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PROTOCOL NUMBER

Human Subjects Research Protocol

The Common Human Subjects Protocol Cover Form **must** be completed and **attached** to the front of this form. This Protocol form should be completed for any human subjects research proposal that does not have a specific "protocol," such as a grant application. This form must be submitted along with a copy of the complete grant proposal and all the information in this form **must** be consistent with that proposal. This protocol form, once IRB approved, will be the working protocol for that research. **When completing this document, do not refer to page numbers within your grant**. If revisions are necessary during the course of the research, amendments should refer to this protocol form, not the grant proposal. Enter responses for all sections. Check N/A if the section does not apply.

PROTOCOL SUMMARY

Project Title:	Protocol Version Date:
A randomized trial to compare switching to very low nicotine content cigarettes vs reducing cigarettes per day	9/20/2016

Principal Investigator: Elias Klemperer

Grant Sponsor: **NIH** Grant Numbers: **1 P50 DA036114; T 32 DA07242**
(For grants routed through UVM, indicate the OSP Proposal ID # located at the top of the OSP Routing Form)

Lay Language Summary: *(Please use non-technical language that would be understood by nonscientific IRB members to summarize the proposed research project. The information must include: (1) a brief statement of the problem and related theory supporting the intent of the study, and (2) a brief but specific description of the procedure(s) involving the human subjects. Please do not exceed one single-spaced 8 ½ X 11" page.)*

The FDA recently gained the authority to regulate the nicotine content of cigarettes. Prior research suggests that smokers who switch to very low nicotine content (VLNC) cigarettes experience reduced addiction to nicotine and are more likely to quit smoking. Currently, the most common method for smokers to reduce their nicotine intake is to reduce their number of cigarettes per day (CPD). No research has compared reducing smokers' nicotine intake by switching to VLNC cigarettes vs by reducing CPD with regard to decreasing dependence or quitting; thus we plan to examine the two strategies by randomizing smokers to 1) switch to VLNC cigarettes or 2) reduce CPD. In addition, all smokers will use the nicotine patch to help them reduce their nicotine intake.

Primary aims:

1. Determine whether it is easier to switch to VLNC cigarettes or reduce CPD.
2. Determine whether switching to VLNC cigarettes or reducing CPD reduces nicotine addiction more.

Secondary aims

3. Determine whether switching to VLNC cigarettes or reducing CPD increases attempts to stop smoking or ability to stop smoking more.
4. Determine whether switching to VLNC cigarettes or reducing CPD better reduces a) craving, b) withdrawal, c) perceived harm from smoking, and d) enjoyment from smoking.

PURPOSE AND OBJECTIVES

Purpose: *The importance of the research and the potential knowledge to be gained should be explained in detail. Give background information.*

Background

Smoking is the single most preventable cause of death and is associated with over 480,000 deaths per year in the United States.[1] Though the prevalence of smoking has declined dramatically since 1964, it has slowed to less than 1% per year since 1990[1] due, in part, because the majority of smokers do not want to quit in the near future.[2,3] A policy to reduce the nicotine content of cigarettes[4-7] could be useful for those who are not ready to quit. Specifically, the FDA recently gained the authority to regulate cigarettes' nicotine content and switching to very low nicotine content (VLNC) cigarettes has been proposed as a future regulatory policy to give smokers the option to decrease nicotine intake from cigarettes in order to decrease nicotine dependence and quit smoking.[8-11] A review of clinical trials suggest that switching to VLNC cigarettes with and without nicotine replacement therapy (NRT) reduces dependence, carcinogens, and carbon monoxide and increases quitting;[4,6,12-16] however, its long-term effects are unclear.

Nicotine dependence is determined by nicotine intake (i.e., yield) as well as non-nicotine reinforcers conditioned by the repetitive act of smoking (i.e., multiple cigarettes per day).[17,18] Presently, reducing cigarettes per day (CPD) is the most common strategy to reduce nicotine intake[3,19,20] and appears to be an effective[21-23] method of reducing dependence. However, a regulatory policy that introduces VLNC cigarettes will provide smokers with the opportunity to reduce nicotine intake without changing the frequency of their smoking behavior (i.e., CPD). Thus, reducing nicotine by switching to VLNC cigarettes may affect conditioned reinforcers and dependence differently than reducing nicotine intake via reducing CPD. We know of no research that has compared the regulatory policy of reducing nicotine intake via VLNC cigarettes vs the common method of reducing nicotine intake via reducing CPD. This comparison will provide important information regarding the components involved in changing nicotine dependence and the potential effects of a policy that regulates the nicotine content of cigarettes.

