or *12 allele) or slow (two decreased activity *9 or *12 alleles, or one or more loss-of-function *2,*4,*17,*20, *23-*28,*31,*35 alleles) metabolic groups.[79,145] Genotype groupings will be used to examine the impact on cessation. New variants continue to be identified. We will assess known variants of importance for our population as well as plan for the assessment of additional variants as they become identified and characterized. **Phenotype (Wk 0).** Nicotine metabolism phenotype (3HC/COT) will be conducted using standard procedures,[146,147] under the supervision of Dr. Benowitz (co-I) at the University of California, San Francisco. Prior validation studies have shown that the main difference in quit rates is between the first quartile (slow metabolizers) and the second through the fourth quartiles (fast metabolizers).[83] We will use a similar approach to classify participants into a nicotine metabolism phenotype group (slow, fast) in the current study and assess the impact of grouping on cessation.

C8. Statistical Plan

Sample Size. The primary endpoint will be cotinine verified 7-day point prevalence abstinence at Wk 26. We expect a 28% cessation rate in White and a 15% cessation rate in African American participants. Using the chi-square test, along with the assumptions above, 224 subjects in each group will give us 90% power to detect this difference with a type I error rate of 5%. **Basis for Projected Abstinence Rates.** We used quit rates from the existing varenicline trials as the basis for our projections. Wks 24 abstinence rates for White and AA smokers in the existing varenicline RCTs were 32% and 15%, respectively. Because quit rates are lower among the poor, we adjusted these rates down to 28% in Whites to account for the low SES of our target population. Using additional data from our varenicline pilot trial, we chose not to adjust down for AA. Wk 12 abstinence among our sample of low income AA was 24%. In our previous AA clinical trials there has been a 37% reduction in confirmed abstinence between the end of treatment and Wk 26. A similar reduction results in the projected 15% abstinence rate among AA in the proposed study and parallels abstinence rates found for AA in the existing varenicline trials. **Missing Data.** All primary analyses on smoking cessation will be conducted using intent-to-treat and will code lost to follow-up as smokers. Subsequently we will evaluate the missing data pattern. If there is a differential loss based upon race, age, and/or baseline smoking level, multiple imputation techniques will also be used.

Sensitivity Analyses Estimating Power across a Range of Abstinence Rates with 224 Participants Per Group *

	0.13	0.15	0.17
0.26	92%	79%	59%
0.28	97%	90%	76%
0.30	99%	96%	88%

*all assumed an alpha of 0.05 and used a two sample two-tailed Chi-square test.

Hypothesis 1. AAs will have significantly lower cotinine-verified 7-day abstinence at month 6 than Whites: We will compare the cotinine verified 7-day point prevalence abstinence rates at Wk 26 between AA and Whites using the chi-square test. For our primary comparison, those lost to follow-up will be considered as smokers. We also will look at completers only and will utilize multiple imputation techniques to ensure valid comparisons between the two groups if the loss to follow-up is not random. Given this is not a randomized study, we will also utilize multiple logistic regression to compare the 7-day point prevalence abstinence rates between AA and Whites adjusting for our stratification variables (age, gender) along with baseline level of smoking. We will examine both main effects and pairwise interaction effects and determine if the expected

difference between AA and Whites still exist in the presence of these other factors. Interactions not significant at the 0.10 level will be dropped from the model. To evaluate secondary endpoints, we will compare cotinine-verified 7-day point prevalence abstinence rates between AAs-Whites at Wk 12 (end of drug) using the same methods as above.

