Pro00014398

A Randomized Controlled Trial of Varenicline for Adolescent Smoking Cessation

Specific Aims

Cigarette smoking remains the leading cause of preventable death in the United States and the world. The link between smoking and cancer is clear, and cessation at a young age results in a substantial reduction in the risk of cancer. The overwhelming majority of current smokers began smoking during adolescence. While often motivated to quit, adolescent smokers are less likely than adult smokers to succeed when making a quit attempt. Despite the tremendous potential health impact of smoking cessation among adolescents, minimal effort has been made to develop evidence based cessation treatments for this age group.

Psychosocial cessation approaches have generally yielded small effect sizes in adolescents, and pharmacotherapy represents a potential avenue to improve cessation outcomes. To date, though, medications for cessation remain critically understudied and potentially underutilized in this age group. The few adequately powered controlled trials of bupropion SR and nicotine replacement in adolescents suggest potential efficacy improvements over psychosocial interventions, but overall rates remain modest, and long-term post-treatment effects are unclear. Varenicline, an $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist, has demonstrated superior cessation efficacy compared to placebo, bupropion SR, and transdermal nicotine patch in adult smokers, but no controlled trials have focused on its efficacy in adolescent smokers. Results from our recent adolescent varenicline pilot study, coupled with our established history of adolescent smoking cessation pharmacotherapy research, support the feasibility and safety of this line of investigation.

We propose a randomized, controlled, double-blind trial (*n*=166) of varenicline, versus placebo, to assess its smoking cessation efficacy and safety in adolescent smokers, ages 14-21. Participants will receive 12 weeks of treatment and will return for follow-up at multiple post-treatment time points, the last at 6 months. Medication will be titrated to the goal dose during the first week, and the targeted quit date will be set at the end of the first week. All participants will receive quit smoking brochures and brief cessation counseling. A previously established retention-targeted contingency management intervention will be employed within both groups to enhance study retention. Our primary efficacy outcome is cotinine-confirmed, 7-day point prevalence abstinence at the end of treatment.

Specific Aim 1. To examine the efficacy of varenicline, compared with placebo, for smoking cessation in adolescent smokers.

Hypothesis 1: Adolescent smokers treated with varenicline, compared with those treated with placebo, will demonstrate greater 7-day point prevalence abstinence at the end of treatment.

Abstinence will be measured using participant self-report, biologically confirmed by urine cotinine level ≤50 ng/mL.

Specific Aim 2. To examine the safety and tolerability of varenicline, compared with placebo, when used for smoking cessation in adolescent smokers.

Hypothesis 2: Varenicline will demonstrate adequate safety and tolerability, compared with placebo, in the frequency of treatment-emergent adverse events.

We will rigorously assess safety and tolerability throughout treatment using established protocols. Weekly medical visits, including detailed monitoring of psychiatric and general health parameters and assessment of adverse events, will be conducted.

Despite the public health need for aggressive tobacco control during adolescence, there are few medication trials for smoking cessation within this vulnerable age group. A controlled test of varenicline, arguably the most efficacious smoking cessation pharmacotherapy in adults, is clearly indicated. While we acknowledge that post-marketing anecdotal reports of psychiatric adverse events have led to an FDA “black box” warning for varenicline, controlled studies in adults and our pilot adolescent data support varenicline’s safety. In this context, and in light of varenicline’s potential for efficacy in adolescents, we argue that the potential benefits of the proposal far outweigh the risks, especially in a study that will incorporate established, rigorous procedures to monitor safety and outcomes. If our study yields positive outcomes, it will, upon replication, carry both clinical implications and potential regulatory significance. If our study yields null outcomes, it will do the same. Either outcome provides important public health value, and our study is well poised to fill a critical evidence gap in adolescent smoking cessation.

Pro00014398
Research Strategy

A. SIGNIFICANCE

Tobacco smoking remains the leading cause of preventable death in the United States, killing 440,000 Americans annually (1). About half of these deaths are due to lung cancer, an illness with an 80% mortality rate (2). One-fifth of all deaths in the United States result from smoking, a toll greater than those of alcohol, illegal drugs, homicide, suicide, car accidents, and AIDS combined (3).

Nicotine dependence almost universally begins in adolescence. Nearly 90% of adult smokers began smoking before age 18, and adolescent smoking rates range, in steadily increasing numbers, from 6% of 14-year-olds to 37% of 21-year-olds (4,5). Almost all adolescents who smoke regularly will continue smoking well into adulthood, leading to a life expectancy 20 years shorter than nonsmokers (4,6). Daily smoking, a particularly concerning predictor of long-term smoking and adverse health outcomes, is present in 3% of 8th graders, 6% of 10th graders, 11% of 12th graders, and 17% of 21-year-olds (5,7). Nearly two-thirds of adolescent smokers are interested in quitting, but only 4-6% of unassisted quit attempts are successful (8-10).

Surprisingly few controlled studies have evaluated adolescent smoking cessation programs, and almost all have exclusively focused on psychosocial treatments, yielding generally discouraging results. For example, a meta-analysis of 48 studies showed a mean quit rate of 9.1%, compared with 6.2% among control groups, a difference of only 2.9% (odds ratio [OR] 1.5) (11). In the interest of enhancing these very modest quit rates, and in light of clear evidence that adolescent smokers experience nicotine withdrawal and craving (12-14), a handful of recent studies have explored the potential impact of cessation pharmacotherapy in adolescent smokers. Only 6 controlled trials to date have investigated bupropion SR (15-17) and/or nicotine replacement therapy (18-20); these are summarized in **Table 1**. The table suggests some pharmacotherapies may provide better outcomes than psychosocial treatments (11) (though this is an indirect comparison), indicating that medications should be considered as a treatment option for adolescent smoking cessation. Additionally, despite initial efficacy, absolute cessation rates remain modest, and are generally not sustained at post-treatment follow-up.

Table 1. Abstinence outcomes in controlled adolescent smoking cessation pharmacotherapy studies.

Study	Total *n*	Medication	*7-day point prevalence abstinence (% abstinent)*							
			End of Treatment				Post-Treatment Follow-Up			
			Time Point	Active	Placebo	OR	Time Point	Active	Placebo	OR
Hanson, 2003	100	Nicotine Patch	10 wk*	28%	24%	1.2	Not reported			
Killen, 2004	211	Bupropion 150 mg/day+	10 wk*	23%	28%	0.8	26 wk‡	8%	7%	1.2
Moolchan, 2005	120	Nicotine Gum (*n*=46)	12 wk*	9%	5%	1.8	26 wk*	9%	5%	1.8
		Nicotine Patch (*n*=34)		21%		4.9		21%		4.9
Muramoto, 2007	312	Bupropion 150 mg/d (*n*=105)	6 wk‡	11%	6%	1.9	26 wk*	3%	10%	0.3
		Bupropion 300 mg/d (*n*=104)		14%		2.6		14%		1.5
Rubinstein, 2008	40	Nicotine Nasal Spray	8 wk*	0%	12%§	N/A	Not reported			
Gray, 2011	134	Bupropion 300 mg/day	6 wk‡	18%	10%	2.0	12 wk‡	8%	3%	2.6
Proposed	*166*	*Varenicline*	*12 wk‡*				*26 wk‡*			

+all participants (bupropion and placebo) received nicotine patch
§no placebo provided (control condition only involved psychosocial treatment)
*carbon monoxide breathalyzer confirmation
‡cotinine confirmation

The 2006 introduction of varenicline, an $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist, represented an enormous breakthrough in adult smoking cessation pharmacotherapy. In addition to its superior efficacy in comparison with placebo (end-of-treatment ORs 3.9-5.9), varenicline was superior in head-to-head trials with the previously established first-line pharmacotherapies: bupropion SR (OR 2.2) and nicotine patch (OR 1.7) (21-25). Some might argue that varenicline would never provide comparable outcomes for adolescent smokers. However, while overall abstinence rates might be lower among adolescent smokers, the effect size should be comparable, as we have no reason to believe the mechanism by which varenicline works differs by age group

(see below). Thus, given its striking efficacy in adults, varenicline is a strong candidate for evaluation in adolescent smokers. This critical evidence gap needs to be filled.

Only two small pilot feasibility studies of varenicline have been conducted among adolescents. The first was a 2-week pharmacokinetic study (26). Adolescent smokers (ages 12-16, *n*=72) were randomized to receive "high-dose" varenicline (titration to 1 mg twice daily for those >55 kg and to 0.5 mg twice daily for those ≤55 kg), "low-dose" varenicline (titrated to 0.5 mg twice daily for those >55 kg and to 0.5 mg once daily for those ≤55 kg), or placebo. Results indicated that pharmacokinetics were similar to adults for those >55 kg, and that the body weight exposure effect for those ≤55 kg was adequately offset by the reduced dose. Adverse events occurred in more participants in the varenicline groups (64% "high-dose", 73% "low-dose") versus placebo (13%), with nausea, headache, vomiting, and dizziness being most common. Two participants reported abnormal dreams and one had a brief, mild episode of anger. However, there were no serious adverse events or discontinuations due to adverse events in any group. Almost all adverse events were considered mild, and none were more frequent in the "high-dose" versus "low-dose" groups. Though participants were not instructed to reduce or quit smoking, there were moderate reductions in smoking over the 2-week trial (74% cigs/day reduction in "high dose," 52% in "low dose," and 40% in placebo participants).

The second was our recently completed pilot cessation trial, detailed below (Section C1b) (27). Briefly, we demonstrated 1) varenicline may produce abstinence rates superior to other medications, 2) no serious adverse events or discontinuation due to adverse events with varenicline, and 3) feasibility of conducting varenicline smoking cessation trials in adolescents.

The proposed study will have numerous clinical and policy implications. First, there are few options for smoking cessation among adolescent smokers, despite clear evidence that the trajectory of smoking is most malleable during this formative period (28,29). The existing treatment options produce modest effects at best. Many physicians are willing to prescribe a medication off-label to adolescents, particularly if that medication has a strong base of support within another population (30,31). We believe many physicians are either already using varenicline in adolescents on their own accord, or wish to do so. This study will provide the necessary data to support or refute this strategy. Second, we recognize that use of varenicline includes potential added risk, given recent anecdotal reports of psychiatric instability (32,33). Despite the FDA's strong reaction to those anecdotal reports, the vast majority of scientific evidence supports the safety of varenicline. This includes a pooled analysis of 3091 participants randomized to varenicline in controlled trials, revealing no significant increase (relative to placebo) in psychiatric symptoms, aside from sleep disturbance (34) (**Table 2**). Additionally, a "real world" primary care cohort study including 10,973 smokers prescribed varenicline revealed no evidence of increased risk of self-harm, compared with smokers prescribed other cessation pharmacotherapies (35). Nonetheless, the FDA regulatory constraint, including a "black box" warning, remains. We do not suggest that our study alone will provide the necessary information for a change in FDA regulatory practice, nor will our study provide sufficient support for a change in indication for varenicline. It will, however, provide valuable evidence regarding varenicline's potential viability as a treatment for adolescent smokers.

Table 2. Adverse events (AEs) in pooled analysis of varenicline controlled trials (34)

		Varenicline (*n* = 3091)	Placebo (*n* = 2005)	RR	95% CI
Any Psychiatric AE (excluding sleep disturbances)		10.7%	9.7%	1.02	0.86-1.22
Psychiatric AEs occurring in ≥1% of varenicline participants	Sleep Disturbances	25.1%	14.5%	1.70	1.50-1.92
	Anxiety Symptoms	4.5%	5.0%	0.86	0.67-1.12
	Depressed Mood	2.8%	1.9%	1.42	0.96-2.08
	Other Mood Symptoms	2.4%	1.5%	1.21	0.79-1.83
Other psychiatric AEs of particular concern	Suicidal and Self Injurious Behaviors	0.0%	0.1%	N/A	
	Psychiatric Serious AEs	<0.1%	0.1%	N/A	

B. INNOVATION

Despite their tremendous potential public health impact, adolescent smoking cessation treatments remain critically understudied. Pharmacotherapies, in particular, have been the focus of only six controlled trials. While some studies have indicated potential promise, many have been beset by design inconsistencies and

methodological challenges (see **Table 1** above). Trials have varied greatly in several key design features, including medication dosing, length of therapy, span of post-treatment follow-up, nature and intensity of psychosocial treatments, definitions of abstinence, and choice of main outcome variables. This heterogeneity has made it difficult to systematically compare adolescent studies head-to-head, and to contrast findings with those of adult studies. Additionally, significant problems with participant recruitment and retention have led to underpowered trials, often yielding null findings and leaving the impression that pharmacotherapy is ineffective.