NRT appears to increase the feasibility and effectiveness of switching to VLNC cigarettes[13-16] as well as reducing full nicotine CPD.[21-23] In both scenarios, NRT facilitates a net reduction in nicotine.[24] Further, NRT is currently available to smokers who reduce CPD, will be available to smokers if cigarettes' nicotine levels are reduced by the FDA, and is likely to be used as an aid for both.

The present study will compare participants who switch to VLNC cigarettes vs participants who reduce CPD when all participants receive NRT patch. Specifically this comparison will examine differences in feasibility and effectiveness of reducing nicotine dependence.

References*. Include references to prior human or animal research and references that are relevant to the design and conduct of the study.*

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Objectives: *Clearly state the primary and secondary objective(s) of the study.*

Specific Aims

Primary:

1. Determine the relative feasibility of switching to VLNC cigarettes vs reducing CPD when all participants are aided by nicotine replacement therapy (NRT).
2. Determine whether switching to VLNC cigarettes or reducing CPD more effectively reduces nicotine dependence when all participants are aided by NRT.

Secondary:

3. Determine whether switching to VLNC cigarettes vs reducing CPD increases quit attempts and 7-day point-prevalence abstinence more when all participants are aided by NRT.
4. Determine the relative effectiveness of switching to VLNC cigarettes and reducing CPD when all participants are aided by NRT with comparisons of a) craving, b) withdrawal, c) perceived harm from smoking and d) participants' enjoyment from smoking.

METHODS AND PROCEDURES

Study Design: *Describe the research design, including a description of any new methodology and its advantage over existing methodologies.*

We will not begin any study procedures until after IRB approval has been obtained. Consenting participants will be randomly assigned to 1) switch to VLNC cigarettes with NRT or 2) reduce full nicotine CPD with NRT during the 5-week study period (Table 1). All participants will complete baseline measures and receive full nicotine or VLNC study cigarettes as well as weekly supplies of 21-mg nicotine patches with instructions to replace their old patch with a new patch each morning. All study cigarettes are for investigational purposes only and are not available or intended for commercial use. The 21-mg nicotine patch was chosen because it is popular,[25] it provides a consistent dose of nicotine to all participants, and prior studies have demonstrated its safety, feasibility and effectiveness as an aid to VLNC cigarettes[13] and reduction in CPD.[26] We chose this dosing regimen because participants will be smokers who do not want to quit and thus we expect they will require 21-mg patches to replace nicotine as they reduce their nicotine from cigarettes. However, we will also offer all participants the option to take nicotine patches with less nicotine (14 mg and 7 mg). All participants will call a study telephone number nightly throughout the study to report CPD and adherence to study cigarettes and NRT.

Procedures: *Describe all procedures (sequentially) to which human participants will be subjected. Identify all procedures that are considered experimental and/or procedures performed exclusively for research purposes. Describe the types, frequency and duration of tests, study visits, interviews, questionnaires, etc. Include required screening procedures performed before enrollment and while on study. Please provide in table, list or outline format for ease of review. (describe and attach all instruments)*

Note: A clinical research protocol may involve interventions that are strictly experimental or it may involve some aspect of research (e.g., randomization among standard treatments for collection and analysis of routine clinical data for research purposes). It is important for this section to distinguish between interventions that are experimental and/or carried out for research purposes versus those procedures that are considered standard therapy. In addition, routine procedures performed solely for research purposes (e.g., additional diagnostic/follow-up tests) should be identified.

Procedures

Individuals who are interested in this study will be instructed to call a toll free study telephone number. Potential participants will be screened on an initial phone call or online survey (approximately 10 minutes) with a series of questions about their smoking to determine eligibility (see Inclusion/Exclusion Criteria). Eligible participants will be prompted to schedule a study visit. The first study visit will last approximately one hour. Potential participants will be provided with a consent form and information regarding the study during their first study visit. They will be encouraged to ask questions and required to answer a short test to ensure they understand study procedures prior to consenting to participate. Consenting participants will then be randomized to 1) the VLNC or 2) the CPD group. All participants will answer a series of demographic questions and self-report measures regarding their smoking behavior (described below). Finally, participants will receive instructions regarding use of the study cigarettes.

