Facilitating Smoking Cessation with Reduced Nicotine Cigarettes

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A. SPECIFIC AIMS

Cigarette smoking remains the top avoidable cause of death in Florida, while approximately 18% of Floridian adults continue to smoke. As long-term cessation rates with even the most intensive interventions rarely exceed 20-30%, it is vital that research develop and validate novel methods for effective smoking cessation. It has long been understood that nicotine is the primary constituent in tobacco smoke that maintains addiction. Although the Food and Drug Administration (FDA) may place limits on the allowable nicotine levels within cigarettes, such regulatory actions will likely entail a lengthy and complex legal process. In the interim, the availability (via the NIDA Drug Supply Program) of very low nicotine content (VLNC) cigarettes represents a unique opportunity to examine the efficacy of these cigarettes for smoking cessation. The proposed research will develop and evaluate an integrated (behavioral and pharmacological) intervention targeted to maximize the efficacy of VLNC cigarettes as a smoking cessation strategy. The aims of this theory-driven intervention are as follows:

Specific Aim 1: Systematically adapt a strategy that maximizes extinction to nicotine-reinforced smoking behavior via smoking VLNC cigarettes prior to cessation. This aim will draw upon existing basic and clinical literature regarding extinction processes, and employ qualitative methods (e.g., expert/consultant review, in-depth interviews) to develop and refine the intervention. As part of this aim, a developmental pilot study (n=20) will determine the feasibility of the treatment approach and methodology, and lead to refinements for a subsequent randomized controlled trial (RCT).

Specific Aim 2: Examine effects of the targeted intervention, along with two tapering schedules for transition to VLNC cigarettes (immediate vs. gradual), on smoking cessation outcomes through the RCT.

Specific Aim 3: Examine intervention effects on two proximal (intermediate) tests of smoking-related outcomes. Towards this end, two behavioral paradigms will be administered to RCT participants.

Specific Aim 4: Explore several potential moderators and mediators of smoking-related outcomes. Exploratory analyses will examine the potential moderators and mediators of treatment efficacy, for use in future research and applied settings.

We hypothesize that smokers who receive the targeted intervention will demonstrate favorable cessation outcomes and reduced proximal smoking, relative to those who receive a standard intervention. Furthermore, we expect favorable outcomes among those who transition immediately to VLNC cigarettes during the pre-quit period, relative to those who transition gradually (based on greater opportunities for non-reinforced smoking; i.e., extinction).

B. SIGNIFICANCE

Tobacco use remains the most preventable cause of death and disability in the US, with approximately 480,000 deaths per year attributed to cigarette smoking alone (USDHHS, 2014). Each day thousands of adolescents try their first cigarette, and a substantial proportion of these individuals will eventually become regular or daily smokers. Although the majority of smokers express a desire to quit, over 90% of those who make a cessation attempt relapse within a year (Fiore et al., 2008). Developing effective methods for smoking cessation remains a top priority, with the potential to save countless lives and reap meaningful social and economic benefits.

Nicotine and Smoking Cessation

Nicotine is the primary addictive constituent within tobacco that supports the initiation, development, and persistence of smoking behavior. Nicotine serves as a primary reinforcer; for instance, it supports self-administration in both animal and human models (Corrigall, 1992; Corrigall & Coen, 1989; Goldberg et al., 1981; Henningfield & Goldberg, 1983; Rose & Corrigall, 1997). In addition, nicotine appears to be a strong secondary reinforcer, such that initially neutral stimuli that become closely associated with nicotine delivery obtain reinforcing properties (Caggiula et al., 2001; Goldberg et al., 1981; Palmatier et al., 2007). Those secondary (conditioned) reinforcement properties can be attained by sensory (taste, smell, and feel) aspects of smoking (Rose & Levin, 1991), as well as by a variety of exteroceptive stimuli and interoceptive (e.g., mood) states (Oliver et al., 2013).

Nicotine withdrawal is a constellation of subjective/emotional, behavioral, and cognitive disturbances experienced by smokers upon removal of nicotine after an extended period of use. It is important to consider that some symptoms of nicotine withdrawal can onset quite rapidly (within 30 minutes) upon ceasing tobacco use (Hendricks et al., 2006), and that withdrawal is a major impediment to successful cessation outcomes among those attempting to quit. Hence, it is not surprising that pharmacological approaches toward smoking cessation attempt to counteract the disruptive effects of nicotine withdrawal during the quitting process, either by directly replacing nicotine (e.g., gum, patch, inhaler, nasal spray, lozenge), or by addressing the neurochemical actions of nicotine in the brain (e.g., bupropion, varenicline). Given the best long-term smoking cessation rates with pharmacological and/or behavioral treatments rarely exceed 30-35%, there is clearly room to consider other pharmacological and/or behavioral approaches to cessation.

Reduced Nicotine Content and Public Health

It has been proposed that a sub-threshold nicotine dose (below approximately 0.17 mg nicotine yield per cigarette) should significantly reduce the initiation and maintenance of tobacco addiction (Benowitz & Henningfield, 1994). Research has generally supported this contention, demonstrating that very low nicotine content (VLNC) cigarettes (e.g., 0.05 mg nicotine) often produce reductions in smoking behavior and/or nicotine exposure over time, as well as lowered nicotine dependence, withdrawal, craving, and biomarkers of exposure (e.g., Benowitz et al., 2007; Benowitz et al., 2009; Donny et al., 2007; Hatsukami et al., 2010; Pickworth et al., 1999). Some evidence of transient compensation (i.e., increased smoking) has been observed upon switching to VLNC cigarettes, yet these short-lived effects appear to be insignificant in terms of toxicant exposure (MacQueen et al., 2012; Strasser et al., 2007). Recently, the largest study of its kind examined several gradations of nicotine content within cigarettes, including doses above and below the theorized threshold for addiction, using newly available research cigarettes that appropriately control for other tobacco constituents (Donny et al., 2015). In that study, sub-threshold doses were associated with relative reductions in smoking behavior after six weeks among non-treatment seeking smokers, while maintaining adequate acceptability and compliance (see preliminary research section). Importantly, there was no evidence of compensatory smoking, and biomarkers of exposure to nicotine and the tobacco-specific nitrosamine NNK were lower in those smoking VLNC cigarettes. Based on this and prior research, evidence suggests that VLNC cigarettes may lead to beneficial public health outcomes. Indeed, with recent passage of the Family Smoking Prevention and Tobacco Control Act (FSPTCA, 2009), the FDA now has the authority to limit (but not eliminate) the nicotine content of cigarettes.

Reduced Nicotine Content Cigarettes and Smoking Cessation

Whether or not a major policy change to reduce the standard nicotine levels within cigarettes is implemented in the coming years, the availability of research cigarettes with reduced nicotine levels offers an unprecedented opportunity to evaluate these products as a clinical tool for smoking cessation (see Walker et al., 2009). Although most studies that have examined VLNC cigarettes either did not recruit smokers who were motivated to quit, or did not examine effects on cessation-related outcomes, several recent studies have begun to examine the potential efficacy of VLNC cigarettes for cessation. In one study, two weeks of pre-quit VLNC cigarettes in combination with nicotine patch was associated with reduced cravings post-quit date, but there was no beneficial effect on withdrawal symptoms or abstinence outcomes (Rezaishiraz et al., 2007). In another study, smokers assigned to progressively decreasing nicotine content cigarettes showed improved rates of abstinence, but only if the cigarettes were combined with nicotine patch for two weeks before and after the quit date (Becker et al., 2008). In another study, smokers assigned to six weeks of VLNC cigarettes showed a higher rate of cessation, as compared to those who smoked either reduced (but not VLNC) nicotine cigarettes or those who used a nicotine lozenge (Hatsukami et al., 2010). In a fourth study, smokers instructed to use VLNC cigarettes to cope with urges to smoke after a target quit date, in combination with usual quitline care (nicotine replacement therapy and behavioral counseling) showed modest improvements in 6 month point-prevalence abstinence outcomes, relative to those receiving usual care only (Walker et al., 2012). Finally, a comparison between VLNC cigarettes alone, nicotine patch alone, and combined VLNC cigarettes and patch showed less pre-quit smoking and lowered withdrawal severity among those in the combination condition; however, there were no differences in cessation outcomes (Hatsukami et al., 2013). Taken together, these treatment studies provide mixed evidence regarding the clinical efficacy of VLNC cigarettes for smoking cessation.

Surprisingly, none of the prior VLNC treatment studies emphasized strategies that would maximize extinction to cigarette-related reinforcement during the pre-quit period. Theoretically, the sub-threshold nicotine doses with VLNC cigarettes should extinguish both primary and secondary sources of smoking-related reinforcement. The proposed research will develop a behavioral intervention intended to optimize the efficacy of VLNC cigarettes from a learning-based (extinction) perspective. Specifically, the proposed project will (1) develop a theory-driven "facilitated extinction" intervention for use with VLNC cigarettes during the pre-quit period, (2) evaluate the efficacy of pre-quit VLNC cigarette smoking as a cessation strategy by conducting a randomized controlled trial (RCT), and (3) obtain data regarding potential mechanisms that may moderate or mediate treatment effectiveness, to inform future implementation of this novel cessation strategy. If successful, future research may continue to validate this VLNC treatment strategy in comparison with existing methods (e.g., NRT treatment), and determine the most effective methods to disseminate VLNC cigarettes for clinical benefit. Below, we discuss the theoretical foundations of the proposed research.

Facilitated Extinction

Recent advances in learning theory, along with methods from basic and applied research from other domains of psychopathology, can be used to optimize extinction as part of an approach to smoking cessation (e.g., Bouton, 2000; Conklin & Tiffany, 2002; Foa 2011; Laborda et al., 2011). We are currently evaluating such an approach to maximize extinction with extended pre-cessation varenicline. Following strategies employed in that project, we plan to base our initial development of a facilitated extinction workbook for pre-quit VLNC use on the following key techniques:

a) Ensure that participants continue to smoke VLNC cigarettes at their normal rate during the pre-quit period. This will create maximum opportunities for extinction learning. Thus, premature smoking reduction or cessation will be actively discouraged (in contrast to ongoing smokers who may spontaneously reduce smoking when given VLNC cigarettes).
b) Ensure that pre-quit smoking of VLNC cigarettes occurs across a wide range of contexts that have previously been associated with smoking, including rare contexts that could potentially trigger relapse. Extinction does not generalize well across contexts (Bouton, 2002; Bouton et al., 2011; Collins & Brandon, 2002); thus, it is important to smoke VLNC cigarettes across as many contexts as possible during the pre-quit period.
c) Ensure that compound stimuli (i.e., multiple smoking cues) are present on a subset of pre-quit VLNC smoking episodes, based on evidence that compound stimuli produce more potent responding and more complete and persistent extinction (Rescorla, 2006).
d) Ensure that both interoceptive (e.g., mood) and exteroceptive contexts are included for pre-quit VLNC smoking episodes. Indeed, negative affect states are among the most potent cues for smoking and smoking relapse (Baker et al., 2004; Shiffman et al., 2007).
e) Provide education about the extinction process and include self-monitoring of smoking "satisfaction" during pre-quit VLNC smoking. These techniques are based on findings that extinction is enhanced when patients hold positive expectancies about the extinction process, and when they are explicitly aware of diminished reinforcement (Hofmann, 2008).
f) Provide patients with an extinction retrieval cue, based on research indicating that the maintenance and generalizability of extinction (across time and contexts) are enhanced by the use of such a cue (e.g., Brooks & Bouton, 1994; Collins & Brandon, 2002).

Project Summary and Overview

There is currently limited data regarding the potential efficacy of VLNC cigarettes as a treatment strategy for smoking cessation. Prior studies have shown mixed promise, but these did not include supportive interventions to maximize the potential benefit of VLNC cigarettes according to learning/extinction theory. Based on pharmacologic and learning-based aspects of nicotine reinforcement, we suggest that the optimal clinical utility of VLNC cigarettes will depend on facilitating extinction through pre-quit non-reinforced exposure to smoking. To that end, we propose to develop and evaluate such a theory-driven intervention. The proposed research will examine the efficacy of this intervention for smoking cessation outcomes, as well as intermediate (proximal) smoking-related behavior, under two dose tapering regimens. In addition, this clinical research will carefully evaluate trial methods, and provide estimates regarding recruitment, retention and participation rates. This information can guide and support future validation research in this area.

According to NIDA's Stage Model of Behavioral Therapies Research (Onken et al., 1997; Rounsaville et al., 2001), Stage I research represents the initial development of an intervention, whereas Stage II research includes an RCT to test efficacy of the intervention, as well as tests of mechanisms of action and refinement of the treatment. Eventually, Stage III research addresses transportability of the validated intervention, including issues of generalizability, implementation, cost-effectiveness, and marketability. The proposed planning project can be construed as an amalgam of Stage I and Stage II research, with Stage I further divided into two substages (Rounsaville, et al., 2001). Stage Ia includes treatment development and manual creation (Study 1, Specific Aim 1), and Stage Ib focuses on testing feasibility and acceptability of the developed intervention in a small clinical trial (Study 2, Specific Aim 2), as well as effects on intermediate outcomes (Study 2, Specific Aim 3). Stage II goals will be realized through an

adequate sample size for the RCT, and exploration of potential moderators and mediators of treatment efficacy.

In summary, the current project will (1) develop a theory-based, user-friendly, and efficient set of targeted cessation materials to facilitate extinction during pre-quit VLNC smoking, (2) establish the feasibility of recruitment and measurement strategies to be used in the RCT, (3) determine whether immediate vs. gradual pre-quit nicotine tapering in combination with the targeted behavioral intervention has beneficial effects (on cessation-related and intermediate outcomes) for eventual comparison with validated cessation methods (e.g, NRT), and (4) examine several potential moderators and mediators of treatment efficacy.