Drawing on our research team's collective experience, we intend to proactively address the above concerns in the present proposal. The proposed medication dosing is based on published varenicline pharmacokinetic data in adolescent smokers (26). Medication titration schedule, length of therapy, and intensity of psychosocial treatment are designed to parallel those of large-scale varenicline smoking cessation efficacy and safety trials in adults (23,24). Post-treatment follow-up will be extended to 6 months, consistent with expert recommendations (36). Abstinence criteria include biological verification with urine cotinine, recognized as the current gold standard (36,37). Recruitment will be bolstered by several innovative techniques, including the continuation and expansion of a network of smoking cessation research clinics in area high schools. Retention will be enhanced using an aggressive retention-targeted contingency management approach, rewarding participants in escalating fashion for study attendance and adherence with study procedures (38-40). The proposed sample size was chosen based upon consistently conservative estimates from prior relevant research, thereby ensuring sufficient power for hypothesis testing.

The proposed investigation of varenicline in adolescents is timely and supported by the research team's experience with this medication. We have already been granted Investigational New Drug (IND) approval #104451 from the FDA for adolescent (ages 14-21) smoking cessation research with varenicline. Aside from our recently completed pilot study, there have been no published varenicline adolescent smoking cessation trials (pilot or otherwise). Given its superior efficacy compared with placebo, bupropion SR, and transdermal nicotine patch in adults, and given the feasibility and safety/tolerability suggested by our pilot study results, varenicline is an ideal candidate medication for evaluation in adolescents.

C. APPROACH

C1. Preliminary Studies

Very few research groups have conducted controlled pharmacotherapy trials for adolescent smoking cessation. We are among these few, and argue that our experience, also inclusive of adult and adolescent cessation trials of varenicline, uniquely positions us to successfully undertake the proposed study.

C1a. Bupropion SR and Contingency Management for Adolescent Smoking Cessation

We conducted this large-scale 2x2 controlled clinical trial (*n*=134) to evaluate bupropion SR and contingency management, each alone or in combination, for adolescent smoking cessation treatment (see Appendix for manuscript, inclusive of detailed methods and findings) (15). Briefly, we concluded that combined treatment was superior to placebo-only treatment throughout active treatment (cotinine-confirmed 7-day point prevalence abstinence odds ratio 3.6 at end of active treatment). Our completion of this trial demonstrates our ability to conduct an adolescent smoking cessation pharmacotherapy trial on the scale of the proposed study.

C1b. Varenicline versus Bupropion XL for Adolescent Smoking Cessation

With FDA Investigational New Drug (IND) approval #104451 (varenicline and bupropion XL in adolescents age 14-21), we conducted this double blind, randomized pilot trial (*n*=29) to assess the feasibility and safety of evaluating these medications as adolescent smoking cessation pharmacotherapies (27). Participants were randomized to an 8-week trial of either medication, with 1-week titration and 7 weeks at goal dose (1 mg twice daily for varenicline participants >55 kg, 0.5 mg twice daily for varenicline participants ≤55 kg, 300 mg daily for bupropion XL participants), and monitored closely for safety, tolerability, and efficacy. Weekly safety/tolerability assessments included vital sign measurement and physician evaluation, inclusive of a) open-ended inquiry about health issues/complaints, b) structured/extensive review of systems to augment open-ended interview (41), and c) detailed assessment for suicidal ideation or behavior using the Columbia-Suicide Severity Rating Scale (C-SSRS) (42). For efficacy assessment, a participant was considered abstinent on a given week if reporting zero cigarettes smoked during the week and submitting a urine specimen with ≤50 ng/mL cotinine (cotinine-confirmed 7-day point prevalence abstinence). Findings, summarized in **Table 2**, support the feasibility and safety of conducting a controlled trial of varenicline for adolescent smoking cessation. Varenicline efficacy findings, including a 27% biologically verified abstinence rate, as well as substantial reduction in daily smoking among

non-abstainers, provide further support for a larger efficacy trial. Our experience with varenicline in adolescents, including IND approval, demonstrates that we are well positioned to study this medication further.

Table 2. Overview of varenicline vs. bupropion XL pilot trial findings (27)

		Varenicline (*n*=15)	Bupropion XL (*n*=14)
Safety/ Tolerability	Adverse events in >1 participant	Insomnia (4), Nausea (3), Headache (3)	Vivid dreams (5), Insomnia (2), Nausea (2), Chest discomfort (2)
	Discontinuation due to adverse events	None	Increased anxiety (1), "Feeling too focused" (1)
	Significant vital sign changes	None	None
	Suicidal ideation or behavior	None	None
Efficacy	Participants achieving 7-day cotinine-confirmed point prevalence abstinence (primary outcome)	4 (27%)	2 (13%)
	Baseline cigs/day (mean±SE)	8.8 ± 1.2	12.0 ± 1.9
	End-of-treatment cigs/day (excluding abstainers)	1.4 ± 0.9	4.9 ± 1.8
	% Reduction in cigs/day (excluding abstainers)	84%	59%

C1c. Additional Experience with Varenicline

Our ongoing NIDA-funded P50 component study (P50DA16511, Component 4 "Menstrual Cycle and Smoking Cessation in Women", Co-PIs Gray/Saladin) includes a randomized trial of varenicline versus transdermal nicotine patch for smoking cessation in women. To date, 135 women have been enrolled and randomized in the trial, providing us with extensive experience (beyond that gained in the above-mentioned adolescent study) in safety, tolerability, and efficacy monitoring of varenicline treatment.

C1d. Broad Experience with Adolescent Smokers

Our work reflects expertise with and commitment to adolescent smoking research. In addition to the above studies, we have investigated nicotine withdrawal and attention-deficit/hyperactivity (ADHD) symptoms (43), measures to assess nicotine dependence (44), the trajectory of cigarette smoking during treatment for ADHD and substance use disorders (45), and craving (K23DA020482, PI Carpenter) in adolescent smokers.

C1e. Other Relevant Adolescent Research

Our research on cannabis use in adolescents, including a controlled cessation pharmacotherapy trial (R01DA026777, PI Gray), multiple investigations of cue reactivity (46,47), and other laboratory and clinical research (48) contributes to our ability to conduct research in the closely related field of adolescent smoking.

C2. Research Team

The investigative team, ***uniquely experienced with adolescent smoking cessation pharmacotherapy in general and varenicline in particular****, is ideally suited to undertake this study*. Only 6 teams have completed adolescent smoking cessation pharmacotherapy controlled trials, and ours is the only one among these with additional adolescent and adult varenicline clinical trial experience. The team is led by a board certified child and adolescent psychiatrist (Gray), and comprised of three clinical psychologists (Carpenter, Saladin, Simonian), a child and adolescent psychiatrist (Lewis), an addiction psychiatrist (Hartwell), a behavioral psychologist (McClure) and two biostatisticians (DeSantis, Baker), each with expertise vital to the successful completion of the study (see biosketches, budget justification, resources).

Two off-site consultants, both with established history of collaboration and consultation with the research team, will provide input on key areas. Maxine L. Stitzer, Ph.D., will contribute her expertise in designing and conducting contingency management and smoking cessation interventions. Himanshu P. Upadhyaya, M.B.B.S., M.S., will provide input on study design and pharmacotherapy safety and efficacy assessments.

The study will be conducted at a nationally recognized substance abuse treatment research center, assuring the ability to efficiently complete the project while maintaining the highest quality of protection of human participants and data integrity.

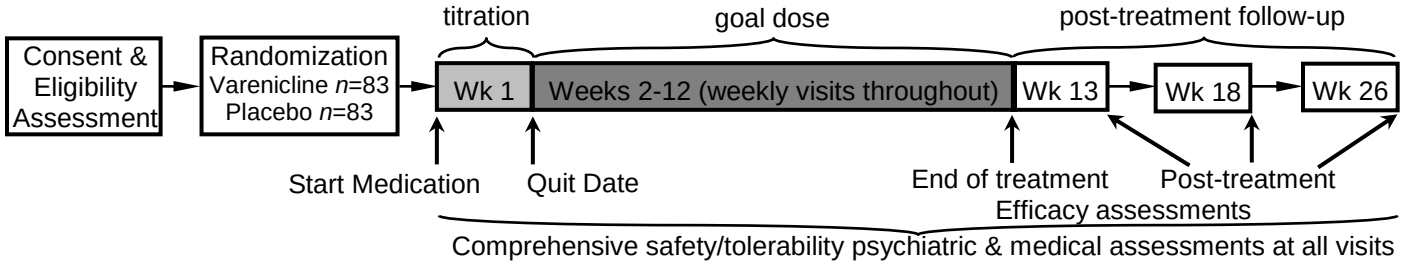
C3. Design and Methods of Current Proposal

C3a. Overview

The objective of this proposal is to examine the efficacy and safety of varenicline for smoking cessation in adolescents. The guiding design philosophy was to model the adult smoking cessation literature (allowing for

indirect comparisons of efficacy in different populations) while fine-tuning some elements specifically geared for adolescents. After assessment and inclusion into the study, participants will be randomized to receive a 12-week double blind course of varenicline or placebo. All participants will concurrently participate in a contingency management (CM) intervention, specifically designed to reinforce participant retention. Participants will provide smoking self-report (cigarettes per day) throughout the study. Biological confirmation with carbon monoxide breathalyzer will occur at all visits, and urine cotinine measurement will occur at key time points (baseline, end of treatment and final post-treatment follow-up). Psychiatric/medical visits will occur weekly throughout active treatment to systematically monitor safety and tolerability. After the 12-week treatment course, participants will return for 3 post-treatment follow-up visits (Week 13, Week 18, and Week 26) (see **Figure 1**). This approach closely parallels those of the adult varenicline phase III clinical trials (23,24).

Figure 1. Overview of study design.



C3b. Participants and Feasibility of Recruitment and Retention

Recruitment Strategies

Adolescents (*n*=166) will be recruited from the community, schools, and clinical settings. We have an aggressive plan for recruitment and are confident that our previously established strategies will ensure success. Assuming an initial 3-month period for study setup, per-participant study duration of 6 months, and a concluding 3-month period for data analysis and publication, we anticipate a recruitment window of 48 months. To meet the recruitment goal, we must recruit ***3.5 participants per month****, which is feasible and realistic*.

Our confidence in successful recruitment stems from a complement of strategies developed over years of experience. At the outset of our prior controlled medication (bupropion SR) and behavioral treatment trial in adolescent smokers (15), we only consented 2.7 and enrolled 2.1 participants per month using traditional methods, such as newspaper advertisements and flyers. Recognizing the need for more aggressive recruitment, we developed an innovative arrangement with the Charleston County School District. With the approval and support of the district and schools, we established smoking cessation research clinics in area high schools, yielding **4.5 consented and 3.5 enrolled participants per month** for the remainder of the trial.

In our recent varenicline/bupropion XL pilot trial (27), we did not have sufficient travel/recruitment funds to utilize the school clinics. To bolster recruitment within budget, we utilized internet-based recruitment strategies, such as advertisements on Facebook and postings on Craigslist, yielding **3.5 enrolled participants per month**. In this pilot trial and in the prior bupropion SR trial, we recruited at this rate even in light of FDA "black box" warnings on all of these medications, reflecting our team's ability to recruit adolescents into smoking cessation pharmacotherapy trials at the targeted goal rate even under the tightest regulatory constraints.

In our adolescent cannabis cessation pharmacotherapy study (R01DA026777), we combined the above strategies, and additionally recruited from area pediatric/primary care clinics and nearby College of Charleston. We **enrolled 7.5 participants per month**, demonstrating impressive recruitment success achieved by combining a number of innovative, aggressive strategies.