During their first study visit, we will provide all participants with a one-week supply of full nicotine study cigarettes (16.5 ± 0.17 mg/g) that totals 150% of their normal number of CPD in order to establish a baseline CPD with novel study cigarettes that are being provided free of charge. The 16.5 mg/g nicotine content NIDA research cigarette is estimated to have a nicotine yield (0.8 mg) similar to many commercial cigarettes. Participants will be instructed to smoke only research cigarettes, but to smoke as usual during the first week of the study. Self-reported CPD during week 1 will serve as the baseline CPD from which we will calculate the number of research cigarettes to provide participants during weeks 2 through 5 (see Table 1).

Switching to VLNC cigarettes

Participants who are randomized to switch to VLNC cigarettes will receive a supply of 100% of their baseline number of CPD during study visits (determined during week 1) throughout weeks 2 to 5 and instructed to smoke as usual (e.g., not to attempt to reduce CPD). They will receive study cigarettes with progressively lower nicotine

content (mg/g tobacco) beginning with 11.26 ± 0.11 mg/g during week 2, 5.54 ± 0.27 mg/g during week 3, 2.54 ± 0.05 mg/g during week 4, and 0.44 ± 0.01 mg/g during week 5. We will also provide participants with an additional 2-day supply of study cigarettes for the beginning of the subsequent week with instructions to only smoke these cigarettes if the participant's next study visit is delayed. For example, at a participant's week 2 study visit, s/he will receive a 7-day supply of 11.26 mg/g study cigarettes and an additional 2-day supply of 5.54 mg/g study cigarettes. Participants will be instructed to return all unused study cigarettes at each study visit. Participants will also receive a supply of NRT patches with instructions to wear one patch per day every day throughout weeks 2 through 5. This schedule was selected based on available VLNC cigarettes and findings that indicate that a gradual transition to cigarettes with a nicotine content of approximately 1 mg/g or less with the NRT patch is safe, effective and feasible.[12,27,28] We will estimate NRT use and compliance with VLNC study cigarettes with daily and weekly self-report.

The only available VLNC cigarettes that have consistent qualities (e.g., filter type and tipping paper perforation) across nicotine contents that allow for a gradual transition to VLNC cigarettes are all mentholated. Therefore all participants will receive menthol study cigarettes and we will limit recruitment to participants who currently smoke or have a history of smoking menthol cigarettes. A minority of smokers use menthol cigarettes and most are African Americans;[42] thus we anticipate a limited number of current menthol smokers in the Burlington, VT area and therefore we do not believe recruiting only current menthol smokers is feasible. Instead we will recruit participants who are currently or have previously been a menthol cigarette smoker and we will block randomize so that the proportion of current to past menthol cigarette smokers will be similar between groups. Importantly, we expect that all participants in our study will have to adjust to the novel flavor of study cigarettes, regardless of their current or prior experience with menthol cigarettes.

Reducing CPD

We will provide participants who are randomized to reduce CPD with full nicotine study cigarettes (16.5 ± 0.17 mg/g) during each study visit throughout the 5-week study period and instruct them to only smoke cigarettes provided by the study. Participants in this condition will also be current or past menthol smokers and will receive menthol study cigarettes in order to be consistent with participants who are randomized to switch to VLNC cigarettes. After establishing a baseline CPD during week 1, participants will receive progressively fewer cigarettes beginning with 70% of their baseline CPD during week 2, 35% during week 3, 15% during week 4, and 3% during week 5. Participants will receive a minimum of 1 CPD during week 5. We will also provide participants with an additional 2-day supply of study cigarettes for the beginning of the subsequent week with instructions to only smoke these cigarettes if the participant's next study visit is delayed. Participants will be instructed to return all unused study cigarettes at each study visit. Participants will also receive a supply of NRT patches with instructions to wear one patch per day every day throughout weeks 2 through 5. This schedule was selected to match the percent reduction in nicotine content of cigarettes for smokers randomized to switch to VLNC cigarettes. Further, this schedule of NRT aided reductions in CPD appears to be safe, feasible and effective.[29] We will estimate reductions in CPD, compliance with study cigarettes, and NRT use with daily and weekly self-report.

All participants

Importantly, all participants will receive study cigarettes that are not commercially available and thus novel. Further, because participants who reduce CPD cannot be blinded, we will inform participants in the VLNC cigarette condition of the nicotine content of their cigarettes each week.