C. INNOVATION

There are several innovative features to this proposed research. Few studies have evaluated VLNC cigarettes as a tool for smoking cessation, and none have used a formative process to develop specific adjunct materials to maximize efficacy. The current project will be the first to develop a set of theory-driven self-help materials to support the use of VLNC cigarettes during the pre-quit period. A combined qualitative and quantitative approach for developing this targeted intervention, as well as evaluating the feasibility of the strategy and methods for its evaluation in the subsequent RCT, is novel. Furthermore, most prior evaluations of VLNC cigarettes have been conducted on non-treatment smokers, without the intention to quit smoking. The present study will recruit treatment-seeking smokers, which places greater emphasis on determining how VLNC cigarettes affect those most likely to quit. Another innovative feature is the unique combination of baseline and outcome measures, which will provide a valuable perspective on the effects of VLNC cigarettes on indices of nicotine dependence and reinforcement, smoking behavior, and motivation to smoke among treatment-seeking smokers. In particular, the measurement of intermediate outcomes (i.e., cue reactivity, cigarette purchase task) will provide unique insights into the effects of VLNC cigarettes on smoking behavior among treatment-seeking smokers. Finally, measurement of potential moderators (e.g., smoking history, nicotine dependence, withdrawal sensitivity, quit motivation, gender) and mediators (compliance, product perception) of the effects of VLNC cigarettes on cessation-related and intermediate outcomes will guide and support optimal utilization of this novel cessation strategy in future research and clinical application.

D. APPROACH

Background of the Investigative Team

The research team is highly qualified to conduct the proposed research. Dr. Simmons (PI) provides substantial expertise in the development of self-help smoking cessation materials, including the integration of qualitative and quantitative methods for maximizing relevance and enhancing user acceptability of treatment materials. Dr. Drobes (Co-I) has been conducting research on smoking motivation and behavior for over 25 years, including studies of craving, cue reactivity, smoking topography, nicotine direct effects, nicotine withdrawal, and genetic relationships with smoking-related variables. He is joined by an experienced team of tobacco researchers. Dr. Brandon (Co-I) also has over 30 years of tobacco research experience, including laboratory studies of smoking motivation and behavior, as well as large scale RCTs involving both intensive theory-driven interventions and self-help materials for cessation and relapse prevention. In addition, he is PI on an ongoing study to develop and evaluate a facilitated extinction approach for extended pre-quit use of Varenicline. Finally, Dr. Sutton is a psychologist and biostatistician, and has worked with our group on multiple tobacco-related laboratory and treatment development studies. As a member (and coordinator) of the Moffitt

biostatistics core, he will also draw upon the strengths of various core faculty and staff members to fulfill the statistical needs of the project.

In addition to the primary research team, we are fortunate that Dr. Eric Donny and Dr. Dorothy Hatsukami (MPI's of the Center for the Evaluation of Nicotine in Cigarettes; CENIC) have agreed to serve as consultants on the current project. Their involvement adds considerable expertise in the study of reduced nicotine products, including laboratory and treatment outcome studies (see letters of support). As one of the Site PI's for the CENIC project, the current Co-I (Drobes) will work with these consultants to adapt methods and measures from the multi-site CENIC projects, as well as discuss with colleagues on that project team the development and implications of this clinical research as a complementary approach to the public health focus of CENIC.

Preliminary Research

Transient Compensatory Smoking with VLNC Cigarettes. Recent work in our laboratory has focused on the effects of nicotine on neurocognitive processes, as well as moderators of these effects (e.g., Evans et al., 2013, 2014). In this research, smoking topography was measured to provide statistical control for potential differences in smoking behavior (between VLNC and normal nicotine content [NNC] cigarettes) in evaluating neurocognitive outcomes. Findings indicated greater (compensatory) smoking during the first VLNC cigarette (.05 mg nicotine yield), relative to NNC cigarettes (.6 mg), among non-treatment seeking smokers in a within-subjects design (n=67). These differences were apparent across indices of total puff volume, total puff duration, and inter-puff interval (see Figure 1). However, note that these increases in smoking behavior dissipated quickly, with return to normal smoking by the second cigarette across four sequential cigarettes of each type (approximately 45 minute inter-cigarette interval) (MacQueen at el., 2012).

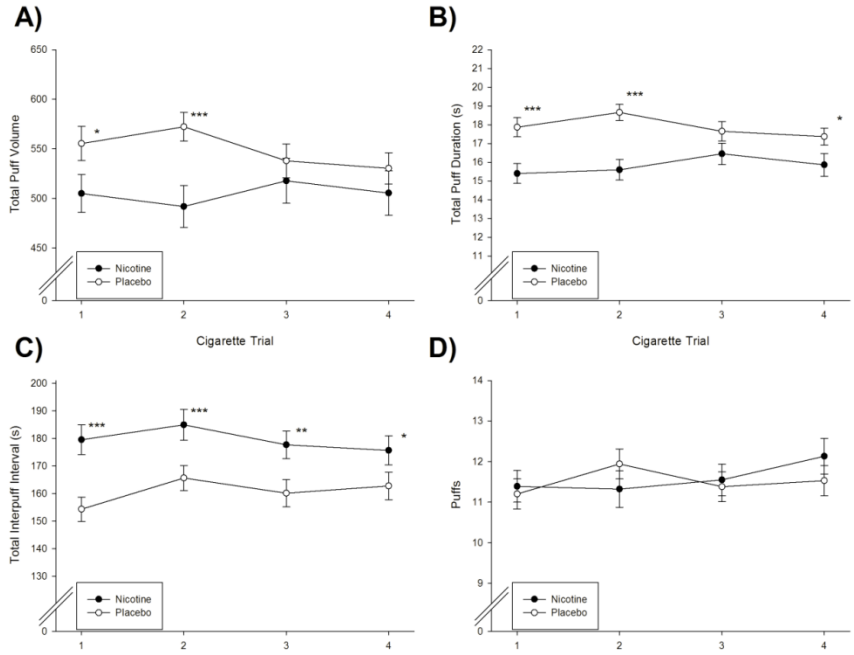


Figure 1. Comparison of normal nicotine content (solid circles) versus VLNC (open circles) Quest cigarettes across sessions on: (A) Total Puff Volume; (B) Total Puff Duration; (C) total interpuff interval; and (D) number of puffs. Error bars indicate standard error. * $p <$ .05; ** $p <$ .01; *** $p <$ .001.

Genetic Moderation of Smoking VLNC Cigarettes. In a

subsequent analysis of the data in Figure 1, we examined the Alpha 5 Nicotinic Acetylcholine Receptor Subunit Gene (CHRNA5; rs16969968) as a moderator of smoking behavior in this paradigm. As shown in Figure 2, the smoking behavior of minor allele carriers was not influenced by the level of nicotine, relative to non-carriers who engage in greater puff volumes when smoking VLNC cigarettes (MacQueen et al., 2014). **Together these studies demonstrate the investigators experience with VLNC cigarettes in a lab context, and support the contention that differing nicotine content within cigarettes is associated with changes in smoking behavior, and that these changes may be moderated by individual differences.**

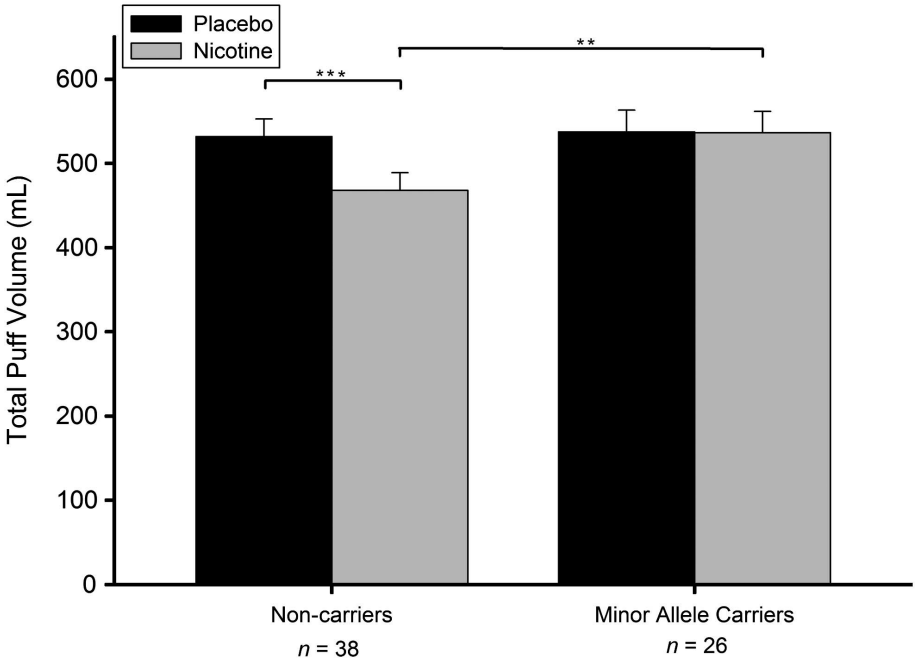


Figure 2. Total puff volume in non-carriers versus minor allele carriers.

CENIC: Project 1, Study 1. A double-blind, parallel, randomized clinical trial of 840 daily smokers was conducted at ten sites (including Moffitt Cancer Center) between June 2013 and July 2014. Eligibility criteria included age ≥18 years, 5+ cigarettes per day, and no current interest in quitting smoking. Participants were randomized to smoke either their usual brand or investigational cigarettes for 6 weeks. Investigational cigarettes varied in nicotine content from levels comparable to most commercial cigarettes (17.7 mg per g tobacco; primary control condition) to levels only 2% that amount (0.4 mg/g). The primary outcome measure was the average number of cigarettes smoked per day during Week 6. Findings at week 6 (93% retention) indicated that participants randomized to cigarettes with 2.5 mg/g nicotine or less smoked fewer cigarettes per day compared to the normal nicotine content control group (see Figure 3). Reduced nicotine content cigarettes resulted in less nicotine dependence and fewer withdrawal symptoms when abstinent. Biomarkers of exposure to nicotine and the tobacco-specific nitrosamine NNK were lower in those smoking low nicotine cigarettes. Smoke exposure (i.e., expired carbon monoxide) did not significantly vary by nicotine content, suggesting minimal compensation. Adverse events were generally mild and determined to be unrelated to participation. These data provide evidence that a federally-mandated reduction in the nicotine content of combustible tobacco products is likely to improve public health (see Donny et al., *in press*). However, this project did not specifically address the potential direct benefits of using

reduced (or very low) nicotine content products as a tool for smoking cessation. The proposed research applies a well-developed theoretical model of extinction to develop such a treatment approach.

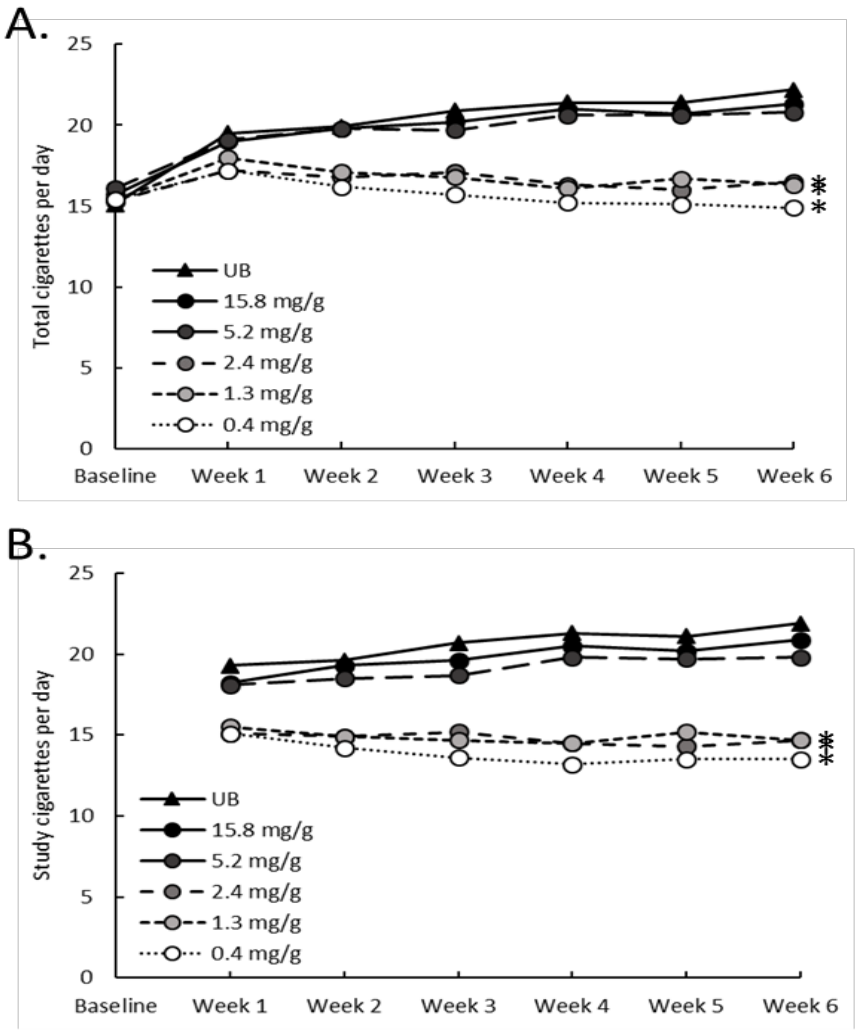


Figure 3. Average number of study cigarettes and total cigarettes smoked per day over six weeks.