For the proposed study, we plan to continue our established combined approach, utilizing high school-based clinics (see attached support letters from the principals of the two largest high schools in Charleston County, with combined enrollment >5,000 students), internet/media advertisements, pediatric/primary care clinic referrals, and College of Charleston postings. In the event that we encounter unforeseen recruitment difficulty, we will broaden our school-based clinic program to additional high schools. We can additionally utilize strategies that have been successful for other MUSC studies, including (a) advertising on billboards along area highways, (b) establishing research clinics in existing suburban/rural MUSC clinics, (c) conducting oral presentations at local schools and community groups around the Charleston area, and (d) establishing additional sites within the South Carolina node of the NIDA Clinical Trials Network.

Respondent-Driven Sampling (RDS) will be used to enhance recruitment of the sample. The RDS sampling methodology is based on recruiting the eligible friends and acquaintances of each participant so that the sample "snowballs". Each eligible participant who is randomized into the study, and agrees to take part in this recruitment assistance, will be given coupons to pass on to other potential participants. The coupons will have a unique code linked to the person who passes them out. A referral will be instructed to call the study team for screening. If that person successfully completes a screening assessment, the participant who referred them can redeem the coupon for $10. If the referral is eligible and returns for the Day 0 study visit (randomization), the participant referring them will earn an addition $10 coupon. Additionally, a correspondence that reminds consented participants of the RDS option will be sent. The brief contact will reinforce that their participation in the process is voluntary and does not impact their study participation in this or any future study activity. It is our intent that the communication can be sent either by email or mail based on the information given by the consented participant at screening. Reminders will be sent to a given participant no more frequently than once per year to lessen any burden/demand to the participant. Participants are encouraged to contact the study team if they have any questions or concerns about the RDS process or the received mailer in general.

Following the RDS model, the study will incorporate a Community Recruitment Vendor (CRV) campaign to assist in reaching out to the targeted study population. By identifying persons/businesses in the local area we will establish an agreement whereby for a monthly retainer, the CRV will promote the study using IRB approved recruitment materials within their unique network. The CRV will also be able to receive a bonus if a prospective participant identifies the CRV as their referral source and is successfully enrolled into the study protocol.

Additionally, within the local school environments we will incorporate the use of a recruitment raffle to generate interest at our lunchroom recruitment table. Students will be asked to complete a submission slip that provides for their first name, telephone number, smoking status, and their willingness to be contacted to learn more about a research opportunity. In return for completing the slip, students will be given a raffle ticket. The $50 gift card raffle prize will be available to all students in the school regardless of their smoking history or interest in study participation. Students will only be able to submit once per raffle and raffles will occur at the school once submission slip entries slow and it appears that all students wanting to participate have had an opportunity to do so. Study personnel will maintain the raffle needs and have a third party/school administrator perform the raffle selection to remove possible suspicion of bias.

We have also pursued the use of a direct mailing. Through the approval and cooperation of the CCSD, meeting the standards of FERPA and the use of directory information, a postcard/flier will be sent to the homes of all students within the protocol's targeted age range.

Retention Strategies

Retention, like recruitment, is a considerable challenge in adolescent smoking cessation medication studies. Among the few large-scale randomized trials, only 30-60% of enrolled participants completed the full course of treatment (15-19). Given intent-to-treat analysis (including all randomized participants and assuming that participants were smoking at each missed visit), poor retention may result in an underestimate of treatment effects. It also limits participant exposure to treatment, which further attenuates treatment effects.

Emerging literature supports the potential to address this issue by implementing a contingency management (CM) strategy specifically targeting treatment adherence and retention. CM is an established behavioral intervention, based on instrumental conditioning principles, in which target behaviors are contingently reinforced. CM has been widely adopted in smoking cessation research, but is typically only used to reinforce smoking abstinence (i.e., reinforcement is contingent upon biological verification of abstinence) (49), an approach we have used in the past with adolescent smokers (15). Recent reports indicate that attendance-based CM may also be successfully used to target treatment adherence and retention (39). While some early findings were mixed (50), it has subsequently become clear that <u>higher magnitude reinforcement is associated with significantly improved retention</u> (38-40). Additionally, cash rewards, relative to gift cards or other tokens, are associated with improved session attendance (51). Adult and adolescent studies reveal that contingent rewards are generally not used to purchase cigarettes or other substances of abuse (51,52). We implemented a retention-targeted CM strategy (visit-by-visit escalating magnitude cash reward for session attendance, with reset to base reward after a missed session, based on methods utilized by Carroll and colleagues [38]) in our adolescent cannabis cessation pharmacotherapy study (R01DA026777) with great success. Of participants engaging in the CM program (i.e., all participants presenting for ANY visits after medication initiation), 84% completed the entire 8-week course of treatment. Even accounting for all dropouts at all time points (including initial enrollees that did not return after assessment or medication initiation), *we enrolled **4.5 treatment completers** per month*. While

the current proposal's intent-to-treat approach will include all randomized participants, it is important to note that *we can feasibly recruit at a **completion rate** that exceeds our goal **enrollment rate***.

Based on the above literature support and history of success, we will provide compensation contingent upon completing each visit in the proposed study, at a rate appropriate to the relative participant burden to travel to and complete the visit (**Table 3**). Of note, we have specifically chosen not to implement abstinence-targeted CM, as such an approach may compromise our ability to detect medication versus placebo efficacy differences. Participants will be eligible for $40 compensation for completing the Assessment visit and Weeks 0, 4, and 8 visits; $30 compensation for completing the Weeks 1, 2, 3, 5, 6, 7, 9, 10, 11, 13, and 18 visits; and $50 compensation for completing the Weeks 12 and 26 visits.

Table 3. Retention-targeted contingency management (CM) compensation schedule

Visit	Assessment	Wk 0	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Wk 18	Wk 26
Compensation ($)	$40	$40	$30	$30	$30	$40	$30	$30	$30	$40	$30	$30	$30	$50	$30	$30	$50
Maximum Possible Grand Total $590																	

Inclusion/Exclusion Criteria

Inclusion Criteria

1. Age 14-21
2. Daily smoker for ≥6 months
3. Desire to quit smoking, with at least one prior failed quit attempt and willingness to participate in a treatment study
4. If under age 18, parent(s) or guardian(s) able to participate in informed consent and initial assessment (unless the participant provides evidence of emancipated status)
5. If female, agreement to use birth control (any form of hormonal contraception such as Depo-Provera, daily oral contraception, transdermal patch, or Nuva-ring; intrauterine device; sterilization; or double barrier contraception, which is a combination of any two of the following methods: condoms, spermicide, diaphragm) to avoid pregnancy

Exclusion Criteria

1. Lifetime history of any DSM-IV-TR mood or psychotic disorder (e.g., major depressive disorder, bipolar disorder, schizophrenia)
2. Lifetime history of suicidality, homicidality, or clinically significant hostility/aggression
3. Current substance dependence, other than nicotine
4. Current unstable major medical disorder
5. Current pregnancy or breastfeeding
6. Current use of medications with smoking cessation efficacy
7. Known hypersensitivity to varenicline

Age Range

The participant age range (14-21) for the proposed study was chosen for multiple reasons. Broad agreement exists to support this range. The Maternal Child Health Bureau defines adolescence as age 11-21, and the Center for Disease Control and Prevention defines it as ages 10-24. NIH defines individuals up to age 21 as children. Given considerable developmental variability from age 10-24, though, a sample inclusive of this range might be overly heterogeneous. Additionally, while many adolescents initiate smoking between ages 10-13, very few smoke at the rate necessary for study inclusion (only 3% of 8th graders smoke daily, and many of those smoke <5 cigarettes per day) (7). Given the potential identification of individuals 22-24 as adults, we opted to exclude this age range as well. We acknowledge that the previous "adult" varenicline clinical trials included participants as young as age 18, but given the studies' mean age of 43 ± SD 11, exceedingly few were age 21 or younger, and there have been no published reports on safety, tolerability, and efficacy within these younger participants. As such, varenicline remains almost completely unstudied among adolescents, even by the broadest age definition.

We do recognize that the developmental context varies considerably even within the narrowed 8-year range of 14-21. To address this, we plan to stratify randomization by age, ensuring that equivalent proportions of those

age 14-17 ("younger adolescents") and those age 18-21 ("older adolescents") are represented in varenicline and placebo treatment groups. Given our prior success in recruiting younger adolescents with high school-based clinics and other strategies, we anticipate recruiting similar proportions of younger versus older adolescents, and will adjust strategies if the proportions become skewed. This stratified approach will convey the added opportunity to compare outcomes (in exploratory fashion) between younger and older adolescents.

C3c. Intake and Randomization

All participants (and parents/guardians, as appropriate) will receive a brief telephone screening to determine potential study eligibility. They will then be scheduled for an initial assessment session, consisting of a variety of self-report forms, semi-structured interviews (including comprehensive psychiatric evaluation), and laboratory tests, to determine study eligibility. Parents/guardians of participants under 18 years old will participate with the adolescent in the screening, evaluation, and informed consent/assent procedure. Participants 18 years and older will be able to provide their own informed consent. The informed consent process will include a thorough discussion of potential risks associated with participation, including potential adverse effects of study medication. The FDA "black box" warning for varenicline will be reviewed in detail, and the investigational nature of this medication in adolescents will be emphasized. The complex issues of informed consent and assent, and related limitations of confidentiality, as they apply to adolescents and their parents/guardians, are understood by the PI and will be communicated clearly during the telephone screening and assessment visit. In the case of adolescents in South Carolina Department of Social Services custody, state guidelines regarding consent for clinical research participation will be followed.

If volunteers complete the informed consent/assent process and are eligible for participation, they will be randomized to double blind varenicline or placebo and will proceed with treatment. In order to avoid accidental bias, we will utilize a stratified urn randomization procedure. We will stratify by the prognostic covariates age (14-17 versus 18-21) and baseline smoking level (<12 versus 12 or more cigarettes per day, based on median baseline smoking in our prior randomized adolescent smoking cessation trial). The age stratification will ensure that both younger and older adolescents will be equally represented in the varenicline and placebo groups. The smoking level stratification will help avoid significantly discrepant baseline smoking between treatment groups. We considered additional stratification variables (e.g., gender, severity of nicotine dependence, presence of other smokers in household, history of attention-deficit/hyperactivity disorder), but, amid concern over excessive division of participants among multiple cells, judged that these could be adequately explored as covariates during efficacy analyses (see Section C3f).

C3d. Treatment

Pharmacological Intervention

The MUSC Investigational Drug Service (IDS) will obtain varenicline 0.5 mg and 1 mg tablets and matched placebo tablets. All tablets will be packaged in blister packs, with individual labels for time/date of each dose (e.g., Tuesday morning October 5th). This date- and time-labeled blister pack method has demonstrated superior participant adherence, compared to traditional packaging, and offers the additional advantage of tracking the exact timing of any missed doses (53-55). The IDS successfully used identical methods for medication/placebo dispensing in our adolescent varenicline pilot study.

If assessment procedures reveal that a participant meets inclusion criteria, the IDS will randomize the participant to varenicline or placebo in double-blind fashion. He/she will be given a 7-day supply of medication to take home. Participants will be given an additional 7-day supply "replacement pack" of medication for use in the event that they cannot make it back for a visit within the 7-day window between visits.

In keeping with recommendations from an adolescent varenicline pharmacokinetic study (26), participants >55 kg will take varenicline/placebo 0.5 mg once daily for 3 days, titrated to 0.5 mg twice daily for 4 days, titrated to 1 mg twice daily thereafter. Participants ≤55 kg will take varenicline/placebo 0.5 mg once daily for 7 days, titrated to 0.5 mg twice daily thereafter. In our previous experience with varenicline within adolescents, most participants (80%) weighed enough to receive the 2 mg per day dosage.

During weekly visits, study personnel will review medication logs, inspect blister packs, and perform pill counts to monitor medication adherence. Participant compensation at medication visits will be, in part, contingent upon bringing in blister packs and completing medication logs. The study medical clinician (physician or physician assistant) will systematically assess medication tolerability and effects, including neuropsychiatric effects (see Section C3e below). Medication supply will be refreshed for ongoing use over the following week. Participants will be encouraged to contact the study medical clinician between visits to address any immediate concerns regarding adverse effects. The study medical clinician will be available "on call" at all times for

evaluation and management of adverse events. If a participant experiences intolerable medication-related adverse effects at any point during the study, a dose reduction may be undertaken. If a participant is unable to tolerate the reduced dose, medication will be discontinued, and the participant will be encouraged to remain in the study for monitoring and non-medication study procedures.