Hypothesis 2.1-2.4. Smoking, psychosocial, treatment process, and biological factors will mediate and/or moderate the relationship between race/ethnicity and cotinine-verified 7-day abstinence at month 6 in AA and White smokers. If the racial differences hypothesized in Aim 1 are found, we will explore the mediation and moderation hypothesized in Aim 2. For this type of modeling the number of events is more relevant than the total sample size. Assuming a total of ~100 confirmed quitters at Wk 26 (see sample size calculation above) and the general guideline of 10 events per factor in a model, we can expect to accommodate 10 factors (including race and intercept) in the model. We will first individually assess the factors in each of the four proposed paths. We will use the methods proposed by Baron and Kenney for assessing mediation and moderation.[111] To demonstrate that a variable mediates the effect of race on abstinence: 1) race must be associated with abstinence, 2) race must be associated with the mediator, 3) the mediator must be associated with abstinence, and 4) the relation between race and abstinence must be reduced or eliminated when controlling for the mediator. The mediation effect estimate will be computed according to MacKinnon who describes mediation as the difference of the race effect on the outcome variable with and without the presence of the mediators, or alternatively, the product of the effect of race on the mediators and the mediators on the outcome controlling for race.[148] Criteria 1 and 3 will be tested using chi-square test and criterion 4 will be tested using logistic regression. Criterion 2 will be evaluated using two sample t-tests for continuous variables (e.g., nicotine dependence) and chi-square tests for categorical variables (e.g., menthol), that are measured only at baseline. For factors measured longitudinally (e.g.,cpd, dependence, support, affect), the mediation could be inherent at baseline and/or due to longitudinal change. For each of these longitudinal variables we will construct a linear mixed model, controlling for baseline levels of the specific variable, race and time, as well as a race by time interaction to model these variables over time, assuming a random slope and intercept. The interaction term or the main effect for race (if interaction not significant) will allow us to determine if the measure differs over time between AA and Whites. If measures differ, the random slope estimate for each individual on the measure will be the potential mediating variable. If the baseline measure is a significant factor in the model, then the baseline level of the measure will be a potential mediating variable. Thus, we will assess if the baseline effect and/or longitudinal change in the measure are mediating factors. To be conservative we will test these at the 0.10 level of significance. For criterion 4 (mediation), race will be entered on the first step of a logistic regression model, and the potential mediating variable (baseline and/or slope estimate if longitudinal effect exists) will be entered on the second step. We will then compare the association of race with abstinence after the first step (without the potential mediator in the model) to the association after the second step (with the potential mediator in the model) by examining the regression and correlation (R) coefficient. If the relation between race and abstinence is reduced or eliminated by including the variable, we will presume that mediation has occurred.

To assess moderation, we must determine if race and the potential moderator have a statistical interaction on the dependent variable cessation.[111] To determine this, we will construct a multiple logistic regression model that includes the main effect of race, the main effect of the potential moderating variable, and the interaction of the two. Each potential moderator whose interaction term is significant at the 0.10 level of significance will be considered a potential moderator.

The same mediation/moderation approach will be used to examine how the hypothesized factors explain the relationship between race/ethnicity and quitting at Wk 12, where more factors can be accommodated by the model. Assuming confirmed Wk 12 quit rates of 49% in Whites and 24% in African Americans (based on our pilot in AA and quit rates among Whites in varenicline RCTs), we expect a total of ~155 subjects to be confirmed abstinent at Wk 12. Based upon the generally accepted guideline of 10 events per factor in the model, we can expect to accommodate 15 factors (including race and intercept).

If multiple mediators and/or moderators are identified, we will construct a global structural equation model to examine the interrelationship of factors within and across causal paths using Mplus software package version 6.[149] Due to the estimated number of people quit, our global model can accommodate no more than 7 variables. To optimize the likelihood of fitting a significant global model to the data, only factors identified as independent mediators/moderators will be considered for inclusion and we will systematically delete non-significant paths (weakest paths first), until all paths are significant based on the methods described by MacCallum.[150] Standard fit indices will be used to determine how well the global SEM model fits the data.[150-155]

If the racial differences in quitting hypothesized in Aim 1 are not found, we will construct separate models exploring the predictors of quitting for AA and for Whites because of the likelihood that barriers and facilitators to cessation may differ in AA and in Whites. Specifically, logistic regression will be used to assess the individual relationship between each of the factors and Wk 26 and Wk 12 abstinence for AA and for Whites. Multiple logistic regression analysis with full stepwise and best subset selection procedures will then be used to construct a multivariate model identifying the best subset of factors predicting abstinence in AA and in Whites. Main effect terms for each factor found to be significantly related to abstinence at $p<0.10$ in bivariate analysis will be included in the model selection process. All of the subset of predictors in the final model will be statistically significant at $p<0.05$.