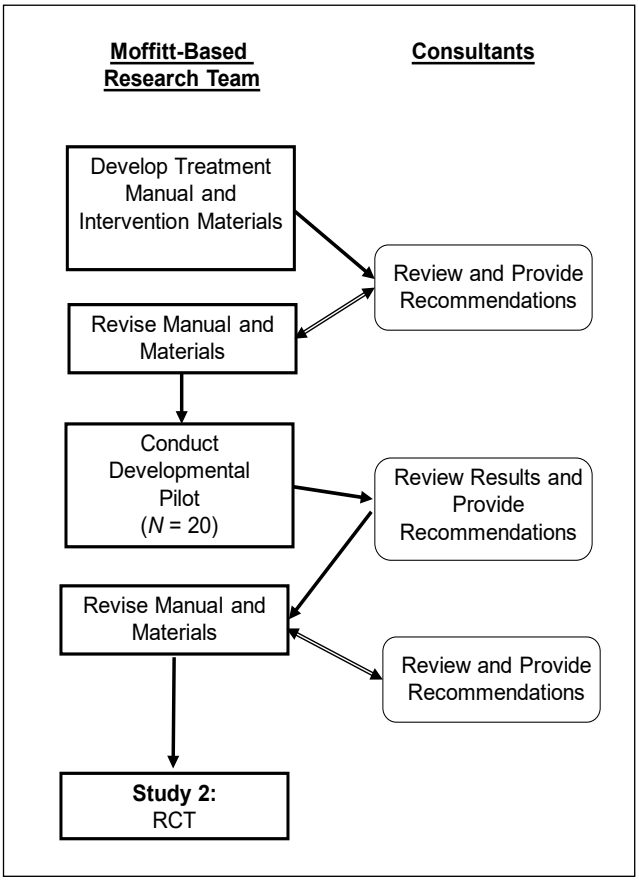
Proposed Research

Study 1. Intervention Development (Aim 1)

Initial Development. In keeping with the Stage Model of Behavioral Therapies Research (Onken et al., 1997; Rounsaville et al., 2001), this proposal component will focus on development of Facilitated Extinction (FE) treatment materials (Stage Ia research). This will primarily consist of a self-help workbook, tentatively entitled *"Countdown: Preparing to Quit Smoking with Low-Nicotine Cigarettes"*. Specifics of the intervention will be subject a systematic process of creation and refinement by the primary study team, as well as review and feedback by the study consultants. The planned developmental process is summarized in Figure 4. As shown, the primary research team will develop the initial treatment manual and workbook, which

will then be reviewed by the study consultants, followed by revision based on their feedback. In this figure, two-headed arrows represent points of possible iteration. That is, more than one round of revision and review may be necessary. In addition, a developmental pilot study (see below) will be used to obtain initial information about feasibility and user acceptability.

Figure 4: Intervention Development Study Flow



The workbook (and accompanying therapist manual) that have been developed for our ongoing research on facilitated extinction (i.e., with extended pre-quit varenicline) will serve as a starting point for this developmental process. The resulting intervention will contain didactic information (e.g., the rationale for smoking VLNC cigarettes to maximize extinction), worksheets, tracking forms, and intervention evaluation measures, with content that is consistent with basic and applied research on extinction. The information and format of the workbook will be designed to enhance smokers' positive expectancies about extinction, and to provide practical, interactive exercises and worksheets to aid in the structuring of extinction (smoking) trials. For example, one technique will involve creating a checklist of smoking locations and situations. Participants will be asked to indicate the situations where they smoke at least on occasion, and instructed to smoke in each of these situations at least once per week during the pre-quit period, and to record doing so on a worksheet. As another task, participants will be encouraged to expose themselves to the high-risk situations that they would typically be asked to avoid after quitting smoking (e.g., handling cigarettes, being around other smokers, use of alcohol), to ensure that they are exposed to those situations while smoking VLNC cigarettes during the pre-quit period. These examples address the need for extinction trials to cover a broad range of smoking situations.

Specific exercises will be introduced in an orderly fashion across the pre-quit period. For instance, explicit exposure to interoceptive cues will begin later in the pre-quit period, after the participant has mastered techniques associated with exteroceptive cue exposure. However, the counselor will begin to address interoceptive cues earlier, while the participant is mastering exteroceptive cue exposure. In addition, participants will receive a rubber wristband (along with a spare) with a "Countdown" logo that will serve as an extinction retrieval cue, in order to improve the generalizability of extinction and reduce renewal to conditioned responding (Brooks & Bouton, 1994; Collins & Brandon 2002). Participants will be instructed to wear this wristband only while smoking during the last week of the pre-quit period, and to wear it continuously for up to one month after the target quit date (TQD). The worksheets will be collected at the end of the pre-quit period and scored to assess adherence to instructions (e.g., monitoring of smoking situations; extinction strategies used).

The bulk of the intervention will be provided via the self-help workbook, including advice for minimizing withdrawal and managing cravings after the TQD. In order to maximize treatment fidelity at this developmental stage, the workbook will be supported by brief in-person counseling provided at each VLNC cigarette distribution session. Counseling sessions will review the didactic information included in the workbook, including the extinction-facilitation strategies, exercises, and worksheets. Counselors will encourage participants to continue using the FE techniques throughout the pre-quit period, and highlight the importance of restricting all smoking during the treatment period to the study cigarettes provided. Counselors will also introduce techniques that are timed for different points during this period. For instance, as mentioned above, introduction of exposure to interoceptive cues will occur later in the pre-quit period, after the participant has mastered techniques associated with exteroceptive cue exposure. The TQD will be scheduled for one week after the fifth weekly session (+/- 3 days). Participants will receive brief counseling during a final session one week (+/- 3 days) after the TQD. Additional details regarding the content of the treatment sessions will be specified upon completion of the intervention development process.

Developmental Pilot Study. Once the study team agrees that the intervention is sufficiently developed, we will conduct a developmental pilot study to gather pragmatic information about the administration of the treatment and its acceptability to both participants and counselors. This pilot study will generally follow the procedures described for the larger (Stage 2) RCT (see Study 2 below), but without the laboratory and extended follow-up assessments. Participants for this pilot study (N = 20, with 10 receiving immediate reduction to the lowest nicotine content cigarette, and 10 receiving a gradual reduction schedule, see below for details) will be recruited from the community via advertising methods that have been successful in our recent studies, including: newspaper and radio ads, press releases, public postings, PSA's, online sources (e.g., Craigslist), social media (e.g., Facebook), word of mouth, and from an existing database of previous study participants at the Tobacco Research and Intervention Program (TRIP). Potential participants will be given the option to respond via telephone or computer. If they opt to respond by computer, they will complete a pre-screen using Survey Monkey, prior to the telephone screen. If the participant is eligible they will be given directions to the lab verbally or through email.

Study Eligibility Criteria.
Study 1 inclusion criteria include: (a) ≥18 years of age; (b) smoke at least 5 cigarettes daily for the past year; (c) expired-air carbon monoxide (CO) > 8 ppm (if ≤ 8 ppm, then NicAlert Strip > 2); (d) current motivation to quit smoking; and (e) able to speak and read English sufficiently for completion of consent form and questionnaires. Exclusion criteria include: (a) pregnant or breastfeeding; (b) significant unstable medical/psychiatric or substance use disorders, or

medically/psychiatrically at risk in the judgment of the study physician (or licensed medical professional designated to consult in his absence) or PI; (c) positive urine screen for cocaine, opiates, methadone, benzodiazepines, barbiturates, amphetamines, methamphetamines, or PCP (NOTES: THC will be tested but will not be an exclusionary criterion; participants with valid prescriptions for opiates, benzodiazepines, barbiturates, amphetamines or methadone will not be excluded; participants failing the toxicology screen will be allowed to re-screen once); (d) breath alcohol level > 0.01 (one re-screen allowed); (e) binge alcohol drinking (4/5 [female/male] drinks per day more than 9 days in the past month); (f) systolic/diastolic BP greater than or equal to 160/100, or below 90/50 (one re-screen allowed); (g) heart rate greater than or equal to 105bpm, or below 45bpm (one re-screen allowed); (h) ever used reduced nicotine cigarettes; (i) smoke 'roll your own' cigarettes exclusively, (j) used smoking cessation medications within the past three months, (k) are currently enrolled in a smoking cessation program; (l) actively trying to quit; (m) used other tobacco products (including e-cigarettes) more than 9 days in the past month, and (n) currently taking the following medications:

- Phenytoin [Brand Name: Dilantin]
- Carbamazepine [Brand Name: Tegretol, Carbatrol, Equetro, Epitol]
- Oxcarbazepine [Brand Name: Trileptal]
- Primidone [Brand Name: Mysoline]
- Phenobarbital
- Bendamustine (Treanda)
- Clopidogrel (Plavix)
- Clozapine (Clozaril, FazaClo)
- Erlotinib (Tarceva)
- Flecainide (Tambocor)
- Fluvoxamine (Luvox)
- Irinotecan (Camptosar)
- Olanzapine (Zyprexa)
- Ropinirole (Requip)
- Tacrine (Cognex)
- Theophylline (Theo Dur, etc.)

Measures to assess each of these criteria are described below (see Study 2). If the participant needs to be rescreened, or if their eligibility is pending review by the P.I., Co-I, or LMP, they will be required to attend an additional visit.

During the baseline session eligibility will be assessed during the following checkpoints: The first checkpoint will be during the physiological measures portion. If the participant fails the breath alcohol test, urine drug screening (minus valid Rx or THC), pregnancy test, or if the blood pressure reading is outside of the permissible range, they will receive $10. If the participant does not pass the smoking confirmation tests (if CO ≤ 8ppm, and NicAlert Strip ≤2), they will be dismissed without payment. While awaiting results for physiological measures, participants may begin completing questionnaires in order to expedite the screening process. The second eligibility checkpoint will be after the participant answers the self-administered forms (Brief Medical History, Prime MD, etc.). If the participant is deemed ineligible at the second eligibility checkpoint they will receive $15. The third eligibility checkpoint will be after the interviewer administered forms (Timeline Follow-Back, Tobacco Use History Questionnaire, etc.). If the participant is deemed ineligible at this point they will receive the full $25 for the session.

Intervention Phase. If a participant is deemed to be eligible, they will be distributed a 1-week supply (based on typical # cigarettes/day x 1.5) of NNC (.8 mg nicotine yield) study cigarettes to smoke exclusively during one baseline week. Next, ten participants will be randomly selected to receive the lowest VLNC nicotine dose (.03 mg nicotine yield) each of four pre-quit weeks (immediate reduction), and the remaining ten participants will receive cigarettes containing nicotine yields of .7 mg for week 1, .26 mg for week 2, .12 for week 3, and .03 for week 4 (gradual reduction). Thus, we will assess the feasibility of these tapering regimens in this pilot study. Study cigarettes provided will match participant's preference for menthol or non-menthol, with menthol doses adjusted slightly based on availability. Participants will be strongly

encouraged to smoke the study cigarettes exclusively, and to avoid smoking their usual brand or any NNC cigarettes.

Weekly Sessions. All participants will receive brief counseling at each weekly session (+/- 3 days) to support their use and understanding of the materials and exercises prescribed in the treatment workbook. These sessions will also be used to collect breath samples (for CO and alcohol testing) and vital signs (e.g., blood pressure, heart rate, and weight), daily smoking and craving assessments, and any negative health changes. If the participant's breath alcohol level is > 0.03 the interviewer will not start the session. Counselors may include two of the study investigators (Drs. Drobes and Simmons), doctoral students in clinical psychology at the University of South Florida, post-doctoral fellows, and research staff who have undergone training in the provision of smoking cessation counseling. Supervision meetings will be held with the PI or Co-I on a weekly or bi-weekly basis, depending on current cases and needs. Sessions may be observed and/or recorded during some of the study visits. This is done to monitor the session and for staff training purposes.

If a participant runs out of cigarettes or loses them, they will be allowed to return to the lab prior to the next scheduled visit to collect more study cigarettes. This will improve the validity of the data by avoiding the use of their usual brand of cigarettes. However if they lose their cigarettes a second time they will not be given more study product until the next visit.

Feedback from participants will be gathered using instruments described below as well as an in-depth debriefing interview. Results from the developmental pilot study will be reviewed by the full research team (including study consultants), who will make recommendations for additional modifications. The revised intervention will, in turn, be reviewed again by the study team in another potential iterative step. Once the team approves the intervention, it will be tested in the Stage 2 RCT, described below. We anticipate Study 1 to encompass the first 1.5 years of funding, as shown in Table 1.

Table 1. Expected Timeline of Intervention Development (Study 1)

Months	Activity
1-2	Initial draft of the treatment workbook, support materials, and evaluation measures
3-4	Review and feedback from study team and consultants
5-6	Modification of treatment workbook, support materials, and evaluation measures, with additional feedback from consultants, as necessary
7-14	Developmental pilot study of intervention (n=20)
15-16	Modification of treatment materials based on developmental pilot study
17-18	Review and feedback from study team and consultants; finalize intervention and materials

Feasibility Assessment. Despite a lack of standard methods for assessing feasibility, recent reviews have described several areas in which feasibility can be examined to support larger or more comprehensive studies (e.g., Arain et al., 2010; Bowen et al., 2009). The current pilot

study will examine three feasibility constructs that seem particularly relevant, as a prelude to the subsequent RCT:

1) Acceptability of the intervention will be assessed during as well as at the end of the treatment phase and at follow-up assessments, as follows: (1) Client Satisfaction Questionnaire (CSQ; Attkisson & Greenfield, 1994), a standard assessment of treatment satisfication; (2) a questionnaire developed for this study that asks the participant to evaluate specific aspects of the intervention workbook and counseling sessions; and (3) in-depth interviews conducted by the PI, a Co-I, or a member of the research staff using a series of guided questions to further glean reactions to specific treatment components, to follow-up on questionnaire answers, and to gather more nuanced information that could guide revisions to the intervention. In addition, we will attempt a structured telephone interview with any participant who drops out of the study early, in order to ascertain reactions to treatment and potential reasons for early withdrawal. Finally, study counselors will complete an evaluation form following each session. Other indices of acceptability will be the rate of adherence to both behavioral (i.e., completing assignments in the FE workbook) and pharmacological (i.e., smoking VLNC cigarettes as prescribed) instructions.