Psychosocial Intervention

During the assessment visit, participants will be given adolescent-targeted smoking cessation brochures and briefly counseled on cessation strategies. Participants will be instructed to set a quit date that will occur one week after medication initiation. At weekly visits, participants will be provided with brief (<10 minute) individual skills-based cessation counseling (i.e., enhancing motivation, enlisting social support, recognizing smoking triggers, managing craving/withdrawal/stress), paralleling psychosocial interventions in similarly structured adolescent (17) and adult (23-25) cessation pharmacotherapy studies. We considered implementing a more intensive/formal counseling approach, but opted against it for multiple reasons: 1) the main test is a pure comparison of varenicline versus placebo, 2) the absence of intensive behavioral treatment is consistent with "real world" clinical practice (physician provision of pharmacotherapy without intensive/formal counseling), and 3) utilizing psychosocial methods that closely parallel prior research improves our ability to compare outcomes with the existing adolescent (17) and adult (23-25) cessation literature.

C3e. Instruments/Measures/Materials

Baseline Screening, Diagnostic, and Motivation/Self-Efficacy/Psychosocial Assessments

1. **Demographic** and **Smoking History Questionnaire**: Basic demographics, including age, gender, race, social history, and a detailed smoking history will be collected.
2. **Locator Form:** Contact information including address, phone, email, etc. will be collected. Contact information will be reviewed and updated as necessary throughout the study. The research team will have a Facebook page. Privacy settings will be such that only the research team will be able to see the list of "friends" associated with the account, no one can post on the "wall", and the research team will not post on the walls of any "friends" associated with the account. The research team will use private messages to contact participants through Facebook.
3. **History and Physical Examination**: This will be used to assess for any significant medical conditions that would preclude study participation. The physical examination will include all major systems that may be examined non-intrusively (i.e., excluding breast and genitourinary examination).
4. **Mini International Neuropsychiatric Interview** (**MINI**) (56, 57): The MINI is a structured interview designed to ascertain a current, past, or lifetime history of the major Axis I psychiatric disorders in DSM-IV and ICD-10. Based on the original MINI, an expanded version (MINI Plus) and a pediatric version (MINI Kid) have been developed and validated. The appropriate instrument (MINI Plus for participants ≥18 years and MINI Kid for participants <18 years) will be administered by trained staff and used to evaluate for potentially exclusionary co-morbid psychiatric and substance use disorders.
5. **Structured Clinical Interview for DSM-IV (SCID-I/P)** (89)**:** The SCID-P is a structured diagnostic interview that assesses each of the criteria for DSM-IV diagnoses. The substance use disorder modules from the SCID are used as an alternative for these modules in the MINI. The SCID has proven to have excellent inter-rater and test-retest reliability.
6. **Adolescent Smoking Consequences Questionnaire** (**ASCQ**) (59): The ASCQ is a validated 30-item instrument used to assess outcome expectancies of cigarette smoking among adolescents.
7. **Adolescent Reasons for Quitting Smoking** (**ARQS**) (60): The ARQS is a validated measure of adolescent motives for smoking cessation.
8. **Modified Fagerström Tolerance Questionnaire** (**mFTQ**) (61): The mFTQ is a modified version of the Fagerström Test for Nicotine Dependence self-rating questionnaire for nicotine dependence developed specifically for adolescents. It will be used to determine nicotine dependence status.
9. **Autonomy Over Tobacco Scale** (**AUTOS**) (62): The AUTOS is an adolescent-validated questionnaire that assesses severity of nicotine dependence via determination of loss of autonomy over tobacco use.
10. **Readiness to Quit** and **Confidence in Ability to Quit**: These will be assessed on 10-point scales.
11. **Satisfaction With Life Scale** (**SWLS**) (63): This 5-item instrument measures global cognitive judgments of satisfaction with one's life.
12. **Generalized Self-Efficacy Scale** (**GSES**) (64): This 10-item self-report measure will be used to assess participant general self-efficacy.

13. **Smoking Abstinence Self-Efficacy** (65): We will use Velicer's 9-item scale of the ability to resist temptations to smoke in various contexts. We will additionally use a single item (0-10 visual analog scale) measure of smoking abstinence self-efficacy (66).
14. **Multidimensional Scale of Perceived Social Support** (**MSPSS**) (67, 68): The MSPSS is an adolescent-validated 12-item instrument that assesses perceived support from family, friends, and a significant other.
15. **Barratt Impulsiveness Scale** (**BIS-11**) (69): The BIS-11 is an adolescent-validated 30-item self-report questionnaire of impulsive personality traits.
16. **Toronto Alexithymia Scale (TAS-20)** (87): The TAS is a scale which measures alexithymia, a condition in which people have trouble identifying and describing feelings. Items are rated using a 5-point Likert scale whereby 1 = strongly disagree and 5 = strongly agree. Both the original, 1985 version and the revised, 1992 version will be administered at the assessment visit.
17. **Wisconsin Predicting Patient's Relapse (WI-PREPARE)** (88): The WI-PREPARE is a 7-item scale that predicts relapse to smoking through assessment of nicotine physical dependence, environmental factors, and individual difference characteristics.
18. **Technology Acceptability Questionnaire:** This 54-item, locally developed questionnaire will be administered to participants once during the course of the study to gain information on their technology use and acceptability.

Psychiatric Symptom Assessments (to be administered at all visits)

1. **Psychiatric Interview**: The study medical clinician (directly supervised by the PI, a board certified child & adolescent psychiatrist) will conduct an interview inquiring about symptoms of depression, mania/hypomania, pathological anxiety, psychosis, substance abuse, sleep disturbance, and suicidality since the last visit. The screening items from the MINI (56,57) will be modified for use as a prompt to evaluate all major components of psychiatric symptomatology.
2. **ADHD Rating Scale-IV** (**ADHD-RS**) (70): This validated measure will assess ADHD symptom severity.
3. **Hospital Anxiety and Depression Scale (HADS**) (71-73): This self-report instrument, validated in adolescents and adults, will be used to monitor anxiety and depression symptoms.
4. **Columbia-Suicide Severity Rating Scale** (**C-SSRS**) (42): The C-SSRS is a brief, low-burden suicide assessment scale administered by a clinician, which provides a validated measure of variables such as impulsivity, poor frustration tolerance, sadness, and hopelessness. We have successfully used this instrument, regarded as the gold standard suicidality assessment instrument in pediatric and adult clinical trials, in our prior adolescent varenicline pilot study and in our ongoing adult varenicline trial.

Cigarette and Other Substance Use Assessments

1. **Timeline Follow-Back** (**TLFB**) (74): The TLFB is a calendar-based instrument that measures daily amounts of drug consumption for a specified period of time by patient self-report. Study personnel will administer this instrument. A 30-day calendar will be used at baseline for cigarettes and other substances to gather information related to amount of use for each day. TLFB will again be utilized at the post-treatment follow-up visits to assess cigarette smoking and other substance use. We have successfully used TLFB in our prior adolescent smoking studies.
2. **Cigarette and Other Substance Use Diary**: Participants will maintain a daily diary of cigarette and other substance use during active medication treatment and will return the diary for review at each weekly visit. We have successfully utilized this method in our prior adolescent smoking studies.
3. **Cotinine**: Nicotine is metabolized to cotinine by the liver. Cotinine has a longer half-life than nicotine, and thus serves as a more reliable biomarker of cigarette smoking (75). Urine samples will be collected and delivered to the MUSC Clinical Neurobiology Lab for determination of cotinine level at three key time points: baseline, end of treatment (week 12) and final 6-month follow-up (week 26). Expert consensus guidelines support urine cotinine testing to biologically confirm 7-day abstinence, with a recommended "cutoff" of 50 ng/mL (37). Cotinine may also be measured through saliva samples provided by participants at these three time points.
4. **Carbon Monoxide Breathalyzer** (*Bedfont*): This method, less intrusive and costly than urine cotinine measurement, will be used during all study visits to detect residual levels of carbon monoxide from recent cigarette use. Per expert consensus guidelines, a "cutoff" of 8 parts per million will be used as a biological abstinence confirmation measure (37).
5. **Urine Drug Screen** (**UDS**) (iScreen, US Screening Source): The UDS will be used to assess for recent non-nicotine substance use, including marijuana, cocaine, opioids, and amphetamines.

6. **Penn Alcohol Craving Scale (PACS)** (86) consists of five items that assess the frequency, intensity, and duration of alcohol craving. Individuals rate their responses on a scale of 0–6, with a range of possible scores falling between 0–30. The PACS will be administered at all study visits.

Medication Monitoring and Safety/Tolerability Assessments

1. **Medication Log**: Participants will be asked to maintain a log to report adherence with medication. This log will be reviewed at each medication-monitoring visit.
2. **Concurrent Medications Form**: The use of other medications will be monitored and documented at each clinic visit for safety purposes.
3. **Vital Signs**: Blood pressure, pulse, height, and weight will be monitored to assess medical stability and monitor for any changes during study participation.
4. **Urine Pregnancy Test**: This will be monitored among female participants. All pregnancy testing will be done prior to conducting the urine drug screens. If a participant tests positive for pregnancy at the initial assessment, the participant will be ineligible to participate in the study and no further study procedures will be conducted. At subsequent study visits, urine pregnancy testing will be done prior to urine drug testing. If a pregnancy test is positive, study medication will be discontinued immediately and no further urine drug testing will be performed. We will encourage any participant testing positive for pregnancy to continue participating in all non-medication and non-drug testing components of the study, and will, with participant consent, follow the participant through the course and outcome of pregnancy.
5. **Adverse Events**: During psychiatric and medical evaluation at each visit, adverse events will be documented and rated as mild, moderate, or severe. The study medical clinician will additionally assess relatedness of adverse events to study interventions (i.e., not at all, unlikely, uncertain, possible, probable, definite). The Data and Safety Monitoring Board (See Human Subjects Section 4) will evaluate adverse event information (e.g., frequency, severity, number leading to discontinuation) by treatment group during closed sessions of yearly meetings. Established procedures will be used in the event of a serious adverse event (SAE; see Human Subjects Section 4.6).
6. **Review of Systems**: A detailed, structured psychiatric and medical review of systems (41) will be conducted during weekly medication monitoring visits to augment open-ended adverse event questioning. We have utilized this method with success in prior adolescent smoking cessation pharmacotherapy studies. This exhaustive, systematic method reduces the likelihood of underreported adverse events.
7. **Penetration of Blind Assessment:** <u>At key time-points during the study, participants</u> will be asked by a study clinician if they think they are receiving active study medication or placebo. The study clinician will also document whether they think the participant is receiving active medication or placebo.

Self-Report Craving, Withdrawal, and Satisfaction Forms

1. **Questionnaire on Smoking Urges—Brief** (**QSU-B**) (76): Participants will complete this brief form detailing symptoms of nicotine craving. Participants will additionally complete ratings of current level of craving and maximum & average levels of craving over the last week. Similar measures of current, maximum, and average ratings of ability to resist temptation to smoke will be collected.
2. **Minnesota Nicotine Withdrawal Scale** (**MNWS**) (77): The MNWS, a DSM IV-based instrument that assesses symptoms of nicotine withdrawal, will be used to track participants' nicotine withdrawal symptoms.
3. **Modified Cigarette Evaluation Questionnaire** (**mCEQ**) (78,79): The 12-item mCEQ assesses the reinforcing effects of smoking and contains 5 subscales (smoking satisfaction, psychological reward, enjoyment of respiratory tract sensations, craving relief, aversion).
4. **Craving and Temptation to Smoke:** These will be assessed on 10-point scales at every visit.

<u>C3f. Statistical Methods</u>

Outcome Measures

The primary efficacy outcome is cotinine-verified 7-day point prevalence abstinence at the end of treatment (Week 12). The primary safety outcome is frequency of treatment-emergent adverse events.