Hypothesis 3.There will be no difference in side effect profiles by smoking level. For each subject we will create a count of the total number of side effects reported at Wk 4, 8 and 12, and also subset that for moderate to severe side effects. We will globally report the mean of these at each week. Finally, we will compare the number of side effects reported at each week among participants smoking 3-5, 6-10, 11-15, and >15 cpd using a one-way analysis of variance. Given the potential for skewness and uneven distribution of subjects within the three strata based upon smoking, the Kruskal-Wallis procedure may be utilized. Similar analyses will be done for the number of moderate and severe side effects reported.

C9. Limitations and Concerns

Generalizability. As with most studies, we are recruiting participants who are interested in quitting, therefore results may not generalize beyond our sample of mostly low income, motivated AA-White smokers. However, we are intentionally sampling from this subgroup because they represent a high-risk but understudied population. Efforts to better understand and improve cessation among low income groups could significantly improve tobacco use treatment outcomes and tobacco-related morbidity and mortality. **Other Mechanisms.** This is the first prospective study to examine racial differences in quitting. The factors selected for inclusion based on those receiving the most attention and support in the literature and those with the most potential to inform practice. We recognize that other mechanisms beyond those explored in this study may underlie racial differences. This study represents a realistic starting point for better understanding these differences and for highlighting areas for further study. **Varenicline in select populations.** Although varenicline is a highly effective medication that appears to be safe in the vast majority of smokers, the FDA has recently issued drug safety communications related to neuropsychiatric and cardiovascular symptoms in a select group of smokers. We will stay abreast of these developments and revise our inclusion criteria, consent documents, and monitoring protocol, as needed, to assure the safety of our participants.

PROTECTION OF HUMAN SUBJECTS

1. Risks to Human Subjects

Human Subjects Involvement, Characteristics, and Design . The proposed research is a prospective cohort intervention study, stratified on race, age (< 40, > 40), and gender, to evaluate varenicline for smoking cessation in 448 AA versus White smokers (224 AA, 224 White). AA and White smokers have been selected as the target population because of the noted disparities in smoking and quitting in AAs relative to Whites. We have chosen to stratify on age and gender, in addition to race, because these factors are known to impact cessation. Stratification on these factors minimizes threats to internal validity and allows for the best possible study design. Participants will be recruited from Swope Health Central, a community-based health center in Kansas City, Missouri. Participation will last for 6 months.

To be eligible, participants must meet the following inclusion criteria:

- Non-Hispanic African American or non-Hispanic White
- ≥ 18 years of age
- Smoked 3-20 cigarettes per day
- Smoked 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

Participants will be excluded if any of the following criteria are met:

- Renal impairment
- Evidence or history of clinically significant allergic reactions to varenicline
- Hospitalization in the past 2 months for any cardiovascular disease, including but not limited to:
  - Angina
  - Myocardial infarction
  - Peripheral vascular disease
  - Stroke
- New onset of chest pain or arrhythmia in the past 2 monthsHistory of alcohol or drug dependency 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

Exclusion criteria are consistent with documented contra-indications for varenicline and the criteria used in previous RCTs. Participants must smoke 3-20 cpd to minimize possible confounds in treatment response and smoke on ≥ 25 days of the past 30 to avoid enrolling smokers who are in the transitory phase between daily smoking and quitting. Other ethnic groups will be excluded as our primary aim is to evaluate varenicline in non-Hispanic AA and non-Hispanic White smokers.

Eligible and consented participants will receive varenicline for 12 weeks and 6 sessions of health education counseling. Varenicline, a first-line, non-nicotine medication, is a α4β2 nicotinic acetylcholine receptor partial agonist approved by the FDA for tobacco use treatment in 2006. It was selected for use in this study because it is the most effective of currently available smoking cessation pharmacotherapy. Standard dosing guidelines will be followed, which include 0.5 mg once per day for Days 1-3, 0.5 mg twice per day for Days 4-7, and 1.0 mg twice per day from Days 8 through the end of treatment (Week 12). Medication will be dispensed in 3, 30-day pill boxes (Months 1, 2, 3) at entry into the study. Health education counseling was selected because it is consistent with the current *Tobacco Use and Dependence Clinical Practice Guideline* and because our work

and the work of others have documented the efficacy of this approach for smoking cessation. The number of sessions is consistent with our previous studies where we have achieved visit completion rates of around 80%.