2) Demand will be estimated by noting accrual rates into the study. To quantify accrual, we will calculate recruitment costs per participant, with a target benchmark of ≤ $100 based on our previous clinical trials.

3) Practicality represents the broadest of the feasibility constructs. This will encompass the degree to which we are able to carry out all the elements of the planned developmental pilot study successfully and efficiently. This includes recruitment, screening, randomization, and treatment components. For these elements of the study, we will record number of attempts, duration, protocol deviations and errors, and suggestions for improvement.

Study 2. Randomized Controlled Trial (Aim 2), Intermediate Outcomes (Aim 3), and Mechanisms (Aim 4)

Study Goals and Overview. The primary goals of Study 2 are to test effects of the targeted intervention developed in Study 1 on smoking cessation (Aim 2) and intermediate outcomes (Aim 3), as well as to explore potential mechanisms that could guide future implantation of this treatment strategy (Aim 4). Approximately 300 treatment-seeking smokers will be screened using similar methods and inclusion/exclusion criteria as in Study 1. The expectation is that 80% of participants (n=208) will be eligible and randomized to one of four conditions (52 per condition) over a 3 year period. The four conditions will comprise a 2 x 2 between-subjects design, with facilitated extinction (targeted) treatment (present vs. absent) crossed with tapering schedule (immediate vs. gradual). As in Study 1, once a participant has been deemed eligible, a baseline week of smoking NNC study cigarettes will be followed by four weeks of smoking VLNC cigarettes, either through immediate or gradual reduction to the lowest level. Five weekly counseling sessions will occur (at the start of each week), and the Target Quit Date will occur one week after the fifth weekly session (+/- 3 days). On the Target Quit Date, participants will attend an additional session, including counseling as well as two tests of intermediate outcomes (cue reactivity and cigarette purchase task). Follow-up visits will occur at 2 and 6 months following the TQD (+/- 7 days). Please see Appendices on pages 33-34 for further details.

Exclusion Criteria: Study 2 exclusion criteria will match those of Study 1, with the following modifications: (a) use of smoking cessation medications will be exclusionary only for the past month and with the exception of sporadic use of NRT for non-cessation purposes, (b) use of

other tobacco products (including e-cigarettes) will only be exclusionary if participants use them as their primary source for tobacco intake, (c) will limit the number of participants from the same street address to one, and (d) will not include any participants that participated in the pre-cessation Varenicline study conducted at our facility due to the similarity in the protocols. Additionally, eligibility determination may require outside medical clearance, as determined necessary by the LMP, either prior to or after the screening visit.

Recruitment: Recruitment methods will include those used for Study 1, along with the following additions: (1) local fairs/ markets (e.g., USF "Bull Market"), (2) expanded social media platforms to include Reddit, Instagram, and Twitter, and (3) an online research panel (Plaza Research Tampa). Participants recruited through the research panel will receive an email about the study and will undergo a brief online survey and/or telephone pre-screening conducted by the research panel staff, which will include basic eligibility criteria (e.g., age, smoking status, interest in quitting smoking, and specific medical criteria). Additionally, we will establish a study webpage for participants to visit and obtain more information about the clinical trial. The study webpage link will be included within the advertisements. Once directed to this page, participants will have the option to call the study number, send an email, or provide their contact information.

Telephone Screening: Potential participants will be screened via the telephone prior to attending their first visit. In addition to assessing the criteria listed below for Study 2, participants must express interest in quitting within the next 30 days.

Baseline/Screening Session: Participants who meet study inclusion/exclusion criteria based on telephone/internet screening will be scheduled for a baseline/screening session at the Tobacco Research and Intervention Program (TRIP). Upon arrival for the session, study information will be presented and written informed consent will be obtained prior to any data collection. After consent is obtained, breath testing will occur to verify smoking status (CoVita Micro+ Smokerlyzer® CO meter (Bedfont Instruments) and alcohol abstinence (Intoximeter IV; St. Louis, MO). A urine sample will be collected to assess for psychoactive drug use (Andwin Scientifi 9-Panel Drug Card Test), to further verify smoking status if applicable(CO levels ≤ 8ppm) (i.e., cotinine; NicAlert; Nymox Corp., Hasbrouck Heights, NJ), and to ensure that women are not pregnant via HCG detection (Fisher HealthCare™ Sure-Vue™ Urine hCG Test Kits). Blood pressure and heart rate will be measured using a CritiCare monitor, with manual measurements taken as a back-up if elevations are detected. Next, the following general and smoking-related questionnaires and interviews will be administered, selected according to established psychometric properties and relevance to inclusion/exclusion criteria and study aims:

General: A demographic form and health status questionnaire will collect information on age, gender, race, ethnicity, socioeconomic status, employment, education, marital status, height, weight, current health status, medical history, and current medications. An alcohol use questionnaire will be given to collect alcohol use information over the past month (NIAAA, 2003) as well as a drug use questionnaire that will capture use over the past year. The MINI International Neuropsychiatric Interview (v. 7, 1/5/15; Sheehan et al., 1998) will be administered by trained staff to diagnose DSM-V Axis I disorders (only sections relevant to inclusion/exclusion criteria will be administered). The Prime MD, a brief questionnaire developed for evaluation of mental disorders by primary care physicians (Spitzer et al., 1999), will be administered, as well as the Beck Depression Inventory (BDI; Beck, Ward, & Mendelson, 1961), if applicable, to assess depression in participants who endorse suicidal ideation or Major Depressive Disorder on the Prime MD. Participants will also complete a contact information

sheet for two family members and/or acquaintances that the study team can communicate with in the instance that subjects become lost to follow-up. Lastly, participants will be asked to read and sign an agreement that summarizes study expectations (e.g., using only study cigarettes, attending study visits, and completing required assessments according to the study schedule).

Smoking-related: A detailed smoking history will be obtained using a Tobacco Use History questionnaire and the Smoking Timeline-Follow Back interview (Brown et al., 1998). The Timeline-Follow Back method will also be used to assess alcohol and other drug use over the past 30 days (Sobell & Sobell, 1992). Nicotine dependence will be assessed using the Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991) and the Wisconsin Inventory of Smoking Dependence Motives (WISDM-68; Piper et al., 2004). The (Brief SCQ-A) Brief Smoking Consequences Questionnaire-Adult (Rash & Copeland, 2008) will be administered to assess beliefs about the consequences of smoking a cigarette. A Nicotine Consequences Questionnaire (Hendricks & Brandon, 2008) will be administered to assess beliefs about the consequences of nicotine. In addition, the Cigarette Purchase Task (CPT), the Cigarette Evaluation Scale (CES) and the Questionnaire of Smoking Urges Brief (QSU-brief) will be administered at baseline to assess motivation to smoke and perceived effects from smoking their usual brand. Motivation to quit smoking will be assessed using the Contemplation Ladder (Biener & Abrams, 1991), a continuous index of quitting motivation on a 0-10 scale.

Intervention Phase. As in Study 1, all participants will be given a supply of normal nicotine content (NNC; .8 mg yield) study cigarettes to smoke for a baseline week, based on typical # cigarettes/day x 1.5. However, if a participant normally smokes 120mm cigarettes, then the amount supplied will be determined by multiplying their typical number of cigarettes/day x 2 (because the Spectrum cigarettes are regular length at approximately 80mm). This will introduce participants to the taste and feel of Spectrum research cigarettes, prior to receiving reduced nicotine cigarettes, thereby avoiding the confounding of changing brand and nicotine content simultaneously. Prior to the baseline session, participants will be randomly assigned to one of four treatment conditions, that vary according to a 2 x 2 between subject design: (1) targeted intervention with immediate transition to VLNC cigarettes, (2) targeted intervention with gradual transition to VLNC cigarettes, (3) standard intervention with immediate transition to VLNC cigarettes, (4) standard intervention with gradual transition to VLNC cigarettes. Overall, the intervention phase will consist of six visits, with five of them preceding the TQD which will occur one week after the fifth weekly session. The sixth session will occur on the TQD. At each of the pre-quit visits, participants will (1) receive their supply of study cigarettes for the upcoming week, (2) complete assessments related to compliance and reactions to assigned study cigarettes, (3) answer questions regarding health changes (if any) and date/length of last menstrual period for pre-menopausal women (to assess potential pregnancy), which will be documented on the 'Health Changes Questionnaire' (4) complete a Cigarette Purchase Task for their study and usual brand cigarettes (5) complete the QSU-brief for study and usual brand cigarettes (6) complete a Cigarette Evaluation Scale for the study cigarettes (7) complete the Drug Effects/Liking Scale for their study cigarettes (8) complete the Timeline-Follow Back interview to update their smoking, alcohol, and drug use since the prior visit*,* and (9) receive brief counseling according to condition. As in Study 1, if the participant's breath alcohol level is > 0.03 the researcher will not start the session.

Based on participant and counselor feedback from Study 1, the FE workbook was converted to a series of weekly booklets. The content is similar to what was included in the pilot study, but the workbook series now includes additional cessation-related advice and enhanced graphics. The targeted intervention will consist of the FE workbook series and supportive counseling (as developed and refined in Study 1), whereas the standard intervention will consist of the "Clearing the Air" booklet (National Cancer Institute; NIH Publication No. 11-1647), along

with a brief study introduction booklet which will explain the rationale for using reduced nicotine cigarettes as a cessation aid. Additionally, the standard intervention will entail an equal duration (relative to targeted intervention) of cognitive-behavioral smoking cessation counseling that follow recommendations from the USPHS Clinical Practice Guidelines along with supplemental handouts (Fiore et al., 2008). Counseling sessions for all conditions will include discussion of compliance with smoking only study cigarettes, as well as other study procedures. Although all participants will be strongly encouraged to smoke only study cigarettes, they will be told there is not a penalty for use of non-study cigarettes, and that it is crucial for them to report any use of non-study cigarettes or other nicotine or tobacco products. The VLNC immediate and gradual tapering conditions will be as described above, with participants, counselors and experimenters blind as to condition assignment.

Target Quit Date Participants will attend a session on their Target Quit Date. During this visit, all study cigarettes distributed during their prior visit will be collected, additional cessation counseling will be provided, physiological measures (i.e., carbon monoxide, breath alcohol, blood pressure, and heart rate) will be collected, and possible health changes will be assessed. Participants will also complete a Cigarette Evaluation Scale for their study cigarettes, the QSU for their study and usual brand cigarettes, the Drug Effects/Liking Scale for their study cigarettes, and the Timeline-Follow Back interview. In addition, two tasks will be administered to obtain intermediate smoking-related outcomes: cue-reactivity and cigarette purchase task (see descriptions below). Lastly, those randomized to the targeted intervention will be provided with the final Countdown booklet.

Intermediate Outcomes (Aim 3). Intervention effects on proximal smoking outcomes (as indicators of potential effects on long-term outcomes) will be assessed using two validated tasks:

1) **Cue Reactivity:** The cue reactivity task will assess the effect of VLNC cigarettes and facilitated extinction techniques on cue-provoked cravings. A validated picture-viewing paradigm will be used to assess cue reactivity (e.g., Brandon et al., 2011; Brandon et al., in press). Twelve (12) smoking-related and 12 neutral control images will be randomly presented to each participant while craving measures are obtained. Smoking cues will include photos that have elicited substantial craving reports in our prior research. Neutral cues will consist of pictures from the International Affective Picture System (IAPS; Center for the Study of Emotion and Attention 1995) or other standardized picture sets or internet sources, and will include objects, people and situations that have been rated as neither pleasant, unpleasant, or arousing. Different sets of pictures will be counterbalanced across the two cue reactivity assessments to minimize familiarization. During the baseline and target quit date visits, participants will be instructed to view the 24 pictures on a high resolution computer monitor located 2.5 ft. in front of them, for 6 seconds each. Participants will be instructed to watch each picture for the entire time that it is displayed. Following picture offset, subjective smoking craving ratings will be obtained on a visual-analog scale. The cue reactivity assessment will take approximately 12 minutes to complete.

2) **Cigarette Purchase Task:** This task will be used to assess the reward value of cigarettes throughout the treatment period. Participants will be asked to report the number of cigarettes that they would hypothetically consume in a day at various costs (Jacobs & Bickel, 1999). This task will be completed by participants each week; the study cigarette version will be administered after the screening/baseline visit and through the follow-up phase, while the usual brand cigarette version will be administered at every visit (inclusive of the screening/baseline session). Several indices of demand are generated from the raw values, including demand

intensity (consumption at zero price), Omax (maximum amount of money allocated to cigarettes), breakpoint (the first price at which a participant reports zero consumption) and Pmax (the price at which Omax occurs). This task will indicate whether prolonged VLNC use reduces cigarette demand and increases sensitivity to increases in cigarette costs.

Smoking Cessation Outcomes:

1) **Daily Abstinence Assessments.** Daily abstinence for each of the first seven days of the quit attempt will be assessed through participant self-report. Depending on participant preference, they may be contacted through text, telephone, and/or e-mail. If contacted through email or text, participants will be prompted to a study survey link, where they will complete the brief assessment online.

2) **Follow-up Assessments**. Participants will attend follow-up sessions at 2 and 6 months following the TQD (+/- 7 days). Smoking status using established self-report and biochemical indices will be measured. As in Study 1, we will continue to obtain indices of feasibility and acceptability (see above) to inform and support future clinical trials and mechanistic studies to understand the effects of VLNC cigarettes for smoking cessation. At these sessions the participants will be asked about possible health changes, complete a drug use questionnaire, a Cigarette Purchase Task, the QSU for their study and usual brand cigarettes, and complete the Timeline-Follow Back interview. In addition, a brief questionnaire (the 2 and 6-month follow-up form) will capture their stage in the quitting process, use of additional cessation products/methods (if any), and wristband use for those randomized to the targeted intervention. Participants will be compensated ($30) for each follow-up session attended. If a participant is unable or unwilling to attend either of these follow-up visits in-person, we will attempt to obtain these data over the telephone. If participants conduct these follow-ups via the telephone, they will be provided a compensation of $30 (gift card) through the mail. If participants are unable to complete the follow-ups via the telephone or in-person, they will be mailed the 2 and 6-month follow-up questionnaire, accordingly. If a participant completes the 2 or 6-month follow-up questionnaire via the mail, they will receive a $20 gift card. If a participant is lost to follow-up after at least 5 contact attempts have been made, a certified letter will be mailed with a scheduled appointment time and a request to return investigational study product.