Sample Size and Power

The proposed study is powered on the primary efficacy hypothesis that varenicline will increase abstinence (cotinine verified 7-day point prevalence abstinence), relative to placebo, at the end of treatment (Week 12). While 30-day point prevalence abstinence or continuous abstinence outcomes are ideal, we do not believe an adequately powered study for either approach is feasible within the proposed funding period. There is considerable precedent for using 7-day point prevalence as primary outcome in adolescent smoking cessation

pharmacotherapy trials (see **Table 1**). We have recently published a conversion method to estimate continuous abstinence from point prevalence outcomes with a fair degree of confidence (80), and we will track other abstinence outcomes as secondary measures.

The first step towards a sample size analysis is estimating cotinine-confirmed 7-day point prevalence abstinence at end of placebo treatment. We estimate this to be 6.25%, based on the placebo-only end of treatment group abstinence rate in our prior bupropion SR/contingency management smoking cessation study, which was conducted in a nearly identical population to that of the proposed study (15). This estimate is consistent with placebo group end of treatment outcomes in other adolescent smoking cessation trials (e.g., 5% in Moolchan et al., 2005; 5.6% in Muramoto et al., 2007) (17,19). The slightly higher rate in our trial will result in a conservative estimate of the expected effect size (active – placebo), thereby increasing sample size and ensuring sufficient power for hypothesis testing.

The second step towards a sample size analysis is to estimate the effect of varenicline within adolescent smokers. The only existing adolescent varenicline abstinence data come from our recent pilot trial, in which 26.7% of participants achieved cotinine-confirmed 7-day point prevalence abstinence (27). This results in an anticipated effect size (odds ratio) of 5.5. We recognize that this estimate is based on a small sample size (n=15 in the pilot trial varenicline group). However, we do not believe the absolute end of treatment 7-day point prevalence abstinence rates from adult varenicline studies (ranging from 50 to 60%) would be appropriate for sample size estimation in this case, as absolute adolescent abstinence rates (see **Table 1**) are consistently lower than those in adult studies (23,24,81). We do, however, believe that varenicline effect sizes may be comparable across adult and adolescent trials. By this measure, our estimates converge. For example, end of treatment abstinence odds ratios in adults were as follows: 3.8 (23), 4.1 (24), and 9.1 (82).

Thus, the sample size estimation is based on anticipated abstinence rates of 6.25% (placebo) and 26.7% (varenicline), for an odds ratio of 5.5. With a type 1 error rate of 5% ($\alpha = 0.05$) and power ($1- \beta$) of 80%, this would require 51 participants per group using a two-sided Pearson's Chi Square test statistic. However, we still wish to aim even more conservatively, recognizing that (a) this effect size may be an overestimate since the varenicline abstinence rate came from a small sample pilot study, and (b) we must account for attrition for the intent-to-treat analysis. In light of the range of odds ratios in prior adult varenicline studies, we have conservatively targeted detection of an odds ratio of 4.0 for power analysis. Original plans were that we will enroll and randomize **83 participants per group**, for a **total sample size of 166**. This will allow us to detect an odds ratio of 4.0 over the anticipated placebo rate of 6.25%, which would correspond to a varenicline abstinence rate of 21.1%. Due to the higher than expected retention losses within our target population of adolescents and following the current ratio of successfully consented to randomized participants, we estimate that 240 participants will need to be enrolled (consented) to meet our sample size needs.

Efficacy: Primary Analysis

Categorical clinical and demographic variables will be assessed by chi-square tests of independence, while continuous variables will be assessed using Student's *t*-test. The effect of varenicline versus placebo on abstinence at end of treatment will be examined using logistic regression. Models will be computed both unadjusted and adjusted for significant covariates found in the descriptive analysis. For these efficacy analyses, 7-day point prevalence abstinence will be defined as having no cigarettes (or other tobacco/nicotine products) for 7 days, confirmed by urine cotinine level ≤50 ng/mL. All randomized participants will be included in the analyses (intent-to-treat approach), and participants will be considered non-abstinent at any missed visit.

Safety: Primary Analysis

Similar to adult varenicline phase III studies (23,24), we define any treatment-emergent adverse event any adverse event occurring between treatment initiation and one week following treatment conclusion. Non-inferiority analysis will be utilized to compare adverse event rates between varenicline and placebo groups (84). With a type 1 error rate of 5% ($\alpha = 0.05$) and power ($1- \beta$) of 80%, the proposed total sample size of 166 and an estimated placebo rate of treatment-emergent adverse events of 75% (23) will afford a non-inferiority margin (NIM) of 16.7% for the varenicline adverse event rate. We considered incorporating a larger sample size that would afford a smaller NIM. However, even to detect a 12.5% NIM, a total sample size of 376 participants would be necessary. That sample size would not be feasible within the proposed funding period.

Smoking-Related Outcomes: Secondary Analysis

Secondary outcomes include the following: a) 7-day biologically confirmed point prevalence abstinence at 6 months, b) continuous abstinence, c) time to lapse (first puff), d) time to relapse (first of 3 consecutive days

smoking ≥ 1 cigarette), and e) longitudinal efficacy of varenicline. These will be tested via logistic regression to examine a) point prevalence at 6 months and b) continuous abstinence from targeted quit date (Week 1) to both treatment conclusion (Week 12) and final follow-up visit (Week 26), Cox Proportional hazard models (83) to examine c) time to first lapse (first puff, first cigarette), d) time to relapse (first of 3 consecutive days smoking ≥1 cigarette), and e) Generalized Estimating Equation (repeated measures) to examine the entire study time course. Repeated measures analysis of variance will be used to assess treatment effects of varenicline on craving (QSU-B), withdrawal (MNWS), and smoking reinforcement (mCEQ) throughout the study. All efficacy analyses (primary and secondary) will be repeated among participants with ≥80% medication adherence, per protocol analysis, and completers analysis. Medication adherence (pill counts), nicotine dependence (mFTQ, AUTOS), motivation/readiness to quit (baseline rating), self-efficacy (GSES), perceived social support (MSPSS), and impulsivity (BIS-11) will be explored as possible moderators influencing the effect of varenicline on abstinence.

Safety: Secondary Analysis

Of particular interest will be adverse events leading to medication discontinuation and the occurrence of treatment-related serious adverse events (SAEs) (see Human Subjects Section 4.6). We will specifically compare neuropsychiatric adverse events (Psychiatric Interview) using non-inferiority testing, as well as depression/anxiety (HADS) and suicidality (C-SSRS) ratings using one-sided 2-sample t-tests. Based on adult literature (34,35), we anticipate no serious adverse events, and appropriate stopping plans are in place (see section C3g) for added precaution.

Participant Retention Analysis

Total number of treatment visits attended will be compared using a Student's *t*-test, while the number of days retained will be assessed using Cox Proportional Hazards regression models.

C3g. Clinical Management Issues

Study Termination

Study termination may be initiated by a study participant (or parent/guardian, as applicable) for personal reasons, or by the PI or members of the Data Safety and Monitoring Board for reasons of participant safety or the additional requirement for more intensive or a different form of therapy for addiction, medical, or psychiatric disorders. Another cause for termination would be any participant behavior that is felt to present a threat or harm to staff, including sexual or verbal harassment. Other terminations may be due to a participant becoming lost to follow up and/or moving from the geographic area. Frequency counts for reasons for termination will be analyzed for both treatment groups using chi square analytic procedures. If a participant is terminated for any reason, attempts will be made to continue collecting adverse event and smoking data over the 12-week treatment trial and follow-up period so that data can be entered for the intent-to-treat analysis.

Clinical Deterioration "Rescue Plan"

A clinical deterioration "rescue" plan will be in place for participants that experience psychiatric or substance use deterioration during the study. Symptoms will be monitored closely throughout the trial to assess for deterioration. Any participant demonstrating gross clinical deterioration will be discontinued from the trial and appropriate intervention will be arranged. The rescue measures will include withdrawal from the study, immediate assessment by the PI or physician Co-I for a comprehensive psychiatric and substance abuse evaluation and determination of appropriate intervention, as well as emergency therapy sessions if the participant does not meet criteria for withdrawal from the study. In the case that the participant is aged 14-17, the PI will contact the parent/guardian to discuss the clinical deterioration and enlist involvement with proposed intervention. The intervention may include outpatient, day treatment, partial hospitalization, or inpatient treatment in the Medical University of South Carolina Institute of Psychiatry. These programs have highly trained clinicians competent in treating all psychiatric and substance use disorders. The PI holds admitting privileges for all of these clinical programs, allowing for efficient referral and management.

Referral for Participants Needing Continuing Treatment

At the end of the study, if a participant (or parent/guardian, as applicable) requires or requests continuing treatment for nicotine dependence, we will make a treatment referral to an appropriate smoking cessation clinical program or the state Quitline.

C3h. Operational Plan and Research Timetable

Funding for five years is requested. The first three months will be used for hiring and training personnel, submitting regulatory documents, and preparing for study initiation. Fifty-four months will be needed for participant recruitment (48 months) and data collection (additional 6 months for last enrolled participants). The

final three months will be used for data analysis and manuscript preparation. At a targeted recruitment rate of 3.5 participants per month, an adequate sample will be obtained within the time allotted.

C4. Conclusion

Despite the tremendous potential health impact of smoking cessation among adolescents, minimal effort has focused on developing evidence based cessation treatments for this age group. Given varenicline's superior efficacy in adults, and the limited efficacy of other treatments previously investigated in adolescents, a controlled trial of varenicline in adolescents is warranted. The research team, experienced with adolescent smoking cessation clinical trials in general and varenicline in particular, is ideally suited to conduct this trial. Specific strengths of the trial design include: a) methods that parallel those of adult smoking cessation studies (allowing for indirect adolescent versus adult comparisons), b) comprehensive safety/tolerability assessments (addressing potential medication safety concerns), c) outcome measures informed by expert guidelines (allowing for the most stringent evaluation of efficacy), and d) established methods to address the considerable challenges of recruitment and retention of adolescent smokers in pharmacotherapy trials. We believe that this study has the potential to substantially advance adolescent smoking cessation treatment.

1. Risks to Human Subjects

1.1 Human Subjects Involvement and Characteristics

The PI and Co-Is have all completed the University of Miami computer-based CITI Human Subjects Research Education Course. A total of 240 male and female adolescent smokers, between 14 and 21 years old, will be recruited over 48 months. The sample size was determined based on statistical power analysis (Section C3f). Participants will be recruited from clinical sites, schools, and the general community. Advertisement will be used for study recruiting. The inclusion/exclusion criteria are as follows:

Inclusion Criteria

a) Age 14-21
b) Daily smoker for ≥6 months
c) Desire to quit smoking, with at least one prior failed quit attempt and willingness to participate in a treatment study
d) If under age 18, parent(s) or guardian(s) able to participate in informed consent and initial assessment (unless the participant provides evidence of emancipated status)
e) If female, agreement to use birth control (any form of hormonal contraception such as Depo-Provera, daily oral contraception, transdermal patch, or Nuva-ring; intrauterine device; sterilization; or double barrier contraception, which is a combination of any two of the following methods: condoms, spermicide, diaphragm) to avoid pregnancy

Exclusion Criteria

a) Lifetime history of any DSM-IV-TR mood or psychotic disorder (e.g., major depressive disorder, bipolar disorder, schizophrenia)
b) Lifetime history of suicidality, homicidality, or clinically significant hostility/aggression
c) Current substance dependence, other than nicotine
d) Current unstable major medical disorder
e) Current pregnancy or breastfeeding
f) Current use of medications with smoking cessation efficacy (e.g., bupropion, nicotine replacement, clonidine, nortriptyline)
g) Known hypersensitivity to varenicline

Demographics

The 2007 South Carolina Youth Tobacco Survey reveals that, among South Carolina high school students, 6.6% of males, 4.2% of females, 6.6% of whites, and 3.0% of African Americans are “heavy” smokers (≥6 cigarettes per day) (http://www.scdhec.gov/health/chcdp/tobacco/docs/ytsbook2007.pdf). The rates among other minority groups are not reported. United States Census data from 2009 reveal that the population in South Carolina is 68.9% white (64.9% white, not Hispanic origin), 28.2% African American, and 4.5% Hispanic (http://quickfacts.census.gov/qfd/states/45000.html). Other minority groups collectively comprise only 2.4% of the population. Given these data, we anticipate enrolling a sample that is a) 60% male and 40% female, and b) 82% white, 15% African American, and 3% Hispanic. These numbers are generally consistent with those in our prior large-scale controlled pharmacotherapy trial in adolescent smokers (15).