In addition to investigators at the University of Kansas Medical Center (KUMC; Drs. Nollen, Cox, and Mayo), investigators are located at the University of Minnesota (Dr. Ahluwalia), University of California San Francisco (Dr. Benowitz), and University of Toronto (Dr. Tyndale). The study will be conducted at KUMC and all source documents will be housed at KUMC. Dr. Benowitz (UCSF) will be responsible for the analysis of samples for nicotine intake, 3HC/COT, and cotinine (described below). Dr. Tyndale (Univ. of Toronto) will be responsible for the analysis of samples for CYP2A6 genotyping (described below). Dr. Ellerbeck (Univ. of Kansas Medical Center) will serve as the study physician. He will be responsible for determining medical eligibility of participants to take varenicline and addressing any questions warranting medical attention. All investigators have completed the required human subjects training at their respective institutions.

Sources of Materials. Survey assessments will be completed at in-person visits (Weeks 0, 4, 8, 12, and 26). Surveys will include questions about participants demographic characteristics, smoking patterns (cigarettes per day, menthol status), as well as psychosocial (e.g., negative affect, depression, stress) and behavioral factors (social support, withdrawal, craving). Biological samples will be taken for analyses by the laboratories of co-investigators Drs. Neal Benowitz (UCSF) and Rachel Tyndale (University of Toronto). Urine will be taken at Week 0 for analysis of nicotine intake, represented as the sum of cotinine + cotinine-glucuronide + trans-3'-hydroxycotinine + 3HC-glucuronide (Benowitz laboratory). Blood will be also taken at Week 0 for analysis of nicotine metabolism phenotype (3HC/COT) (Benowitz laboratory) and genotype (CYP2A6) (Tyndale laboratory). Blood will be drawn again at Week 4 for analysis of varenicline steady-state levels (Benowitz laboratory). Saliva will be taken at Weeks 12 and 26 among self-reported quitters for analysis of cotinine-verified smoking status. All specimens will be assigned a unique identification number only and will contain no individually identifiable private information. Specimens will be accessible only to identified research staff at the respective institutions.

The KUMC Department of Preventive Medicine has a well-developed structure for data management. Working data is maintained on a single large file server that services the entire section. Inactive files are moved to archival storage under control of an automated system, itself controlled by a DBMS (Ingres) based request system which ensures that all data movement is appropriately logged and commented. The archival storage is hosted on the institutional mainframe computer, which also supports billing and registration. The use of the mainframe ensures several high level support functions for the archive system (e.g., storage in separate fire zones, regular copying of data to new media, guaranteed availability, etc.) The data management will be governed by standard procedures within the section with regard to data security and access. All subjects will be identified with a sequentially assigned subject number, and subject initials. To ensure subject confidentiality, no names, social security numbers, hospital or clinic numbers will be included in the shared databases. Names, addresses, telephone numbers, and any other information needed for recruitment, study involvement, and tracking will be obtained and maintained locally by the project personnel. All computer files and systems will be password protected and accessible only by authorized personnel. Assigning each participant a study number and numerically coding all data will maintain confidentiality. The association of the ID-code and names of the participants will be kept by Dr. Nollen (PI) in a locked file drawer. Only summaries of findings will be reported in any publications or presentations, with no identification of individuals. Audio tapes of counseling sessions will be identified by a number, not a name, and will be stored in a locked file cabinet. No one other than the study team will have access to the audio tapes. Audio tapes will be kept for 15 years. After that, it will be destroyed.