Retention: We will provide study participants with small items (e.g., notepads, pens, water bottles) upon completion of each visit (following the baseline session), to improve retention. In addition, a letter will be sent to participants reminding them of their upcoming 2 and 6-month follow-up visits accordingly. If study staff are unable to locate participants during the treatment or follow-up phase, third-party directory services may be utilized in order to reach them (i.e., whitepages.com).

Study Debriefing: After data collection from all participants is complete, participants will be mailed a letter informing them of their condition assignment (and preliminary findings, if available).

Data Entry: For both Study 1 and Study 2, forms will either be directly administered to the participants and then entered into REDCap by an experimenter at the end of each visit, or the forms will be filled out by the participant in REDCap. The paper forms entered into REDCap by an experimenter will then be entered in again (Double Data Entry) and compared to ensure accuracy.

VLNC Cigarette Procurement and Accountability. Until recently, there were no adequate research tools for examining effects of nicotine levels (without confounding with tar). Quest cigarettes (Vector Tobacco, Inc.) had three levels, but only one was below the proposed .17mg threshold for addiction (Benowitz & Henningfield, 1994). Fortunately, through a contract with NIDA, Spectrum cigarettes (22nd Century Group, Inc.) containing varying nicotine levels (via genetically engineered tobacco) are being produced specifically for research purposes, with production and testing overseen by the Research Triangle Institute (RTI; Research Triangle Park, NC). These research cigarettes are very similar to commercial cigarettes (e.g., manufacturing process, filter, paper), yet they are not currently marketed as a consumer brand. Nonetheless, the manufacturer is sponsoring clinical trials and plans to seek a clinical indication for smoking cessation. The PI will submit an Investigational Tobacco Product (ITP) application (as needed) to the FDA for authorization to use Spectrum cigarettes for the proposed research. The investigators and consultants have been using these cigarettes (and their predecessor -- Quest cigarettes) extensively for several years, and are thoroughly familiar with the procurement process (via the NIDA Drug Supply Program) and regulatory requirements. We do not anticipate any problem obtaining approval and the necessary supply of study cigarettes. Study participants will be required to keep track of all the cigarettes provided to them, and to return all unused cigarettes and empty cigarette packs to the laboratory each week during the pre-quit period. Any discrepancies in the product dispensed vs. returned will be discussed and recorded. Unopened packs of cigarettes may be re-distributed, and any remaining unused cigarettes (from opened packs) will be destroyed periodically.

Modifications Related to COVID-19
In order to prevent the spread of COVID-19, the study team may temporarily discontinue in-person regular and screening visits. During this time period, study staff may obtain questionnaire data and conduct counseling sessions remotely (i.e., over the telephone or a secure web-based platform). These measures are being applied to prioritize participant and staff safety during the COVID-19 outbreak, while maintaining the integrity of the study as much as possible.

Due to the nature of the COVID-19 pandemic we are building increased flexibility in order to progressively integrate face-to-face interactions in line with institutional guidelines and based on participant availability. The following adjustments will be implemented in order to minimize exposure and maintain study integrity during in-person assessments until institutional, local, and federal guidelines permit our return to regular operations:

- Participants may visit the facility to complete specific limited assessments, including: CO and BAL, pregnancy and urine toxicology, heart rate and blood pressure.
- Participants may visit the facility to complete questionnaires for the screening visit, and to receive and/or return study product at subsequent visits.
- Participants may be consented virtually (e.g., via Zoom) in order to minimize face-to-face interactions while they are at the facility.
- Participants may elect to have counseling sessions done virtually (e.g., via Zoom) while at the facility, or at home via the telephone or virtually (except for the screening visit, during which they will have counseling conducted virtually at the facility to ensure adherence to study procedures).
- Questionnaires may be administered virtually (e.g., via Zoom) while the participant is at the facility during the screening visit in order to minimize face-to-face interactions.

- Questionnaires that pertain to eligibility may be administered first and items that are not related to eligibility may be administered after a participant is deemed eligible during the screening visit.
- Questionnaires for treatment visits (Visits 2 through 6) and follow-up visits may be conducted remotely (i.e., over the telephone) to avoid extended visit duration at the research facility (please see relevant forms noted in the Appendix).
- BAL and CO devices will be sanitized after each use and the study team will alternate devices for participants to avoid contamination.

Statistical Considerations

Sample Size Determination. The planned sample size (n=20) for the developmental pilot study (Study 1; Aim 1) is based on considerations of practicality and usefulness. A primary focus of Study 1 will be on evaluation of feasibility (acceptability, demand, practicality) of the procedures, and determining potential improvements to incorporate into the subsequent RCT (Study 2). In the context of the goals and project timeline, the planned sample size for the developmental pilot study should provide the team with ample information to inform the RCT (Study 2). The planned sample size (n=208) for the RCT (Study 2) is based on considerations of statistical power and anticipated effects for the primary hypothesis regarding treatment outcomes (Aim 2). We assume those who receive the standard intervention (n=104) will achieve a 20% 7-day point prevalence abstinence rate at the 6-month follow-up. Based on an intent-to-treat data analytic approach and a two-sided alpha = .05, the proposed sample will have .80 power to detect approximately an 18% improvement in abstinence rate among those who receive the targeted intervention. This magnitude of improvement would be clinically significant, and worthy of further refinement and application. A similar magnitude of effect would be detectable as a function of tapering schedule. No interaction effects (between intervention and tapering schedule) are predicted. Power is likely to be greater for detecting treatment effects on dichotomous cessation outcomes at the 2-month follow-up, continuous cessation outcomes at both follow-up timepoints, and intermediate (proximal) behavioral outcomes (Aim 3). Moreover, within-condition correlations as small as 0.28, and total-sample incremental R^2 as low as 0.07 (based on six predictors) would be detected, suggesting that the moderator analyses (Aim 4) would be adequately powered to detect clinically significant effects.

Aim 1 - Feasibility. The developmental pilot study will obtain data that will help determine the feasibility of the targeted treatment materials and the methodology for examining its efficacy in Study 2. We conceptualize feasibility as a multidimensional construct, as suggested by the multiple indices (described above) that we will collect. Each feasibility index will either be compared to published norms (e.g., for the CSQ) or our prior experience with clinical trials for smoking cessation, or subject to evaluation by the investigative team (including consultants). We expect that we will be able to recruit adequate numbers of eligible participants during the study timeframe with efficient cost expenditures, retain 80% through the end of the treatment phase, and retain 70% through the end of the follow-up phase. Furthermore, indices of treatment acceptance and satisfaction for those who receive the targeted intervention are expected to be 80% or higher. Finally, participants are expected to comply with use of VLNC cigarettes (e.g., >80% exclusive use of VLNC cigarettes). For any indices that fall below expectations, the research team will judge the impact of its underperformance upon the planned RCT (Study 2) and/or treatment dissemination and implementation, and whether corrective actions are possible. The team will take performance across all indices into account when determining whether modifications are warranted prior to the planned RCT.

Aim 2 – Treatment Efficacy. Analyses will focus on the incremental efficacy of targeted intervention, in combination with two tapering regimens for transition to VLNC cigarettes during the pre-quit period, on clinical outcomes. The primary outcome variable will be 7-day point prevalence abstinence at each follow-up assessment, with secondary outcomes that include continuous abstinence since the TQD, days to first smoking lapse, and smoking reduction relative to baseline (see Ditre et al., 2012). Mixed modeling will be used to test hypotheses related to these treatment outcome effects. The advantages of these models is that they allow for data that is missing at random and are more flexible than repeated measures ANOVA in terms of the underlying variance/covariance matrix (Littell et al., 2006). For point prevalence and continuous abstinence variables, a 2 (intervention: targeted vs. standard) x 2 (transition: immediate vs. gradual) analysis will be used to test the independent and combined effects of each treatment factor on these cessation outcomes, using Generalized Estimating Equations (GEE) with a logistic function for dichotomous outcomes.

Aim 3 - Intermediate Outcomes. Aim 3 includes testing effects of the intervention on intermediate (proximal) outcomes during the cue reactivity and cigarette purchase tasks. Findings may support decisions regarding which tapering schedule is optimal for further testing and/or dissemination, and may provide insight as to the mechanisms that underlie positive cessation outcomes. As in Aim 2, mixed modeling will be used to independently test the effects of targeted intervention and tapering schedule on outcomes from these two paradigms. Indices of smoking-related behavior from each paradigm (cue reactivity: self-reported craving in response to smoking cues; cigarette purchase task: hypothetical cigarette consumption across a range of prices) will be examined through separate models that test effects of intervention (targeted vs. standard) and tapering schedule (immediate vs. gradual) on these outcomes. In addition, Generalized Estimating Equations (GEE) models with a logistic function will be used to examine intervention effects on dichotomous outcomes.

Aim 4 - Exploratory Mechanisms. As a Stage II study, we will evaluate potential moderators and mediators of treatment efficacy with VLNC cigarettes, as well as intermediate outcomes. Potential moderators include demographic variables (gender, age), smoking history, nicotine dependence, withdrawal sensitivity, and initial quit motivation. For these analyses, mixed models described for Aims 2 and 3 will be repeated, with potential moderator variables entered as interaction terms. Given multiple potential moderators and outcome variables, the Benjamini-Hochberg approach will be used to control the false discovery rate (FDR; Benjamini & Hochberg, 1995). Mediation analyses will examine smoking reinforcement, compliance with pre-quit VLNC smoking rate and other recommendations (e.g., smoking in multiple cue contexts), nicotine withdrawal during VLNC transition and post-TQD, and product perceptions (e.g., ratings of taste, likeability, and acceptability) as potential mediators of treatment effects on smoking cessation and intermediate outcomes. For these analyses, we will first apply a traditional *causal steps* approach (e.g., Baron & Kenny, 1986), using a series of regression equations to infer an indirect effect of the potential mediator. Regardless of the outcome from that approach, we will also utilize a bootstrapping approach in order to provide a more powerful and interpretable test of the indirect effects of potential mediators (Preacher & Hayes, 2008).

Study/Design Considerations

Biomarkers. We are not proposing extensive biomarker analyses in the present application. We considered this to be redundant with comprehensive safety analyses already undertaken with these and similar products, leading to the overall conclusion that they are no less safe than commercial cigarettes (already being used by all participants), and that they are not associated with sustained compensatory smoking that might increase toxicant exposure. By focusing on

intervention development and testing, we hope to reduce participant burden and expense, and more closely represent a real-world application of this potential treatment method. Nonetheless, we will carefully track smoking rate (all sessions), carbon monoxide (all sessions), and urinary cotinine (baseline and follow-up sessions, as applicable) levels, and use medically established cut-offs (established by the Center for the Evaluation of Nicotine in Cigarettes; U54, MPI's: Donny/Hatsukami) to guide decisions regarding early termination.

Project Timeline

Study 1 is expected to comprise the first 1.5 years of funding (see details above). Study 2 will be completed over the remaining 3.5 years (Table 2).

Table 2. Project Timeline

Task	Year 1		Year 2		Year 3		Year 4		Year 5	
Study 1	X	X	X							
Study 2 - Recruitment				X	X	X	X	X	X	
Study 2 - Follow-up Assessments					X	X	X	X	X	X

Note: Expected number of sessions for Study 2 is 208 screening/baseline, 198 week 1 pre-quit, 188 week 2 pre-quit, 178week 3 pre-quit, 168 week 4 pre-quit, 158 target quit date, 148 2-month follow-up and 138 6-month follow-up which equals 1384 sessions in 42 months. This is approximately 33 sessions/month.

Participant Compensation (cash or gift card):

- Participants will receive $25 for completing the baseline session. If an additional visit is needed (e.g., to rescreen for alcohol or drugs, or due to a pending LMP/PI/Co-I eligibility determination), a $20 payment will be provided for completing the additional visit.

- Following the screening visit, they will receive $25 for completing each weekly session (including Target Quit Date for Study 2), and an additional $10 for each session in which they arrive on time, without rescheduling, and bring the treatment booklet with tracking exercises completed.

- COVID-19 considerations: The $10 weekly session bonus will apply to timeliness and preparedness regarding the in-person assessments, as well as the timely completion of telephone assessments.
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- For Study 1 they will receive $35 for completing a follow-up session after the TQD. This session will include brief counseling, as well as obtaining feedback using a standardized form and a debriefing interview.

- For Study 2 participants will receive $30 for each of the follow up sessions (2 month and 6 months from the TQD) that they attend in-person. If these assessments are conducted over the telephone they will be compensated with a $30 gift card. If the assessments are conducted via the mail by completing the 2 or 6-month follow-up questionnaire, they will receive a $20 gift card.

- Participants will be paid $10 if dismissed early from the screening session based on meeting any of the following exclusion criteria: breath alcohol test >0.01, positive toxicology screen minus valid Rx and THC, positive pregnancy test, Systolic BP >159 or <90, Diastolic BP >99 or <50, HR >104 or <45.

- Participants will not receive any compensation if they do not pass the smoking confirmation measurements (if CO ≤ 8ppm, and NicAlert Strip ≤2).

- Participants dismissed early from any subsequent sessions (e.g., breath alcohol test >0.03) will be paid $10.

- Participants who drop from the study during the treatment phase and attend a visit to return study product will be paid $25.