1.2 Sources of Materials

Research materials obtained from participants include responses to questionnaires, psychiatric and physical examination results, urine tests (cotinine, drug metabolites, and pregnancy), and expired air carbon monoxide breathalyzer tests. Materials will be obtained specifically for research purposes. There will be no use of existing specimens, records, or data. Every effort will be made to maintain participant confidentiality, in accordance with HIPAA.

1.3 Potential Risks

Questionnaires and interviews are all non-invasive and, as such, involve minimal physical risk to participants. Potential risks incurred by participants include:

1. Adverse events related to study medication
2. Loss of confidentiality

1.3.1 Adverse events related to study medication

The varenicline package insert (http://www.pfizer.com/files/products/uspi_chantix.pdf) details adverse events associated with the medication. Specifically, it reports that "the most common adverse reactions (>5% and twice the rate seen in placebo-treated patients) were nausea, abnormal (e.g., vivid, unusual, or strange) dreams, constipation, flatulence, and vomiting."

Meta-analyses of the four main adverse events in varenicline versus placebo groups in adult trials yielded relative risks (RRs) of 3.21 (95% CI 2.71, 3.80) for nausea, 1.50 (95% CI 1.26, 1.79) for insomnia, 2.79 (95% CI 2.09, 3.72) for abnormal dreams, and 1.20 (95% CI 1.00, 1.45) for headache (85). Similarly, adverse events in our adolescent pilot cessation trial included insomnia (4/15 participants) nausea (3/15 participants), and headache (3/15 participants) (27). No other adverse events were reported by more than one participant (including abnormal dreams – 1/15 participants). In a 2-week adolescent varenicline pharmacokinetic study, the most common adverse events were nausea, headache, vomiting, and dizziness (26).

While post-marketing anecdotal reports of psychiatric adverse events (32,33) led to an FDA "black box" warning for varenicline, a meta-analysis of controlled varenicline trials in adults (total *n*=3091 randomized to varenicline) yielded no significant increase, relative to placebo, in any psychiatric adverse events aside from sleep disturbance (see **Table 2** in Section A) (34). Additionally, a "real world" primary care cohort study including 10,973 smokers prescribed varenicline revealed no evidence of increased risk of self-harm, compared with smokers prescribed other cessation pharmacotherapies (35). The 2-week adolescent pharmacokinetic study by Faessel and colleagues (26) revealed 2 participants with sleep disturbances and 1 with a brief, mild episode of anger/irritability (out of 57 participants taking varenicline). Our adolescent pilot data similarly did not reveal psychiatric adverse events with any notable frequency. We are nonetheless, especially in light of regulatory and public caution surrounding varenicline, committed to excluding potentially vulnerable individuals (i.e., those with any lifetime history of mood or psychotic disorders, suicidality, or clinically significant hostility/aggression) and providing detailed, rigorous monitoring and management of potential psychiatric adverse events enrolled participants.

1.3.2 Loss of confidentiality

Any communication of personal information carries the potential risk of breach of confidentiality.

2. Adequacy of Protection Against Risks

2.1 Recruitment and Informed Consent

Recruitment of the participants will be from clinics, schools, and the community. The Medical University of South Carolina (MUSC) Institutional Review Board (IRB) approved Informed Consent (IC) will be obtained prior to the initial assessment. The consent will be explained orally and in the written form, and will be documented by the signature of the participant on the IC. For participants under 18 years old, a parent/legal guardian will provide consent and the participant will provide assent. The consent document will contain a thorough review of potential risks associated with trial participation, including potential medication-related risks (i.e., neuropsychiatric adverse events). Details of varenicline's "black box" warning status will be provided to participants and parents/legal guardians, and will be discussed at length.

For re-consenting purposes for those participants under 18 years of age whose parent/legal guardian is not available to attend a study visit, we would conduct the re-consent process over the phone. We understand the importance of parental/guardian presence in the initial consenting procedures of study participation due to the seriousness of study medication (i.e. black box warnings). The issue that may arise, however, is that it may become intrusive and demanding for them to return for a re-consent need when in most cases the IC revisions are very minor and more editorial and administrative in nature. We would not want their child's study participation to potentially negatively impact the parent/guardian's employment, nor do we want such a need to be a barrier in the child's study participation.

The process that study personnel would follow includes: Discussion with the parent/guardian by trained/approved study personnel would be completed prior to the next scheduled visit where a re-consent is to take place. When possible, study personnel will have forwarded the new ICF (electronically or hard copy) to the parent so he/she they could have the document in front of him/her during the re-consent discussion. Study personnel would clearly document the conversation and

detailing the changes in the ICF. If the parent/legal guardian expresses understanding of the study changes and approves the child's continued participation and the ICF is available to the parent/legal guardian, he/she will sign and date the ICF accordingly, returning it for the minor's assent and study personnel's signature at the subsequent visit. If the parent/legal guardian does not have access to the ICF at the time, then the document will be sent home with the minor after their next completed study visit where the assent and staff's signature was obtained. The parent will sign the form accordingly and it will be returned to the study site at the following study visit. A copy of the fully signed document would be provided to the parent/legal guardian either by hardcopy (postal mail or minor's delivery) or electronically (email or fax) per the parent/legal guardian's preferred method. If the parent/legal guardian does not feel comfortable with the changes, requesting to have additional in person discussion with study personnel, then the minor's next visit would be cancelled/rescheduled for a date when the parent/legal guardian is able to attend the visit. At that time, routine in person consenting procedures would occur.

Absence of Coercion: Participation in the study is voluntary. Participants will be compensated $40 for the initial assessment. The informed consent agreement that will be read to each volunteer (and parent/guardian as applicable) prior to enrollment in the study explains the following:

a) Compensation is supplied at each study visit.
b) Participants may discontinue participation in the study at any point.
c) Withdrawing from the study will not result in any adverse consequences to the participants.

2.2 Protection Against Risk

2.2.1 Adverse events related to study medication

The informed consent process will be used to thoroughly educate participants and parents/guardians about potential medication-related risks (including neuropsychiatric adverse events). This discussion will include thorough review of the FDA "black box" warning for varenicline, and clear communication that varenicline's use in adolescents is investigational. Rigorous screening procedures and strict exclusion criteria are designed to exclude potential participants at elevated risk for adverse events. This includes comprehensive psychiatric assessment and evaluation to exclude individuals with any lifetime history of mood disorder, psychotic disorder, suicidality, homicidality, or clinically significant hostility/aggression. The study medical clinician (physician or physician assistant, directly supervised by the PI, a board certified child & adolescent psychiatrist) will conduct serial psychiatric and medical evaluations weekly throughout treatment, providing comprehensive, detailed adverse event monitoring (see Section C3e). Additionally, vital signs and validated ratings of depression, anxiety, and suicidality symptoms (in light of caution around potential psychiatric adverse events) will be collected and reviewed at each visit. Participants and parents/guardians will have access to the study medical clinician 24 hours, 7 days a week for emergencies. Participants experiencing intolerable adverse events will have the opportunity to reduce dose or discontinue medication altogether, while remaining in the study for ongoing monitoring. The PI has admitting privileges for a full spectrum of psychiatric treatment services, including outpatient, day treatment, partial hospitalization, and inpatient programs, in the event that symptom acuity warrants intensive intervention. Urine pregnancy tests will be conducted weekly throughout treatment for female participants.

2.2.3 Loss of confidentiality

The research team has established procedures in place to minimize the risk of any confidentiality breach. Participant records are stored in locked files within locked offices in areas that are locked during holidays, weekends, and non-working hours. Information contained in computer databases is password protected, maintained by participant number only, and devoid of specific identifiers. No specific or general participant information will be left in public access areas, and no oral communication regarding participants with identifiers will be made in any public areas. Research staff members have been given extensive training in maintaining confidentiality as well as HIPAA regulations.

3. Potential Benefits of the Proposed Research to the Participants and Others / Importance of the Knowledge to be Gained

Despite considerable public health implications, minimal research has focused on developing efficacious adolescent smoking cessation treatments, particularly pharmacotherapies. As the most efficacious cessation

pharmacotherapy in adults, varenicline is a strong candidate for evaluation in adolescents. Results of this study will fill a critical evidence gap, providing key information to guide clinical practice.

Participants in the study, regardless of randomization to varenicline or placebo, will benefit by receiving a) comprehensive medical and psychiatric evaluation, and b) weekly smoking cessation counseling throughout active treatment.

4. Data and Safety Monitoring Plan

This section is based on the recommendations in NIDA's "Guidelines for Developing a Data and Safety Monitoring Plan" (http://www.nida.nih.gov/funding/dsmbsop.html).

4.1 Summary of the Protocol

This application proposes a randomized, placebo-controlled trial (*n* = 166) of varenicline, testing its efficacy and safety for adolescent smoking cessation. Treatment-seeking adolescent smokers will be recruited via schools, clinics, and the community. The primary efficacy outcome of interest is cotinine-confirmed 7-day point prevalence abstinence at the end of treatment in varenicline-randomized participants, relative to those randomized to placebo. The primary safety outcome is frequency of treatment-emergent adverse events in varenicline-randomized participants, relative to those randomized to placebo. Inclusion/exclusion criteria are outlined above. Power and sample size calculations are in Section C3f.

4.2 Trial Management

All aspects of the study will be run through the MUSC Department of Psychiatry and Behavioral Sciences, where the PI holds his faculty appointment. The target population is described in Section C3b, Human Subjects Section 1.1, and the adjoining Targeted/Planned Enrollment Table. The timetable is as follows:

	Year 1 (months)	**Year 2** (months)	**Year 3** (months)	**Year 4** (months)	**Year 5** (months)
Refine all procedures	1-3				
Procure supplies	1-3				
Refine recruitment methods	1-3				
Train Personnel	1-3				
Study Enrollment					
Cumulative *N* to enroll*	(30)	(72)	(114)	(156)	(166)
First Participant Enrolls	4				
First Participant Completes	10				
Last Participant Enrolls					51
Last Participant Completes					57
Data Analysis					58-60
Manuscript Preparation					58-60

All numbers reflect months within total study duration (*with the exception of cumulative *N*)

4.3 Data Management and Analysis

Data will be collected by the appropriate individual (research assistant, PI, Co-I) using standardized paper forms or will be directly entered using iPads. Data will only be identified with the study's ID of the participant. The codes linking the name of the participant to the study ID will be kept confidential in a secured cabinet by the PI. All data will be transferred to and managed in the REDCap system. REDCap provides: 1) an intuitive interface for data entry (with data validation); 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R); 4) procedures for importing data from external sources; and 5) advanced features, such as branching logic and calculated fields. These procedures are effective in minimizing data entry errors (e.g., missing or errant data). The data analysis plan is outlined in Section C3f.

4.4 Quality Assurance

Accuracy and completeness of the data collected will be ensured by weekly review. A 10% random sample of the primary source document will be crosschecked with the database on a quarterly basis. If inaccuracies exceed 4%, then a second 10% will be randomly chosen for audit. The REDCap system does not accept outliers, illogical response patterns, etc. The PI will have weekly meetings with the research assistants to discuss qualitative comments received during data collection and any problems in data collection or entry. The statistician will periodically examine the database to look for irregularities. Initial data analyses will examine distributions of variable scores and comparability of baseline characteristics across conditions in case analyses need to be adjusted for these. Confidentiality protections are outlined above.

4.5 Regulatory Issues

Prior to the start of the study, the protocol will be registered on the clinical trials registry (www.clinicaltrials.gov). All serious adverse events will be reported to the MUSC Institutional Review Board (IRB) within 24 hrs. Follow-up of all serious adverse events will be reported as well. All adverse events are reviewed weekly by the PI and yearly by both the DSMB and the IRB. Any significant actions taken by the local IRB, including significant protocol changes, will be relayed to NIDA. We anticipate the serious adverse event rate to be extremely low. If monitoring indicates otherwise, we will convene a special meeting of the DSMB.