Potential Risks. We will use varenicline 1 mg twice daily made by Pfizer. Varenicline is approved by the FDA and its safety and efficacy have been published in medical journals. The most common adverse events are nausea, insomnia, vivid dreams, dry mouth, flatulence, constipation, irrability, headaches, dizziness, and fatigue. In July 2009, the FDA introduced a black box warning about neuropsychiatric complications (depressed mood, suicidal behavior) reported in patients attempting to quit smoking with varenicline. We will minimize these risks by using strict exclusion criteria. Use of varenicline will be under the supervision of Drs. Nollen (PI) and Ellerbeck (study physician). Participants will be prompted to discuss side effects at each visit and given the study phone number to report adverse events at interim time points. FDA guidelines for reporting adverse events will be followed. Any problems needing medical attention will be referred to Dr. Ellerbeck who will carry a study pager. Treatment protocols (per Pfizer Global Pharmaceuticals) will be followed for reducing or discontinuing varenicline in the event of severe adverse events. In Phase 2 and 3 placebo-controlled

studies, the treatment discontinuation rate due to adverse events in patients dosed with 1 mg, twice daily was 12% for Chantix compared to 10% for placebo in studies of three months treatment.

Other risks of the study include the risk of drawing blood and extracting DNA to be used by our study team for analysis of the biological aims. The risks of drawing blood include brief pain, slight bruising, and rarely, infection where the needle went in. We take every precaution to minimize these risks. Some people feel dizzy when they have blood drawn, but this goes away when the person lies down. There is a small risk that if people other than the researchers got a hold of participant's genetic facts they could misuse them. In order to minimize these potential risks, participants will be identified by a number, not by name, whenever possible and access to study-related information will be limited to the following agencies and/or collaborators: Dr. Nollen and all key personnel on this study, Pfizer, the Food and Drug Administration, the Human Subjects Committee of the University of Kansas Medical Center, the University of Kansas Medical Center Research Institute, Dr. Rachel Tyndale and her staff at the University of Toronto, and Dr. Neal Benowitz and his study staff at the University of California at San Francisco. In addition, participation is voluntary and participants may withdraw from the study at any time without penalty.

Other risks for participating in the study are minimal and include those associated with the inconvenience of completion of several questionnaires and interviews, telephone follow-up assessments, providing saliva and urine for analysis of nicotine intake, and the inconvenience of coming to Swope for in-person and telephone counseling sessions. We believe the risks involved in this study are reasonable given the potential impact of the knowledge to be gained on smoking cessation treatment.

Alternatives to participating in this study are to quit cold turkey, use other smoking cessation programs, purchase nicotine gum or patches from the pharmacy, and obtain a prescription for nicotine inhaler, nicotine nasal spray, nicotine lozenge, Zyban or Chantix.

2. Adequacy of Protection Against Risks

Recruitment and Informed Consent. We will recruit 448 eligible (224 AA, 224 White) smokers for this study. Our previous research in KIS –I, -II, and –III has provided us considerable knowledge of recruitment of smokers within this urban community in coordination with Swope. We will use both clinic- and community-based recruitment strategies. *Clinic-based recruitment.* Swope clinic staff will be fully informed about the study, the eligibility criteria, and the enrollment process and will be able to refer smokers to the project office. Posters and flyers will be distributed throughout the health center. Finally, letters from Swope physicians will be mailed directly to clinic patients to inform them of the study. To recruit patients at TMC, a TMC employee will query their electronic medical records to identify potential subjects. The TMC employee will mail letters signed by a sponsoring TMC physician on Truman letterhead to potential subjects to inform them of the study. No PHI will be disclosed to KUMC study staff and identities of potential subjects will only be known when they call our study line to find out if they are eligible. The sponsoring TMC physician and TMC employee will not query their records until they have received an approval of waiver of privacy authorization from the TMC Privacy Board. *Community-based recruitment.* We will use additional community-based strategies (word of mouth, radio and television ads, print materials) as needed, to reach our targeted enrollment of 224 AA and 224 White smokers.

During the recruitment phase, the smoker will be informed of the details of the study and the fact that participation in this study is entirely voluntary and will not affect their current or future medical care at any treating facility. The smoker must successfully complete screening and provide informed consent before being enrolled in the study and delivered an intervention. This ensures that all participants meet all inclusion/exclusion criteria as stated in the study protocol and have provided informed consent.