Future Directions

The proposed project will develop and pilot test a targeted smoking cessation intervention strategy based on VLNC cigarette smoking during the pre-quit period, and then conduct an initial RCT to test this cessation method in the context of two distinct nicotine tapering regimens. Future work will likely entail improvements in the targeted treatment materials based on the experience from this project, as well as a determination as to which tapering schedule (immediate vs. gradual) is optimal in terms of acceptability, practicality and effects on cessation-related and intermediate outcomes. The optimal intervention from this project could then be compared to existing validated treatment strategies, such as NRT. Subsequent research may also incorporate newer mobile technologies to more precisely track adherence during the pre-quit period and cessation in the post-quit period. In addition, the current proposal will begin to explore several potential moderators and mediators of treatment efficacy, whereas later research may include replication testing (with increased power) to further refine an understanding of how (and for whom) this cessation approach may be optimal. Future research will also continue to examine the optimal amount, type, and duration of pre-quit VLNC smoking for successful cessation outcomes, as well as how VLNC cessation strategies may be used in in the context of potential FDA regulation to lower nicotine standards in cigarettes at a national level. Finally, successful outcomes in the current project will lead to work intended to broadly disseminate a cessation strategy based on VLNC cigarettes.

E. PROTECTION OF HUMAN SUBJECTS

Risk to the Subjects

Human Subjects Involvement and Characteristics: Cigarette smokers (n=228) who are interested in quitting will be recruited for a developmental pilot study (Study 1; n=20) or a randomized controlled trial (RCT; Study 2; n=208). Males and females will be recruited equally, and ethnic/racial distributions are expected to closely represent the Tampa Bay area. Participants who pass an initial telephone or web-based screening will be invited to attend a

detailed screening/baseline session at the Tobacco Research and Intervention Program (TRIP) of the Moffitt Cancer Center. During this session, informed consent will be obtained, followed by administration of questionnaire and interview-based assessments to determine eligibility based on inclusion/exclusion criteria (see below). Eligible participants will receive study cigarettes for five weeks, using either an immediate or gradual tapering regimen. All participants will receive written materials to assist in their quit attempt, as well as in-person smoking cessation counseling. In the RCT only, participants will engage in two intermediate tests of smoking behavior, and will attend follow-up sessions 2- and 6-months following a target quit date (TQD). Participants will be compensated for attendance at treatment and follow-up sessions, for completing workbook assignments and data collection activities, and for their performance on smoking behavior tests. The potential compensation for each participant in the developmental pilot study (Study 1) is $200, and for the RCT (Study 2) the potential compensation is $260. The eligibility criteria for both studies are as follows:

Inclusion criteria: (a) ≥18 years of age; (b) smoke at least 5 cigarettes daily for the past year; (c) expired-air carbon monoxide (CO) > 8 ppm (if ≤ 8 ppm, then NicAlert Strip > 2); (d) current motivation to quit smoking; and (e) able to speak and read English sufficiently for completion of consent form and questionnaires.

Exclusion criteria, Study 1: (a) pregnant or breastfeeding; (b) significant unstable medical/psychiatric or substance use disorders, or medically/psychiatrically at risk in the judgment of the study physician (or licensed medical professional designated to consult in his absence) or PI; (c) positive urine screen for cocaine, opiates, methadone, benzodiazepines, barbiturates, amphetamines, methamphetamines, or PCP (NOTES: THC will be tested but will not be an exclusionary criterion; participants with valid prescriptions for opiates, benzodiazepines, barbiturates, amphetamines or methadone will not be excluded; participants failing the toxicology screen will be allowed to re-screen once); (d) blood alcohol level > 0.01 (one re-screen allowed); (e) binge alcohol drinking (4/5 [female/male] drinks per day more than 9 days in the past month); (f) systolic/diastolic BP greater than or equal to 160/100, or below 90/50 (one re-screen allowed); (g) heart rate greater than or equal to 105 bpm, or below 45 bpm (one re-screen allowed); (h) ever used reduced nicotine cigarettes; (i) smoke 'roll your own' cigarettes exclusively, (j) used smoking cessation medications within the past three months-, (k) are currently enrolled in a smoking cessation program, (l) actively trying to quit; (m) used other tobacco products (including e-cigarettes) more than 9 days in the past month, and (n) currently taking the following medications:

Phenytoin [Brand Name: Dilantin]
Carbamazepine [Brand Name: Tegretol, Carbatrol, Equetro, Epitol]
Oxcarbazepine [Brand Name: Trileptal]
Primidone [Brand Name: Mysoline]
Phenobarbital
Bendamustine (Treanda)
Clopidogrel (Plavix)

- Clozapine (Clozaril, FazaClo)
- Erlotinib (Tarceva)
- Flecainide (Tambocor)
- Fluvoxamine (Luvox)
- Irinotecan (Camptosar)
- Olanzapine (Zyprexa)
- Ropinirole (Requip)
- Tacrine (Cognex)
- Theophylline (Theo Dur, etc.)

Exclusion Criteria, Study 2: Study 2 exclusion criteria will match those of Study 1, with the following modifications: (a) use of smoking cessation medications will be exclusionary only for the past month and with the exception of sporadic use of NRT for non-cessation purposes, (b) use of other tobacco products (including e-cigarettes) will only be exclusionary if participants use them as their primary source for tobacco intake, and (c) will only enroll one participant per

street address in order to reduce risk for dissemination of information regarding differences in treatment groups.

Sources of Materials: Data collected for research purposes only include: (1) biological specimens, including carbon monoxide (CO) and alcohol breath tests (to verify smoking status and abstinence compliance), and a urine specimen (for drug, cotinine and pregnancy testing); (2) interview and self-report measures (e.g., demographic, medical, psychological, smoking behavior, treatment satisfaction and compliance); and (3) self-reported outcomes during cue reactivity and cigarette purchase tasks.

Potential Risks: Potential risks include loss of confidentiality or discomfort while completing interview or questionnaire assessments. The measures to be used are generally benign, and protection of confidentiality is a high priority within our lab (see below). In addition, participants may experience elevated nicotine withdrawal and/or cravings during pre-quit smoking of very low nicotine content (VLNC) cigarettes or during a smoking cessation attempt. Nicotine withdrawal symptoms include: irritability, frustration, or anger; anxiety; difficulty concentrating; increased appetite; restlessness; depressed mood; and insomnia. Nicotine withdrawal symptoms are uncomfortable but of minimal risk. Finally, the research cigarettes have been previously tested and found to be safe, with side effects that are similar to usual brand cigarettes. In prior studies, compensatory smoking was minimal and transient, and higher levels of toxicant exposure was generally not observed. Nonetheless, compensatory smoking may occur and lead to increased levels of toxicant exposure.

Avoiding Risks to Fetus:
If participants choose to be sexually active, they should use an appropriate “double barrier” method of birth control (such as female use of a diaphragm, intrauterine device (IUD), or contraceptive sponge, in addition to male use of a condom) or the female should be using prescribed “birth control” pills, injections or implants. Female participants with child-bearing potential will be tested for pregnancy at the baseline session, the third weekly visit, and on the Target Quit Date session. If a participant becomes pregnant during the study she will be withdrawn from the study. Approximately 30 days after being withdrawn, the research staff will contact the participant to confirm her due date. The licensed medical professional will follow-up with the participant after delivery to ask questions about the baby’s health.

Adequacy of Protection Against Risk

Recruitment and Informed Consent: Participants will be recruited from the community via advertising methods that have been successful in our recent studies, including: newspaper and radio ads, press releases, a research panel, flyers, public postings, PSA’s, online sources (e.g., Craigslist), social media (e.g., Facebook, Reddit, Instagram), local fairs/markets (including collection of contact information for potentially interested people), word of mouth, and from an existing database of previous study participants at the Tobacco Research and Intervention Program (TRIP). Additionally, a study website will provide a basic description of the study, and direct interested individuals to call, e-mail, or complete a brief on-line contact form to obtain more information. All potential participants will have the study explained to them in full by qualified staff. This will include an explanation of risks and benefits, as well as the monetary compensation schedule. Participants will be informed that they can freely withdraw from the study at any time without penalty. All potential participants will be given an opportunity to ask questions prior to providing consent. Only after the participant and the investigator are fully satisfied that the participant understands the purpose of the study, the confidentiality of the data,

the procedures, the risks/benefits and their rights as a research participant will the consent form be signed and the participant undergo detailed screening procedures.

Protection Against Risk: In order to protect participant confidentiality, all references to specific individuals are removed from files stored on computer media, and code numbers are assigned to all written and computer-stored research data. Participant names will only appear on signed Informed Consent documents, and on a separate study log, both of which will be stored separately from all research data in a locked cabinet. All participants will be informed that they may withdraw from the study at any time without penalty. The level of nicotine withdrawal associated with overnight smoking abstinence is typically not severe, and participants will be informed of potential symptoms they may experience. Similarly, the risks of nicotine withdrawal and craving during a smoking cessation attempt will be described to participants, and should be mitigated by pre-quit tapering of nicotine levels in study cigarettes. Suggestions for further minimizing withdrawal symptoms will be provided via written intervention materials and counseling sessions. Participants will be instructed to call the PI, smoking cessation counselor, or study physician (or licensed medical professional designated to consult in his absence) in the event of excessive side effects while smoking VLNC cigarettes or after the TQD.

Participants who endorse negative mental health changes or suicidal ideation at any visit will complete the Prime MD at that session. Indications of major depressive disorder or other psychiatric conditions will trigger administration of the BDI, which will be reviewed by the LMP and/or PI. An 'Adverse Event Form' and 'Blood Pressure and Heart Rate Symptom Checklist' will be completed and brought to the LMP (or PI/Co-I in lieu of LMP) if an automatic and subsequent manual heart rate measurement during the same visit is out of range (blood pressure at or above 160/100 or below 90/50; heart rate at or above 105 bpm or below 45 bpm).

Collection and Reporting of AEs and SAEs. At each study visit, participants will be asked to report any negative health changes on the 'Health Changes Questionnaire' since the prior visit. Any negative changes will be recorded on an Adverse Event (AE) form. This form will include fields for describing the adverse event, as well as the onset, duration, status (completed vs. ongoing), and any steps taken to resolve the AE. The form will be reviewed by the study physician (or by the study investigators during the follow-up phase) prior to the next study visit, and the AE will be monitored until it is marked as resolved. All AEs will be assessed to determine if they meet criteria for an SAE. Monitoring by the PI will be conducted on an ongoing basis and monitoring by the IRB is conducted at the continuing reviews as scheduled by the IRB and upon receiving reports of AEs from the PI.

Management of SAEs and Other Study Risks. Serious adverse events (SAEs), as defined by the FDA, will be systematically evaluated at each study visit. All product-related adverse events of a non-serious nature will be reported to the IRB at the time of annual renewal. Any SAE, whether or not related to study product or participation, will be reported to the IRB, the study sponsor (State of Florida Department of Health), and the FDA. A participant may be discontinued from the study or withheld from study product if the study physician (or his designee) determines it is the best course of action in order to protect the safety of the participant. In the event that a participant either withdraws from the study or the investigator or study physician(or licensed medical professional designated to consult in his absence) decides to discontinue a participant due to an SAE, the participant will have appropriate follow-up medical monitoring. The participant experiencing a SAE will be followed until the problem resolved, stabilizes, or is clearly unrelated to the study cigarettes. Outcome of SAEs will be periodically reported and a summary of SAEs will be provided in study progress reports to the IRB, sponsor, and FDA.

Stopping Rules. For the participant's protection, participants will be withdrawn immediately from the study if any of the following occur:

1. Cardiovascular disease (CVD) event: typically includes MI (heart attack), PTCA (angioplasty/stenting), bypass surgery, stroke, peripheral vascular disease (arterial blockages in arms or legs leading to procedure or surgery). Less common CVD problems would be new cardiac arrhythmias (e.g., new atrial fibrillation) or new valvular disease (e.g., mitral or aortic regurgitation.)
2. DVT/PE (deep vein thrombosis/pulmonary embolism, i.e., blood clots in the venous system)
3. Suicide Attempt: A participant will be withdrawn if he/she attempts suicide at any time during participation in the study.
4. Psychiatric Hospitalization: A participant will be withdrawn if he/she is hospitalized for psychiatric reasons at any time during participation in the study.
5. Pregnancy: If a participant indicates she is pregnant or has a positive pregnancy test, she will be withdrawn from the study. Approximately 30 days after being withdrawn, the research staff will contact the participant to confirm her due date. This event will remain open until delivery. At that time the study physician (or licensed medical professional designated to consult in his absence) will contact the participant to ask a few questions about the baby's health and will update the open 'Adverse Event Form'.
6. Expired breath CO increase: A participant will be withdrawn from the study if the average of two consecutive CO readings during the same visit is 100 ppm or greater.

Withdrawal Rules: In order to detect significant increases in smoking due to study cigarettes (e.g., compensatory smoking), which could signal increased cardiovascular risk, we will apply guidelines for discontinuation of VLNC smoking due to marked increases in carbon monoxide (CO) levels or smoking, as follows:

a) If the average of two consecutive CO readings during the same visit is 100 ppm or greater
b) If both of the following criteria are met for two consecutive weeks:
    1. Cigarettes per day (CPD) increase: The average CPD increases by more than 100% from the average CPD during baseline
    2. Expired breath CO increase; If the average of two consecutive CO measurements in the same visit is:
        i. CO is greater than 50 ppm if CO at baseline is < 20 ppm
        ii. CO is greater than 60 ppm if CO at baseline is 20 - 34 ppm
        iii. CO is greater than 70 ppm if CO at baseline is 35 - 49 ppm
        iv. CO is greater than 80 ppm if CO at baseline is 50 - 64 ppm
        v. CO is greater than 90 ppm if CO at baseline is 65 - 80 ppm

The CO stopping criteria are derived from recent and ongoing large scale (multi-site) trials with reduced nicotine cigarettes (U54 DA031659; MPI's: Donny, Hatsukami). The criteria represent CO increases of two types: (1) absolute, based on an unacceptable CO level (i.e., 100 ppm) at any study visit, and (2) relative, adjusted according to individually determined baseline values. As CO can be quite variable, relative values are intended to balance increases in individual risk while accounting for baseline values.