4.6 Trial Safety

The potential risks and benefits and methods to minimize these risks are outlined in Sections 1.3 and 2. Guidelines have been developed for managing and reporting of adverse events (AEs), including serious adverse events (SAE; defined as any untoward medical occurrence that results in death, is life-threatening, requires or prolongs hospitalization, causes persistent or significant disability/incapacity, results in congenital anomalies/birth defects, or in the opinion of the investigators represents other significant hazards or potentially serious harm to research subjects or others). Dr. Gray will serve as the Program Manager for AEs. The Adverse

Event Log will be used to document all AEs in tabular form. If an AE is non-serious (self-limited with no intervention needed), no further action will be necessary. However, in the case of a serious, unresolved event, an AE follow-up log will be completed. The clinician will then call Dr. Gray with initial reports within 24 hours of the start of the SAE. The clinician will record the information on SAE Notification Form. He/she will forward hard copies of the complete report (SAE Notification Form, Concomitant Medication Log, and AE Log) to Dr. Gray, who will, in turn notify the IRB, DSMB, and NIH about the SAE. Additionally, Dr. Gray will communicate summary reports of DSMB discussion of the SAE, or any deliberations of IRB regarding the review of the SAE or the trial itself, to NIH. If the event is "Serious, Unexpected and Associated" (an SAE is considered unexpected if it is not described in the Package Insert), Dr. Gray will complete Food and Drug Administration (FDA) Form 3500A and will forward it to the FDA. Dr. Gray also will inform the IRB and the study participants (and parents/guardians, as appropriate) about the SAE. In all of these reviews and reports, strict patient confidentiality will be maintained.

AEs will be coded on a weekly basis using Medical Dictionary for Regulatory Activities (MedDRA) rules and entered into a database. For each weekly study meeting, the research assistants will prepare a summary of all AEs, listed by frequency of each type of event by various demographic characteristics such as gender, ethnicity, age, as well as by severity and relatedness to the study intervention. The PI will review this at the weekly study meeting (or before if more urgent).

Study procedures will follow as much as possible the FDA's Good Clinical Practice Guidelines (www.fda.gov/oc/gcp). We will encourage participants (and parents/guardians as appropriate) to notify their physicians that a) they are in a research study evaluating varenicline, compared to placebo, for smoking cessation in adolescents, and b) the physician should contact the PI directly if he/she has any questions.

The research assistants will be instructed not to reveal whether a person is a participant in the study and will report to the PI any outside requests for information about a participant or any breaches in confidentiality. All requests by participants' physicians and other medical providers will be referred directly to the PI.

4.7 Trial Efficacy

The Data and Safety Monitoring Board (see 4.9) may request a blinded interim efficacy report (blinded to the PI and research team) for review while the trial is ongoing. Final (fully unblinded) efficacy analysis will occur after all participants have completed all visits.

4.8 DSM Plan Administration

Monitoring for this trial will be provided by the DSMB through NIDA and will review safety data on a quarterly basis. The statistician will examine the outcomes database quarterly for missing data, unexpected distributions or responses, and outliers. The PI will weekly check the adverse event database prepared by the research assistants immediately prior to the lab meeting to a) see if any particular MedDRA categories are being endorsed more frequently than anticipated, and b) determine if any side-effect symptom checklist scores are higher than expected. A DSM report will be filed with the IRB and NIDA on a yearly basis, unless greater than expected problems occur. The report will include participant characteristics, retention and disposition of study participants, quality assurance issues and reports of adverse events, significant/unexpected adverse events and serious adverse events. We will report efficacy at the end of the trial.

4.9 DSM Board

Safety and if requested, efficacy data will be reviewed by a Data and Safety Monitoring Board (DSMB) that will meet approximately once every 3 months. The board will be blinded to participants' actual treatment assignments, but may break the blind if safety concerns arise from the blinded data.

The DSMB will meet quarterly (more frequently as needed for emergent situations) to review any AEs related to the study, as well as review any data management related errors. The board may be called at any point if needed for serious adverse events, etc. Modification will be made in the procedures and/or the protocol if necessary based on the findings of the board.

The investigator and/or study physician is responsible for defining, in his/her best judgment, the relationship of the AE/SAE to the study drug/placebo, and their severity. The investigators in this study have the responsibility of promptly reporting all SAEs to the NIDA DSM, IRB, and FDA. Events will be reported when they are serious, unexpected (i.e. not in the medication insert information), and at least possibly related to the study medication.

Any SAEs due to any cause, that occur during the course of this investigation, whether or not related to the investigational agent, must be reported within 24 hours by telephone or entered into the Serious Adverse Event Tracking and Reporting System (SAETRS) to the Study Medical Monitor and the NIDA Medical Monitor.

The IND sponsor is required to report SAEs to the FDA: 1) in 7 days if the SAE is unexpected (or, if expected, unusually serious or rarely seen), life-threatening or lethal, and at least possibly related to the investigational product, with a follow-up written report in 8 days; 2) in 15 days if the SAE is unexpected (or, if expected, unusually serious or rarely seen), at least possibly related to the investigational product, but not immediately life-threatening; and 3) in an annual report in all other cases.

References

1. Centers for Disease Control and Prevention. “Targeting Tobacco Use: The Nation’s Leading Cause of Preventable Death.” 2007. Available online at: http://www.cdc.gov/nccdphp/publications/aag/pdf/osh.pdf Accessed January 24, 2010.

2. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA: A Cancer Journal for Clinicians. 2010;60:277-300.

3. United States Department of Health and Human Services. NIDA Research Report: Tobacco Addiction. NIH Publication Number 09-4342; 2009.

4. Backinger CL, Fagan P, Matthews E, Grana R. Adolescent and young adult tobacco prevention and cessation: Current status and future directions. Tobacco Control. 2003;12 Suppl 4:IV46-53. PMCID: PMC1766138

5. Substance Abuse and Mental Health Services Administration. Results from the 2007 National Survey on Drug Use and Health: National Findings. NSDUH Series H-34, DHHS Publication No. SMA 08-4343. Rockville, MD: Office of Applied Studies; 2008. Available online at: http://oas.samhsa.gov/NSDUH/2k7NSDUH/2k7results.cfm#Ch4 Accessed September 24, 2010.

6. Chassin L, Presson CC, Sherman SJ, Edwards DA. The natural history of cigarette smoking: Predicting young-adult smoking outcomes from adolescent smoking patterns. Health Psychology. 1990;9:701-716.

7. Johnston LD, O’Malley PM, Bachman JG, Schulenberg JE. “Smoking continues gradual decline among U.S. teens, smokeless tobacco threatens a comeback.” Ann Arbor, MI: University of Michigan News Service; December 14, 2009. Available online at: http://www.monitoringthefuture.org Accessed September 24, 2010.

8. Chassin L, Presson CC, Pitts SC, Sherman SJ. The natural history of cigarette smoking from adolescence to adulthood in a midwestern community sample: Multiple trajectories and their psychosocial correlates. Health Psychology. 2000;19:223-231.

9. Stanton WR, McClelland M, Elwood C, Ferry D, Silva PA. Prevalence, reliability and bias of adolescents’ reports of smoking and quitting. Addiction. 1996;91:1705-1714.

10. Zhu SH, Sun J, Billings SC, Choi WS, Malarcher A. Predictors of smoking cessation in U.S. adolescents. American Journal of Preventive Medicine. 1999;16:202-207.

11. Sussman S, Sun P, Dent CW. A meta-analysis of teen cigarette smoking cessation. Health Psychology. 2006;25:549-557.

12. Jacobsen LK, Krystal JH, Mencl WE, Westerveld M, Frost SJ, Pugh KR. Effects of smoking and smoking abstinence on cognition in adolescent tobacco smokers. Biological Psychiatry 2005;57:56-66.

13. Killen JD, Ammerman S, Rohas N, Varady J, Haydel F, Robinson TN. Do adolescent smokers experience withdrawal effects when deprived of nicotine? Experimental and Clinical Psychopharmacology. 2001;9:176-182.

14. Prokhorov AV, Hudmon KS, de Moor CA, Kelder SH, Conroy JL, Ordway N. Nicotine dependence, withdrawal symptoms, and adolescents’ readiness to quit smoking. Nicotine & Tobacco Research. 2001;3:151-155.

15. Gray KM, Carpenter MJ, Baker NL, Hartwell KJ, Lewis AL, Hiott DW, Deas D, Upadhyaya HP. Bupropion SR and contingency management for adolescent smoking cessation. Journal of Substance Abuse Treatment. 2011;40:77-86. PMCID: PMC2997899

16. Killen JD, Robinson TN, Ammerman S, Hayward C, Rogers J, Stone C, Samuels D, Levin SK, Green S, Schatzberg AF. Randomized clinical trial of the efficacy of bupropion combined with nicotine patch in the treatment of adolescent smokers. Journal of Consulting and Clinical Psychology. 2004;72:729-735.

17. Muramoto ML, Leischow SJ, Sherrill D, Matthews E, Strayer LJ. Randomized, double-blind, placebo-controlled trial of 2 dosages of sustained-release bupropion for adolescent smoking cessation. Archives of Pediatrics and Adolescent Medicine. 2007;161:1068-1074.

18. Hanson K, Allen S, Jensen S, Hatsukami D. Treatment of adolescent smokers with the nicotine patch. Nicotine & Tobacco Research. 2003;5:515-526.

19. Moolchan ET, Robinson ML, Ernst M, Cadet JL, Pickworth WB, Heishman SJ, Schroeder JR. Safety and efficacy of the nicotine patch and gum for the treatment of adolescent tobacco addiction. Pediatrics. 2005;115:e407-414.

20. Rubinstein ML, Benowitz NL, Auerback GM, Moscicki AB. A randomized trial of nicotine nasal spray in adolescent smokers. Pediatrics. 2008;122:e595-e600. PMCID: PMC2744418

21. Aubin HJ, Bobak A, Britton JR, Oncken C, Billing CB Jr, Gong J, Williams KE, Reeves KR. Varenicline versus transdermal nicotine patch for smoking cessation: Results from a randomized open-label trial. Thorax. 2008;63:717-724. PMCID: PMC2569194

22. Eisenberg MJ, Filion KB, Yavin D, Bélisle P, Mottillo S, Joseph L, Gervais A, O'Loughlin J, Paradis G, Rinfret S, Pilote L. Pharmacotherapies for smoking cessation: A meta-analysis of randomized controlled trials. Canadian Medical Association Journal. 2008;179:135-144. PMCID: PMC2443223

23. Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, Watsky EJ, Gong J, Williams KE, Reeves KR. Varenicline, an $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: A randomized controlled trial. Journal of the American Medical Association. 2006;296:47-55.

24. Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, Billing CB, Gong J, Reeves KR. Efficacy of varenicline an $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: A randomized controlled trial. Journal of the American Medical Association. 2006;296:56-63.

25. Nides M, Oncken C, Gonzales D, Rennard S, Watsky EJ, Anziano R, Reeves KR. Smoking cessation with varenicline, a selective alpha4beta2 nicotinic receptor partial agonist: Results from a 7-week, randomized, placebo- and bupropion-controlled trial with 1-year follow-up. Archives of Internal Medicine. 2006;166:1561-1568.

26. Faessel H, Ravva P, Williams K. Pharmacokinetics, safety, and tolerability of varenicline in health adolescent smokers: A multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Clinical Therapeutics. 2009;31:177-189.

27. Gray KM, Carpenter MJ, Lewis AL, Klintworth EM, Upadhyaya HP. Varenicline versus bupropion XL for smoking cessation in older adolescents: A randomized, double-blind pilot trial. Nicotine & Tobacco Research. In press. PMC Journal – In Process.

28. Jamner LD, Whalen CK, Loughlin SE, Mermelstein R, Audrain-McGovern J, Krishnan-Sarin S, Worden JK, Leslie FM. Tobacco use across the formative years: A road map to developmental vulnerabilities. Nicotine & Tobaco Research. 2003;5 Suppl 1:S71-S87.

29. Mermelstein R. Teen smoking cessation. Tobacco Control. 2003;12 Suppl 1:i25-i34.

30. Bazzano ATF, Mangione-Smith R, Schonlau M, Suttorp MJ, Brook RH. Off-label prescribing to children in the United States outpatient setting. Academic Pediatrics. 2009;9:81-88.

31. Gazarian M, Kelly M, McPhee JR, Graudins LV, Ward RL, Campbell TJ. Off-label use of medicines: Consensus recommendations for evaluating appropriateness. Medical Journal of Australia. 2006;185:544-548.