Protections Against Risk. Upon enrollment, all enrolled smokers will have the highest level of protection of confidentiality for their participation in this study. Standard language in our consent procedure assures the participants of the confidential nature of the study. Those who elect to participate will be clearly told that they may withdraw from the study at any time without jeopardizing current or future care at any medical facility. Potential participants will also be informed of alternative treatments (i.e., using other smoking cessation programs, purchasing nicotine gum, patches, or lozenge from the pharmacy, obtaining a prescription for nicotine inhaler, nasal spray, or other smoking cessation products from their physician). The consent form will be reviewed with each participant and they will be given a copy of the signed consent form. A copy of the signed consent will be maintained by Dr. Nollen for documentation. These standards are strictly adhered to and monitored by the KUMC Institutional Review Board. Confidentiality will be maintained by assigning each participant a study number and numerically coding all data. The association of the ID-code and the participant's name will be kept by Dr. Nollen in a locked file cabinet. Only summaries of group data will be reported in any publications or presentations, with no identification of individuals. All records will be kept in

locked filing cabinets in offices that are kept locked when unoccupied. Subject files will be kept in a secure area, with access only by designated staff members (PI and Co-Investigators).

In our varenicline pilot study only 2% of participants required discontinuation due to severe AE (neuropychiatric symptoms consistent with the 2009 FDA Black Box Warning); all other AEs were expected and not severe (e.g., nausea). Nonetheless, we have a detailed plan for clinical management of psychiatric or medical problems. The study staff will monitor any reports or observations of severe depression or other psychiatric symptoms in the subjects (i.e., suicidal ideation) or medical problems using the following set of questions as a template for better assessing the participant's current mood, thoughts and feelings:

Developing neuropsychiatric symptoms may be recognized by:

- Participant may report depressed symptoms when staff is capturing adverse events
- Noting a significant change in a participant's affect

Questions that can be asked to gather important information if a participant expresses suicidal ideation:

- Ideation: You indicated you might be having some thought or feelings of hurting yourself. Tell me more.
- History: Have you ever felt like this in the past?
  Have you ever tried to harm yourself in the past?
- Plan: When you are thinking about hurting yourself, do you have any idea what you might do to harm yourself? (Does the person have the resources to carry out this plan?)
- Intent: Do you think you would act on this plan?
  Can you imagine yourself actually doing this?
  Do you think you might harm yourself in the near future?
  (If "no", ask "what would keep you from doing this?"

In the event of such an occurrence, the study assistant will arrange for additional assessment of the subjects symptoms by Dr. Nollen (psychiatric) or Ellerbeck (medical). Individuals who report suicidal intent or other severe psychiatric symptoms will be discontinued from varenicline and referred for treatment and followed throughout the study period. In the event of an emergency (e.g., suicidal plan), KUMC treating psychiatrists will be consulted to refer the participant for treatment at KUMC, Swope Health Central or at a local hospital. Referral for treatment will be made when appropriate. Continued participation with the study will be voluntary and in cooperation with the health care professional treating the subject's psychiatric condition. FDA guidelines for reporting adverse events to the sponsor (NIH), KUMC Human Subject's Committee, and Pfizer Global Pharmaceutical will be followed. Following each in-person or telephone visit, the research counselor or study coordinator will record all data in the participants' data collection book. The study coordinator will serve as the internal monitor and will review and monitor books during the day. Dr. Nollen will review all Adverse Events for all the data books on a weekly basis.

Participants with stable cardiovascular disease (i.e. no hospitalization or onset of cardiovascular symptoms in the past 2 months) will not be excluded. However, given the 2011 FDA Black Box warning regarding the increase of certain cardiovascular risks in patients with cardiovascular disease, we have developed a plan to assess and intervene in the event of a cardiac problem:

1) **Advising participants of risk:** All enrolled participants will be provided with the recommendations as delineated in the FDA advisory (June 2011). This advisory states that varenicline may be associated with a small, increased risk of certain cardiovascular events in patients with cardiovascular disease. As outlined in the FDA advisory, all participants will be instructed to contact study staff and their health care professional if they experience new or worsening symptoms of cardiovascular disease, including but not limited to, shortness of breath or trouble breathing, new or worsening chest pain, and new or worsening pain in the legs.
2) **Ongoing monitoring:** Adverse events, including new or worsening symptoms of cardiovascular disease or intervening hospitalization, will be assessed at each study time point and through spontaneous reports from participants during interim time points.
3) **Stopping medication and reporting:** In the event that a cardiovascular event is reported, the participant will be immediately instructed to stop taking varenicline and to contact study staff. Study staff will contact Drs. Nollen or Ellerbeck who will take necessary action, including conducting additional assessment of the symptoms. An Adverse Events Record Form will be completed that provides a

description of the event, classification of the seriousness, evaluation of the potential relationship to the intervention, and an assessment of need for change in the informed consent or study activities. All serious adverse events will be reported to the KUMC IRB and NIH within 24 hours. If the IRB takes any action limiting approval of the study, NIH will be notified.