The following will be monitored and can lead to the participant being withdrawn by the PI or study physician (or licensed medical professional designated to consult in his absence):

1. Cigarettes per day increase: Continued participation will be evaluated by the site PI if the average number of cigarettes per day (CPD) increases by more than 100% from the average CPD at baseline.
2. Blood pressure (BP) or heart rate (HR) changes: If any of the following occur post-enrollment: 1) BP is at or above 160/100 or below 90/50, or 2) HR is at or above 105 bpm or below 45 bpm a manual blood pressure and heart rate measurement will be taken after 10 minutes have passed.
3. Expired breath CO increase: If the average of two consecutive CO measurements in the same visit is:
    i. CO is greater than 50 ppm if CO at Baseline is <20 ppm.
    ii. CO is greater than 60 ppm if CO at Baseline is 20 – 34 ppm.
    iii. CO is greater than 70 ppm if CO at Baseline is 35 – 49 ppm.
    iv. CO is greater than 80 ppm if CO at Baseline is 50 – 64 ppm.
    v. CO is greater than 90 ppm if CO at Baseline is 65 – 80 ppm.
4. Any hospitalization or debilitation in which participation in the study could be detrimental to the recovery process. This will be self-reported by the participant and will be reviewed by the PI and study physician (or licensed medical professional designated to consult in his absence) to determine whether continued participation in the study is appropriate.
5. If a participant is behaving in an inappropriate or threatening manner, admits to lying about eligibility criteria, is participating in other smoking research studies that could affect the primary outcome measures, or is not complying with key study procedures.

Potential Benefits of the Proposed Research to the Subjects and Others

Participants may benefit from receiving assistance to quit smoking. Although it is premature to suggest that the novel “facilitated extinction” intervention to be developed and tested in this project will enhance smoking cessation outcomes, all participants will receive standard written and verbal assistance in quitting using widely accepted and routine clinical methods. Ultimately, development of intervention materials that may improve smoking cessation outcomes with VLNC cigarettes may reduce smoking rates. The benefits of smoking cessation are well established for individuals and society at large.

Importance of Knowledge to be Gained

Cigarette smoking is a major cause of avoidable illness and death. The knowledge gained from this research might contribute to the development of novel strategies for smoking cessation, and ultimately may improve smoking cessation rates. Consequently, findings from this and related studies may decrease the morbidity and mortality associated with smoking. Given the minimal risks associated with the study, the potential gains far outweigh risks.

Data and Safety Monitoring Plan

The PI, Vani N. Simmons, Ph.D., will be responsible for executing the Data and Safety Monitoring Plan (DSMP), and complying with all reporting requirements. The PI will provide a summary of the Data and Safety Monitoring (DSM) report to NIH on an annual basis. The DSM

report will include participants' sociodemographic characteristics, recruitment rates, any quality assurance or regulatory issues during the past year, summary of Adverse Events (AEs) and Serious Adverse Events (SAEs), and any actions or changes with respect to the protocol. The DSM report to NIH will also include results of any interim data analyses.

Questionnaire/interview data will be collected using paper forms and will only be identified with the participant's study ID. The PI will keep the codes that link the name of the participant and the study ID confidential in a secured cabinet. Data accuracy will be subject to random audit. Monthly data management reports will be made to the PI, including data entry progress, error rates, range checks, and general descriptive statistics. The investigators will conduct all data analyses using primarily SAS and SPSS software.

Regulatory documents and case report forms will be reviewed routinely by the MCC Clinical Research Monitoring Core for accuracy, completeness and source verification of data entry, validation of appropriate informed consent process, adherence to study procedures, and reporting of SAEs and protocol deviations according to MCC Monitoring Policies.

Trained study staff will monitor participants closely throughout each treatment and lab session, and either the study PI or a Co-Investigator will be at the study site to address any concerns that arise. Research staff will report Adverse Events (AE) to the PI and capture the AE data in Oncore, Moffitt's Clinical Trials Database. Serious Adverse Events (using the FDA definition of SAEs) will be reported according to the requirements of the FDA, Moffitt's Protocol Monitoring Committee, and the IRB. Any IRB actions in relation to this protocol will also be reported to NIH.

F. INCLUSION OF WOMEN AND MINORITIES

Inclusion of Women

We plan to recruit equal numbers of males and females. Gender will be examined as a potential moderator in predicting cessation or intermediate outcomes, given that men and women may be differentially reactive to the presence of nicotine during their cessation attempts. We will also be interested in determining if there are gender differences in feasibility-related outcomes (e.g., recruitment, retention, acceptances, satisfaction, and compliance).

Inclusion of Minorities

In terms of minority participation, the two largest counties in the Tampa Bay Area – Hillsborough and Pinellas – will serve as the recruitment base for the proposed research. Based on the 2010 U.S. Census, there are over 2.1 million residents in these counties, with the following racial distributions in Hillsborough and Pinellas, respectively 71.3% and 82.1% White, 16.7% and 10.3% African American, 3.4% and 3.0% Asian, with less than 1% from any other single racial group. Hispanics represent 24.9% and 8.0% of the population in Hillsborough and Pinellas, respectively. We expect our sample to closely reflect this racial and ethnic distribution, as it has in our recent studies.

LITERATURE CITED

Arain, M., Campbell, M.J., Cooper, C.L., & Lancaster, G.A. (2010). What is a pilot or feasibility study? A review of current practice and editorial policy. *BMC Medical Research Methodology, 10,* 67.

Attkisson, C.C., & Greenfield, T.K. (1994) Client satisfaction questionnaire-8 and service satisfaction scale-30. In M. E. Maruish (Ed.), *The use of psychological testing for treatment planning and outcome assessment* (pp. 402-420). Lawrence Erlbaum Associates: Hillsdale NJ.

Baker, T.B., Piper, M.E., McCarthy, D.E., Majeskie, M.R., & Fiore, M.C. (2004). Addiction motivation reformulated: An affective processing model of negative reinforcement. *Psychological Review 111,* 33-51.

Baron, R.M., & Kenny, D.A. (1986). The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology, 51*, 1173-1182.

Beck, A. T., Ward C., & Mendelson, M. (1961). Beck Depression Inventory (BDI). *Archives of General Psychiatry, 4*, 561–571.

Becker, K.M., Rose, J.E., & Albino, A.P. (2008). A randomized trial of nicotine replacement therapy in combination with reduced-nicotine cigarettes for smoking cessation. *Nicotine & Tobacco Research, 10,* 1139-1148.

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. Journal of the Roayl Statistical Society. Series B (Methodological), 289-300.

Benowitz, N. L. & Henningfield, J. E. (1994). Establishing a nicotine threshold for addiction. The implications for tobacco regulation. *New England Journal of Medicine, 331,* 123-125. doi: 10.1056/NEJM199407143310212.

Benowitz, N. L., Dains, K. M., Hall, S. M., Stewart, S., Wilson, M., Dempsey, D. A., et al. (2009). Progressive commercial cigarette yield reduction: Biochemical exposure and behavioral assessment. *Cancer Epidemiology, Biomarkers & Prevention, 18,* 876-883. doi: 10.1158/1055-9965.EPI-08-0731.

Benowitz, N. L., Hall, S. M., Stewart, S., Wilson, M., Dempsey, D. A., & Jacob, P. (2007). Nicotine and carcinogen exposure with smoking of progressively reduced nicotine content cigarette. *Cancer Epidemiology, Biomarkers & Prevention, 16,* 2479-2485. doi: 10.1158/1055-9965.EPI-07-0393.

Biener, L., & Abrams, D.B. (1991) Contemplation Ladder: Validation of a measure of readiness to consider smoking cessation. *Health Psychology, 10,* 360-365.

Bouton, M.E. (2000). A learning theory perspective on lapse, relapse, and the maintenance of behavior change. *Health Psychology, 19,* 57-63.

Bouton, M.E. (2002). Context, ambiguity, and unlearning: Sources of relapse after behavioral extinction. *Biological Psychiatry, 52,* 976-86.

Bouton, M.E., Todd, T.P., Vurbic, D., & Winterbauer, N.E. (2011). Renewal after the extinction of free operant behavior. *Learning and Behavior, 39,* 57-67.

Bowen, D.J., Kreuter, M., Spring, B., Cofta-Woerpel, L., Linnan, L., Weiner, D., Bakken, S., Kaplan, C.P., Squiers, L., Fabrizio, C., & Fernandez, M. (2009). How we design feasibility studies, *American Journal of Preventative Medicine, 36,* 452-457.

Brandon T.H., Drobes D.J., Unrod M., Heckman B.W., Oliver J.A., Roetzheim R.C., Karver S.B., Small B.J. (2011). Varenicline effects on craving, cue reactivity, and smoking reward. *Psychopharmacology,* 218:391-403.

Brandon, T.H., Unrod, M., Drobes, D.J., Sutton, S.K., Hawk, L.W., Simmons, V.N., Brandon, K.O., Roetzheim, R.G., Meltzer, L.R., Miller, R.R., Cahill, S.P. (in press). Facilitated

extinction training to improve pharmacotherapy for smoking cessation: A pilot feasibility trial. *Nicotine & Tobacco Research*. 2017 Sep 12. doi: 10.1093/ntr/ntx203. [Epub ahead of print].

Brigham, J., Lessov-Schlaggar, C.N., Javitz, H.S., McElroy, M., Krasnow, R.E., & Swan, G.E. (2008). Reliability of adult retrospective recall of lifetime tobacco use. *Nicotine & Tobacco Research, 10*, 287–299.

Brooks, D.C., & Bouton, M.E. (1994). A retrieval cue for extinction attenuates response recovery (renewal) caused by a return to the conditioning context. *Experimental Psychology: Animal Behavioral Processes, 20,* 366-379.

Brown, R.A., Burgess, E.S., Sales, S.D., Whiteley, J.A., Evans, M.D., & Miller, I.W. (1998). Reliability and validity of a smoking timeline follow-back interview. *Psychology of Addictive Behaviors, 12*, 101-112.

Caggiula, A. R., Donny, E. C., White, A. R., Chaudhri, N., Booth, S., Gharib, M. A., et al. (2001). Cue dependency of nicotine self-administration and smoking. *Pharmacology Biochemistry & Behavior, 70*, 515-530. doi: 10.1016/S0091-3057(01)00676-1.

Collins, B.N., & Brandon, T.H. (2002). Effects of extinction context and retrieval cues on alcohol cue reactivity among nonalcoholic drinkers. *Journal of Consulting and Clinical Psychology, 70, 3*90-397.

Conklin, C. A. & Tiffany S. T. (2002). Applying extinction research and theory to cue-exposure addiction treatments. *Addiction, 97*, 155-167. doi: 10.1046/j.1360-0443.2002.00014.x.

Corrigall, W. A. (1992). A rodent model for nicotine self-administration. *Neuromethods: Animal Models of Drug Addiction*, *24***,** 315-344. doi: 10.1385/0-89603-217-5:315.

Corrigall, W. A., & Coen, K. M. (1989). Nicotine maintains robust self-administration in rats on a limited-access schedule. *Psychopharmacology, 99*, 473-478. doi: 10.1007/BF00589894.

Cox, L. S., Tiffany, S. T., & Christen, A. G. (2001). Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine & Tobacco Research, 3,* 7-16. doi: 10.1080/14622200124218.

Ditre, J.W., Oliver, J.A., Myrick, H., Henderson, S., Saladin, M.E., & Drobes, D.J. (2012). Effects of divalproex on smoking cue reactivity and cessation outcomes among smokers achieving initial abstinence. *Experimental and Clinical Psychopharmacology*, *20*, 293-301.

Donny, E.C., Denlinger, R.L., Tidey, J., Koopmeiners, J.S., Benowitz, N.L., Vandrey, R.G., al'Absi, M., Cinciripini, P.M., Dermody, S.S., Drobes, D.J., Hecht, S.S., Jensen, J., Lane, T., Le, C., McClernon, F.J., Montoya, I., Murphy, S.E., Robinson, J.D., Stitzer, M.L., Strasser, A.A., Tindle, H., & Hatsukami, D.K. (in press). Reduced nicotine standards for cigarettes: A randomized trial. *New England Journal of Medicine*.

Donny, E. C., Houtsmuller, E. J., & Stitzer, M. L. (2007). Smoking in the absence of nicotine: Behavioral, subjective and physiological effects over 11 days. *Addiction, 102,* 324-334.

Evans, D.E., MacQueen, D.A., Jentink, K.G., Park, J.Y., Lin, H., & Drobes, D.J. (2014). CHRNA5 variants moderate the effect of nicotine deprivation on a neural index of cognitive control. *Genes, Brain and Behavior, 13*, 626-632.

Evans, D.E., Maxfield, N.D., Janse Van Rensburg, K., Oliver, J.A., Jentink, K.G., & Drobes, D.J. (2013). Nicotine deprivation influences P300 markers of cognitive control. *Neuropsychopharmacology, 38*, 2525-2531.

Family Smoking Prevention and Tobacco Control Act (2009), Public Law 111-31.

Fiore, M., Jaen, C., Baker, T., Bailey, W., Benowitz, N., & Curry, S., et al. (2008). *Treating tobacco use dependence: Clinical practice guideline*. Washington, DC*:* U.S. Public Health and Human Services.

Foa, E.B. (2011) Prolonged exposure therapy: Past, present, and future. *Depression and Anxiety, 28,* 1043-47.

Goldberg, S. R., Spealman, R. D., & Goldberg, D. M. (1981). Persistent behavior at high rates maintained by intravenous self-administration of nicotine. *Science, 214*(4520), 573-575. doi: 10.1126/science.7291998.