32. ABC News. "Did Quit-Smoking Pill Lead to Man's Death?" September 19, 2007. Available online at: http://abcnews.go.com/GMA/OnCall/story?id=3623085 Accessed September 24, 2010.

33. De Koff D. "This Is My Brain on Chantix." New York Magazine; February 10, 2008. Available online at http://nymag.com/news/features/43892/ Accessed September 24, 2010.

34. Tonstad S, Davies S, Flammer M, Russ C, Hughes J. Psychiatric adverse events in randomized, double-blind, placebo-controlled clinical trials of varenicline: A pooled analysis. Drug Safety. 2010;33:289-301.

35. Gunnell D, Irvine D, Davies C, Martin RM. Varenicline and suicidal behavior: A cohort study based on data from the General Practice Research Database. British Medical Journal. 2009;339:b3805, doi:10.1136/bmj.b3805 PMCID: PMC2755726

36. Hughes JR, Keely JP, Niaura RS, Ossip-Klein DJ, Richmond RL, Swan GE. Measurements of abstinence in clinical trials: Issues and recommendations. Nicotine & Tobacco Research. 2003;5:13-25.

37. SRNT Subcommittee on Biochemical Verification. Biochemical verification of tobacco use and cessation. Nicotine & Tobacco Research. 2002;4:149-159.

38. Carroll KM, Easton CJ, Nich C, Hunkele KA, Neavins TM, Sinha R, Ford HL, Vitolo SA, Doebrick CA, Rounsaville BJ. The use of contingency management and motivationa/skills-building therapy to treat young adults with marijuana dependence. Journal of Consulting and Clinical Psychology. 2006;74:955-966. PMCID: PMC2148500

39. Ledgerwood DM, Alessi SM, Hanson T, Godley MD, Petry NM. Contingency management for attendance to group substance abuse treatment administered by clinicians in community clinics. Journal of Applied Behavioral Analysis. 2008;41:517-526. PMCID: PMC2606605

40. Sinha R, Easton C, Renee-Aubin L, Carroll KM. Engaging young probation-referred marijuana-abusing individuals in treatment: A pilot trial. The American Journal on Addictions. 2003;12:314-323.

41. Kalachnik JE. Standardized Monitoring for Psychopharmacologic Medication Side Effects. Manual for the Monitoring of Side Effects Scale (MOSES). Columbia, SC: University of South Carolina, School of Medicine, Department of Pediatrics, Center for Disability Resources, Columbia, SC, and the South Carolina Department of Disabilities and Special Needs; 2001.

42. Posner K, Brent D, Lucas C, Gould M, Stanley B, Brown G, Fisher P, Zelazny J, Burke A, Oquendo M, Mann J. Columbia-Suicide Severity Rating Scale (C-SSRS); 2007.

43. Gray KM, Baker NL, Carpenter MJ, Lewis AL, Upadhyaya HP. Attention-deficit/hyperactivity disorder (ADHD) confounds nicotine withdrawal self-report in adolescent smokers. American Journal on Addictions. 2010;19:325-331. PMCID: PMC2911152

44. Carpenter MJ, Baker NL, Gray KM, Upadhyaya HP. Assessment of nicotine dependence among adolescent and young adult smokers: A comparison of measures. Addictive Behaviors. 2010;35:977-982. PMCID: PMC2919624

45. Gray KM, Riggs PD, Min S, Mikulich-Gilbertson SK, Bandyopadhyay D, Winhusen T. Cigarette and cannabis use trajectories among adolescents in treatment for attention-deficit/hyperactivity disorder and substance use disorders. Drug and Alcohol Dependence. In press. PMCID Journal – In Process.

46. Gray KM, LaRowe SD, Upadhyaya HP. Cue reactivity in young marijuana smokers: A preliminary investigation. Psychology of Addictive Behaviors. 2008;22:582-586. PMCID: PMC2605672

47. Gray KM, LaRowe SD, Watson NL, Carpenter MJ. Reactivity to in vivo marijuana cues among cannabis dependent adolescents. Addictive Behaviors. 2011;36:140-143. PMCID: PMC2981614

48. Gray KM, Hart CL, Christie DK, Upadhyaya HP. Tolerability and effects of oral Δ^9-tetrahydrocanabinol in older adolescents with marijuana use disorders. Pharmacology Biochemistry and Behavior. 2008;91:67-70. PMCID: PMC2567109

49. Ledgerwood DM. Contingency management for smoking cessation: Where do we go from here? Current Drug Abuse Reviews. 2008;1:340-349.

50. Lussier JP, Heil SH, Mongeon JA, Badger GJ, Higgins ST. A meta-analysis of voucher based reinforcement therapy for substance use disorders. Addiction. 2006;101:192–203.

51. Festinger DS, Marlowe DB, Dugosh KL, Croft JR, Arabia PL. Higher magnitude cash payments improve research follow-up rates without increasing drug use or perceived coercion. Drug and Alcohol Dependence. 2008;96:128-135. PMCID: PMC2475801

52. Cavallo DA, Nich C, Schepis TS, Smith AE, Liss TB, McFetridge AK, Krishnan-Sarin S. Preliminary examination of adolescent spending in a contingency management based smoking cessation program. Journal of Child and Adolescent Substance Abuse. 2010;19:335-342. PMCID: PMC2928574

53. Huang HY, Maguire MG, Miller ER 3rd, Appel LJ. Impact of pill organizers and blister packs on adherence to pill taking in two vitamin supplementation trials. American Journal of Epidemiology. 2000;152:780-787.

54. Simmons D, Upjohn M, Gamble GD. Can medication packaging improve glycemic control and blood pressure in type 2 diabetes? Results from a randomized controlled trial. Diabetes Care. 2000;23:153-156.

55. Wright JM, Htun Y, Leong MG, Forman P, Ballard RC. Evaluation of the use of calendar blister packaging on patient compliance with STD syndromic treatment regimens. Sexually Transmitted Diseases. 1999;26:556-563.

56. Sheehan DV, Lecrubier Y, Harnett-Sheehan K, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar G. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. Journal of Clinical Psychiatry. 1998;59:S22-S33.

57. Sheehan DV, Sheehan KH, Shytle RD, Janavs J, Bannon Y, Rogers JE, Milo KM, Stock SL, Wilkinson B. Reliability and validity of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). Journal of Clinical Psychiatry. 2010;71:313-326.

58. American Academy of Pediatrics, Pennsylvania Chapter. "Tobacco History Questionnaire." March 12, 2008. Available online at: http://www.helpteensquit.com Accessed May 28, 2011

59. Lewis-Esquerre JM, Rodrigue JR, Kahler CW. Development and validation of an adolescent smoking consequences questionnaire. Nicotine & Tobacco Research. 2005;7:81-90.

60. Myers MG, MacPherson L. Adolescent Reasons for Quitting Smoking: Initial psychometric evaluation. Psychology of Addictive Behaviors. 2008;22:129-134. PMCID: PMC2757254

61. Prokhorov AV, De Moor C, Pallonen UE, Hudmon KS, Koehly L, Hu S. Validation of the modified Fagerström tolerance questionnaire with salivary cotinine among adolescents. Addictive Behaviors. 2000;25:429-433.

62. DiFranza JR, Savageau JA, Wellman RJ. A comparison of the Autonomy over Tobacco Scale and the Fagerström Test for Nicotine Dependence. Addictive Behaviors. In press.

63. Pavot W, Diener E. Review of the Satisfaction with Life Scale. Psychological Assessment. 1993;5:164-172.

64. Schwarzer R, Jerusalem M. Generalized Self-Efficacy Scale. In Weinman J, Wright S, Johnston M, editors. Measures in health psychology: A user's portfolio. Causal and control beliefs. Windsor, UK: NFER-NELSON; 1995. p. 35-37.

65. Velicer WF, DiClemente CC, Rossi JS, Prochaska JO. Relapse situations and self-efficacy: An integrative model. Addictive Behaviors. 1990;15:271-283.

66. Borrelli B, Mermelstein R. Goal setting and behavior change in a smoking cessation program. Cognitive Therapy and Research. 1994;18:69-83.

67. Bruwer B, Emsley R, Kidd M, Lochner C, Seedat S. Psychometric properties of the Multidimensional Scale of Perceived Social Support in youth. Comprehensive Psychiatry. 2008;49:195-201.

68. Canty-Mitchell J, Zimet GD. Psychometric properties of the Multidimensional Scale of Perceived Social Support in urban adolescents. American Journal of Community Psychology. 2000;28:391-400.

69. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. Journal of Clinical Psychology. 1995;51:768-774.

70. DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. ADHD Rating Scale--IV: Checklists, Norms, and Clinical Interpretation. Bethlehem, PA: Guilford Publications; 1998.

71. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatrica Scandinavica. 1983;67:361-370.

72. Olssøn I, Mykletun, Dahl AA. The Hospital Anxiety and Depression Rating Scale: A cross-sectional study of psychometrics and case finding abilities in general practice. BMC Psychiatry. 2005;5:46. PMCID: PMC1343544

73. White D, Leach C, Sims R, Atkinson M, Cottrell D. Validation of the Hospital Anxiety and Depression Scale for use with adolescents. British Journal of Psychiatry. 1999;175:452-454.

74. Sobell LC, Sobell MB, Leo GI, Cancilla A. Reliability of a timeline method: assessing normal drinkers' reports of recent drinking and a comparative evaluation across several populations. British Journal of Addiction. 1988;83:393-402.

75. Zevin S, Jacob P, Geppetti P, Benowitz NL. Clinical pharmacology of oral cotinine. Drug and Alcohol Dependence. 2000;60:13-18.

76. Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. Nicotine & Tobacco Research. 2001;3:7-16.

77. Hughes JR, Hatsukami DK. Signs and symptoms of tobacco withdrawal. Archives of General Psychiatry. 1986;43:289-294.

78. Brauer LH, Behm FM, Lane JD,Westman EC, Perkins C, Rose JE. Individual differences in smoking reward from de-nicotinized cigarettes. Nicotine & Tobacco Research. 2001;3:101-109.

79. Rose JE, Behm FM, Westman EC. Nicotine-mecamylamine treatment for smoking cessation: The role of pre-cessation therapy. Experimental and Clinical Psychopharmacology. 1998;6:331-343.

80. Hughes JR, Carpenter MJ, Naud S. Do point prevalence and prolonged abstinence measures produce similar results in smoking cessation studies? A systematic review. Nicotine & Tobacco Research. 2010;12:756-762. PMCID: PMC2893294

81. Oncken C, Gonzales D, Nides M, Rennard S, Watsky E, Billing CB, Anziano R, Reeves K. Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. Archives of Internal Medicine. 2006;166:1571-1577.

82. Williams KE, Reeves KR, Billing CB Jr, Pennington AM, Gong J. A double-blind study evaluating the long-term safety of varenicline for smoking cessation. Current Medical Research and Opinion. 2007;23:793-801.

83. Van Zundert RM, Ferguson SG, Shiffman S, Engels RC. Dynamic effects of self-efficacy on smoking lapses and relapse among adolescents. Health Psychology. 2010;29:246-254.

84. Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans, SJW. Reporting of noninferiority and equivalence randomized trials. Journal of the American Medical Association. 2006;295:1152-1160.

85. Cahill K, Stead L, Lancaster T. A preliminary benefit-risk assessment of varenicline in smoking cessation. Drug Safety. 2009;32:119-135.

86. Flannery, B.A., Volpicelli, J.R. & Pettinati, H.M. Psychometric properties of the Penn Alcohol Craving Scale. Alcoholism: Clinical and Experimental Research*,* 1999; 23:1289-1295.

87. Bagby, R. M., Parker, J. D. A. & Taylor, G. J. The twenty-item Toronto Alexithymia Scale-I. Item selection and cross-validation of the factor structure. Journal of Psychosomatic Research, 1994; 38: 23-32."

88. Bolt, D.M., Piper, M.E., McCarthy, D.E., Japuntich, S.J., Fiore, M.C., Smith, S.S., Baker, T.B. The Wisconsin predicting patients' relapse questionnaire. Nicotine and Tobacco Research, 2009; 11: 481-492.

89, First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P). New York: Biometrics Research, New York State Institute. 2002.