Stopping Rules. We have developed specific stopping rules to protect the safety of study subjects. In the case of a Serious Adverse Event (as defined by the FDA and the KUMC IRB), the study will be stopped and no further enrollment will take place until an investigation of the event has taken place by the Principal Investigator, the Co-investigators and the study coordinator. A determination of the association of the adverse event with the study intervention will be made and appropriate modification to the protocol will be made if an association is suspected. If protocol modifications to ensure the safety of future study subjects cannot be made, the study will be terminated.

3. Potential Benefits of the Proposed Research to Human Subjects and Others

Participants will have the opportunity to benefit by making behavioral changes in their smoking or by stopping smoking. Participants who stop smoking will experience invaluable health benefits, and family members of participants who stop smoking would be expected to benefit from reduced exposure to second-hand smoke. The participants will receive study medication and counseling free of charge. Participants will receive $40 gift card at Weeks 0, 26 and a $20 gift card at Weeks 1, 4, 8, 12, 16 as compensation for their time/travel and in appreciation for their participation. Participants will be informed that disbursement of the incentives is not contingent on their smoking status.

4. Importance of the Knowledge to be Gained

Racial/ethnic differences in smoking are well documented; African Americans smoke fewer cigarettes per day than Whites but experience disproportionately greater smoking attributable morbidity and mortality. Well documented disparities also exist in smoking cessation with African Americans consistently quitting at lower rates than Whites. However, to-date, no adequately powered study, stratified on race, has been conducted to understand the mechanisms accounting for differential quit rates in African Americans relative to Whites. This application will 1) examine varenicline for smoking cessation among African American and White smokers, 2) examine how smoking, psychosocial, treatment process, and biological factors explain the relationship between race/ethnicity and cotinine-verified 7-day abstinence in African American and White smokers, and 3) examine the side effect profile of varenicline by smoking level. The impact of these findings will be considerable, having ramifications for treatment, clinical practice, and policy. Significant knowledge will be gained about African American-White differences in quitting. These findings have the potential to improve tobacco use treatment by moving the field away from a generic focus on race/ethnicity toward a targeted focus on modifiable smoking, psychosocial, and treatment process factors most relevant to AA and to Whites. The risks involved in gaining this knowledge are reasonable given the potential impact of the knowledge to be gained on smoking cessation treatment.

5. Data and Safety Monitoring Plan

This study is not a clinical trial but involves the use of an FDA approved product, varenicline. The monitoring of the progress of the clinical trial and the safety of participants will be performed by Dr. Nollen (PI) in association with Dr. Ellerbeck and the other study co-investigators. Dr. Nollen will review AE data weekly and discuss at regular meetings with Dr. Ellerbeck. The University of Kansas Medical Center also has a Data and Safety Monitoring Board (DSMB) which provides oversight for clinical trials for which an external DSMB is not in place. If the Human Subjects Committee determines that working with the DSMB is needed, Dr. Nollen will do so accordingly. The KUMC DSMB membership includes internal and external scientists and clinicians, a statistician, an ethicist, and lay representation. All members of the DSMB review written protocols, informed consent procedures, and plans for data and safety monitoring. The investigator is invited to present in an open session in which members of the DSMB may ask questions for clarification. The DSMB general reporting guidelines are then individualized for the specific study taking into consideration the population under the study, any known anticipated adverse outcomes or risks of the specific study protocol, procedure, and/or drug, and any other data monitoring or oversight of the particular study. If necessary, the DSMB will review manuscripts and results from the study to assure that results are fairly presented and conclusions are appropriate.

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