Hatsukami, D. K., Hertsgaards, L. A., Vogel, R.I., Jensen, J. S., Murphy, S. E., Hecht, S. S., Carmella, S. G., al'Absi, M., Joseph, A. M., & Allen, S. S. (2013). Reduced nicotine content cigarettes and nicoitne patch. *Cancer Epidemiology, Biomarkers, and Prevention, 22,* 1015-1024. doi: 10.1158/1055-9965.EPI-12-1439.

Hatsukami, D. K., Kotlyar, M., Hertsgaards, L. A., Zhang, Y., Carmella, S. G., Jensen, J. S., Allen, S. S., Shields, P. G., Murphy, S. E., Stepanov, I., & Hecht, S. S. (2010). Reduced nicotine content cigarettes: Effects on toxicant exposure, dependence and cessation. *Addiction, 105,* 343-355. doi: 10.1111/j.1360-0443.2009.02780.x.

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerström, K. O. (1991). The Fagerström test for nicotine dependence: A revision of the Fagerström tolerance questionnaire. *British Journal of Addiction, 86,* 1119-1127.

Hendricks, P.S., & Brandon, T.H. (2008). Smokers' expectancies for smoking versus nicotine. *Psychology of Addictive Behaviors, 22,* 135-140.

Hendricks, P.S., Ditre, J.W., Drobes, D.J., & Brandon, T.H. (2006). The early time course of smoking withdrawal effects. *Psychopharmacology*, *187*, 385-396.

Henningfield, J. E., & Goldberg, S. R. (1983). Control of behavior by intravenous nicotine injections in human subjects. *Pharmacology Biochemistry & Behavior, 19,* 1021-1026.

Hofmann, S.G. (2008). Cognitive processes during fear acquisition and extinction in animals and humans: Implications for exposure therapy of anxiety disorders. *Clinical Psychology Review, 28,* 199-210.

Jacobs, E.A., Bickel, W.K. (1999). Modeling drug consumption in the clinic using simulation procedures: demand for heroin and cigarettes in opioid-dependent outpatients. Exp Clin Psychopharmacol,7,412–26.

Laborda, M.A., McConnel, B.L., Miller, R.R. (2011). Behavioral techniques to reduce relapse after exposure therapy: Applications of studies of experimental extinction. In T.R. Schachtman & S. Rielly (Eds.), *Associative learning and conditioning theory: Human and non-human applications* (pp79-103). New York: Oxford University Press.

Littell, R.C, Milliken, G A., Stroup, W.W., & Wolfinger, R.D. (2006). SAS System for Mixed Models (second edition), Cary, NC: SAS Institute Inc.

MacQueen, D.A., Heckman, B.W., Blank, M.D., Janse Van Rensburg, K., Evans, D.E., & Drobes, D.J. (2012). Transient compensatory smoking in response to placebo cigarettes. *Psychopharmacology*, *223*, 47-54.

MacQueen, D.A., Heckman, B.W., Blank, M.D., Janse Van Rensburg, K., Park, J.Y., Drobes, D.J., & Evans, D.E. (2014). Variation in the alpha 5 nicotinic acetylcholine receptor subunit gene predicts cigarette smoking intensity as a function of nicotine content. *The Pharmacogenomics Journal, 14,* 70-76.

Oliver, J.A., MacQueen, D.A., & Drobes, D.J. (2013). Deprivation, craving and affect: Intersecting constructs in addiction. In P. Miller (Ed.), *Principles of Addiction: Comprehensive Addictive Behaviors and Disorders* (pp. 395-403). San Diego: Elsevier.

Onken, L.S., Blaine, J.D., & Battjes, R. (1997). Behavioral therapy research: A conceptualization of a process. In: Hennegler, S.W., & Amentos, R. (Eds.). *Innovative approaches for difficult to treat populations*. Washington, DC: American Psychiatric Press, pp. 477–485.

Palmatier, M. I., Liu, X., Matteson, G. L., Donny E. C., Caggiula, A. R., & Sved, A. F. (2007). Conditioned reinforcement in rats established with self-administered nicotine and enhanced by noncontingent nicotine. *Psychopharmacology, 195,* 235-243. doi: 10.1007/s00213-007-0897-6.

.

Pickworth, W. B., Nelson, R. A., Rohrer, M. S., Fant, V. R., & Henningfield, J. E. (1999). Pharmacodynamic effects of new de-nicotinized cigarettes. *Nicotine & Tobacco Research, 1,* 357-364. doi: 10.1080/14622299050011491.

Piper, M.E., Piasecki, T.M., Federman, E.B., Bolt, D.M., Smith, S.S., Fiore, M.C., & Baker, T.B. (2004). A multiple motives approach to tobacco dependence: The Wisconsin inventory of smoking dependence motives (WISDM-68). *Journal of Consulting and Clinical Psychology*, *72*, 139-54.

Preacher, K.J., & Hayes, A.F. (2008). Contemporary approaches to assessing mediation in communication research. In A. F. Hayes, M. D. Slater, and L. B. Snyder (Eds.), The Sage sourcebook of advanced data analysis methods for communication research (pp. 13-54.). Thousand Oaks, CA: Sage Publications.

Rash, C.J., & Copeland A.L. (2008). The Brief Smoking Consequences Questionnaire-Adult (BSCQ-A): Development of a short form of the SCQ-A. *Nicotine & Tobacco Research, 10* (11), 1633-1643.

Rescorla, R.A. (2006). Deepened extinction from compound stimulus presentation. *Experimental Psychology: Animal Behavioral Processes, 32,*135–144.

Rezaishiraz, H., Hyland, A., Mahoney, M.C., O'Connor, R.J., & Cummings, K.M. (2007). Treating smokers before the quit date: Can nicotine patches and denicotinized cigarettes reduce cravings? *Nicotine & Tobacco Research, 9,* 1139-1146.

Rose, J. E., & Levin, E. D. (1991). Inter-relationships between conditioned and primary reinforcement in the maintenance of cigarette smoking. *British Journal of Addiction, 86,* 605-609. doi:10.1111/j.1360-0443.1991.tb01816.x.

Rose, J. E., & Corrigall, W. A. (1997). Nicotine self-administration in animals and humans: similarities and differences. *Psychopharmacology, 130*, 28-40. doi: 10.1007/s002130050209.

Rounsaville, B.J., Carroll, K.M., & Onken, L.S. (2001). A stage model of behavioral therapies research: Getting started and moving on from stage I. *Clinical Psychology: Science and Practice, 8,* 133-142.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G.C. (1998). 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*, *59*, 22-33.

Shiffman, S., Balabanis, M.H., Gwaltney, C.J., Paty, J.A., Gnys, M., Kassel, J.D., Hickcox, M., & Paton, S.M. (2007). Prediction of lapse from associations between smoking and situational antecedents assessed by ecological momentary assessment. *Drug and Alcohol Dependence, 91,* 159-68.

Sobell LC, Sobell MB. Timeline follow-back. A technique for assessing self-reported alcohol consumption(1992). In: Litten R, Allen J, eds. Measuring Alcohol Consumption Psychosocial and Biochemical Methods. New York: Springer-Verlag:41-69.

Spitzer, R. L., Kroenke, K., & Williams, J. B. (1999). Validation and utility of a self-report version of PRIME MD: The PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *Journal of the American Medical Association, 282,* 1737-1744.

Strasser, A. A., Lerman, C., Sanborn, P. M., Pickworth, W. B., & Feldman, E. A. (2007). New lower nicotine cigarettes can produce compensatory smoking and increased carbon monoxide exposure. *Drug & Alcohol Dependence, 86,* 294-300. doi: 10.1016/j.drugalcdep.2006.06.017.

Task Force on Recommended Alcohol Questions (2003). National Council on Alcohol Abuse and Alcoholism recommended sets of alcohol consumption questions. Bethesda, MD: National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health.

U.S. Department of Health and Human Services (2014). *The Health Consequences of Smoking – 50 years of Progress: AA Report of the Surgeon General.* Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 17.

Walker, N., Bullen, C., & McRobbie, H. (2009). Reduced-nicotine content cigarettes: Is there potential to aid smoking cessation? *Nicotine & Tobacco Research, 11,* 1274-1279.

Walker, N., Howe, C., Bullen, C., Grigg, M., Glover, M., McRobbie, H., Laugesen, M., Parag, V., & Whittaker, R. (2012). The combined effect of very low nicotine content cigarettes, used as an adjunct to usual Quitline care (nicotine replacement therapy and behavioural support), on smoking cessation; A randomized controlled trial. *Addiction, 107,* 1857-1867.

Westman E, Levin E, Rose J. (1992). Smoking while wearing the nicotine patch: Is smoking satisfying or harmful? Clinical Research,40,871A

Zacny J. P, Conley K., Marks S. (1997). Comparing the subjective, psychomotor and physiological effects of intravenous nalbuphine and morphine in healthy volunteers. J *Pharmacol Exp Ther* ;280(3):1159-69

FSC-RNC STUDY 2 TABLE: PROCEDURES BY VISIT

Assessment Name	Platform	Visit 1 Screen	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	2Month Follow-Up	6Month Follow-Up
Telephone Recruitment Questionnaire	REDCap	N/A, administered via the telephone prior to the first visit							
VISITASSESSMENTS									
Weight (Height at screen only)	Paper and REDCap	X	X	X	X	X	X	X	X
Pregnancy Test (if applicable)	Paper and REDCap	X		X			X		
Heart Rate & BP	Paper and REDCap	X	X	X	X	X	X	X	X
CO Reading	Paper and REDCap	X	X	X	X	X	X	X	X
NicAlert (if CO ≤8 ppm)	Paper and REDCap	X							
Breath Alcohol Test	Paper and REDCap	X	X	X	X	X	X	X	X
Urine Toxicology	Paper and REDCap	X							
Concomitant Medications	Paper and REDCap *	X	X	X	X	X	X	X	X
Health Changes Questionnaire	Paper and REDCap *		X	X	X	X	X	X	X
Adverse Events	Paper and REDCap *		X	X	X	X	X	X	X
Product Accountability Log	Paper and REDCap	X	X	X	X	X	X		
Counseling Session Notes	Paper (Source only) *	X	X	X	X	X	X		
Study Expectations Agreement Form	Paper (Source only) *	X							
Address Change Sheet	Paper (Source only) *		X				X		
Contact Sheet	Paper (Source only) *		X				X		
Tobacco Use History and Exposure	Paper and REDCap **	X							
Smoking Cessation Therapy	Paper and REDCap **	X							
FTND	Paper and REDCap **	X							
Demographic Information	Paper and REDCap **	X							
Brief Medical History	Paper and REDCap **	X							
Prime MD	Paper and REDCap **	X							
Contemplation Ladder	Paper and REDCap **	X							
Brief NCQ	Paper and REDCap **	X							
BSCQ-A	Paper and REDCap **	X							
Brief WISDM	Paper and REDCap **	X							
MINI Intl. Neuropsychiatric Interview (M.I.N.I.)	Paper (Source only)**	X							

Appendix

FSC-RNC STUDY 2 TABLE: PROCEDURES BY VISIT

Assessment Name	Platform	Visit 1 Screen	Visit 2	Visit 3	Visit 4	Visit 5	TQD	2Month Follow-up	6Month Follow-up
Eligibility Checklist	Paper and REDCap	X							
Alcohol Use Questionnaire - 1 month	Paper and REDCap **	X							
Drug Use Questionnaire - 12 month	Paper and REDCap **	X							
Drug Use Questionnaire - 1 month	Paper and REDCap *							X	X
Authorization form to participate in other TRIP studies	Paper (Source only) *								X
TOBACCO USE MEASURES									
Timeline Follow-back - 30 Days	Paper and REDCap **	X							
Timeline Follow-back - between V2-V5	Paper and REDCap *		X	X	X	X			
Timeline Follow-back – Target Quit Day	Paper and REDCap *						X		
Timeline Follow-back – two-month follow-up	Paper and REDCap *							X	
Timeline Follow-back – six-month follow-up	Paper and REDCap *								X
Two-Month Follow-Up Questionnaire	Paper and REDCap *							X	
Six-Month Follow-Up Questionnaire	Paper and REDCap *								X
ACCEPTABILITY MEASURES									
QSU - Usual Brand	Paper and REDCap *	X	X	X	X	X	X	X	X
QSU - Study Cigarettes	Paper and REDCap *		X	X	X	X	X	X	X
Cigarette Evaluation Scale - Usual Brand	Paper and REDCap *	X							
Cigarette Evaluation Scale - Study Cigarettes	Paper and REDCap *		X	X	X	X	X		
Drug Effects/Liking Scale - Study Cigarettes	Paper and REDCap *		X	X	X	X	X		
TESTS OF SMOKING-RELATED OUTCOMES									
Cue Reactivity Task	Paper and REDCap **	X					X		
Cigarette Purchase Task - Usual Brand	Paper and REDCap *	X	X	X	X	X	X	X	X
Cigarette Purchase Task - Study Cigarettes	Paper and REDCap *		X	X	X	X	X	X	X
AS NEEDED									
Debriefing Letter	Paper (Source only)	N/A, letter will be sent after the trial is complete							
Beck Depression Inventory (BDI-II)(if PRIME MD yields)	Paper (source only) *	X							
Beck Depression Inventory (BDI-II) (if monitoring needed)	Paper (Source only) *		X	X	X	X	X	X	X
Lost to Follow-Up Letter (as needed)	Paper (Source only)		Will be sent only after a subject has missed a visit post-screening session						
PRIME MD – Weekly Monitoring Version (if pt. endorses negative mental health change)	Paper (source only)*		X	X	X	X	X	X	X
EVALUATION MEASURES									
Post-treatment Questionnaire	Paper and REDCap *						X		

**may be administered remotely due to COVID-19*
***maybe be administered via Zoom while participant is at facility*