All study cigarettes will be distributed in re-sealable plastic containers. Each container will be labeled with text from the original Spectrum packaging. Specifically the labels will include the phrases: 1) "Not for resale," 2) "For research purposes only," 3) "Not to be sold," and 4) "Surgeon General's Warning: Smoking Causes Lung Cancer, Heart Disease, Emphysema, and May Complicate Pregnancy." Participants will be instructed to return all unused study cigarettes to the researchers in the re-sealed plastic containers during study visits.

In order to increase the validity of participants' self-report about adherence to study cigarettes, we will 1) inform

participants that self-reported noncompliance will not influence their payment or future participation and 2) employ a bogus pipeline technique that has been used in multiple prior studies.[32] Specifically, we will (falsely) tell participants that breath and urine tests will detect any non-study cigarettes that are smoked. In fact, the breath and urine tests will be used to measure CO and cotinine but cannot detect the difference between study and non-study cigarettes. This deception is intended to increase participants' self-report of any non-study cigarettes that they smoke. Knowing the extent to which participants smoke non-study cigarettes is integral to our primary specific aim (determine the relative feasibility of switching to VLNC vs reducing CPD). Participants will be debriefed about this deception and its rationale during their final study visit after the conclusion of the 5-week study period.

Final study visit and follow-up

After the 5-week study period participants in both conditions will attend a final study visit. During this final study visit we will provide all participants with usual care for smokers who are not ready to quit: information (NIH brochure) regarding the dangers of smoking, information regarding treatment options, and brief advice to quit. We will provide participants who decide to quit with a 4 week supply of 21 mg NRT-patches and instructions regarding how to use them. Also, all participants will be debriefed regarding the use of deception and provided with the Debriefing Form during the final study visit. We will not provide participants with study cigarettes after the 5-week study period. We will mail information regarding the dangers of smoking, information regarding treatment options, a letter with brief advice to quit, and the Debriefing Form to any participant who misses their final study visit. Participants will complete a final online survey at week 9 (4 weeks after the conclusion of the 5-week study period) to assess for quit attempts and point-prevalence abstinence.

Table 1. *Schedule of conditions and outcomes.*

Conditions						
		Week 1[a] (baseline)	**Week 2**[b]	**Week 3**[b]	**Week 4**[b]	**Week 5**[b]
Switch to VLNC cigarettes	*CPD*	Ad lib	100% of baseline	100% of baseline	100% of baseline	100% of baseline
	Nicotine content	16.5 mg/g	11.3 mg/g (**70%** of baseline)	5.5 mg/g (**35%** of baseline)	2.5 mg/g (**15%** of baseline)	0.4 mg/g (**3%** of baseline)
Reduce number of full nicotine CPD	*CPD*	Ad lib	**70%** of baseline	**35%** of baseline	**15%** of baseline	**3%** of baseline[c]
	Nicotine content	16.5 mg/g	16.5 mg/g	16.5 mg/g	16.5 mg/g	16.5 mg/g
Outcomes						
Cotinine		X	X	X	X	X X[d]
Self-report measures		X	X	X	X	X X[d]
Self-report compliance		*Participants will report NRT use and number of study and non-study CPD nightly throughout weeks 1-5.*				

[a]Baseline CPD established during this time; [b]Participants will receive 21-mg NRT patches and instructions to use one patch per day; [c]Participants will be provided with a minimum of 1 CPD; [d]Study visit when participants will be provided with information regarding the dangers of smoking, treatment options, and brief advice to quit; CPD=Cigarettes per day; mg/g=Milligram nicotine per gram tobacco; NRT=21-mg nicotine replacement therapy patch; VLNC=Very low nicotine content; 16.5 mg/g cigarette=NRC601; 11.3 mg/g cigarette=NRC501; 5.5 mg/g cigarette=NRC401; 2.5 mg/g cigarette=NRC301; 0.4 mg/g cigarette=NRC103.

For research involving survey, questionnaires, etc.: *Describe the setting and the mode of administering the instrument and the provisions for maintaining privacy and confidentiality. Include the duration, intervals of administration, and overall length of participation. (describe and attach all instruments)*

☐ ***Not applicable***

Schedule of Study Visits (Table 1)

All participants will complete one study visit per week throughout weeks 1-5 as well as a final study visit at the conclusion of the 5-week study period. Prior research demonstrates that this schedule is feasible.[33] The first visit of the study will last approximately 60 minutes and consist of the consent process, randomization, study instructions, a demographic questionnaire, self-report measures, distribution of study cigarettes, and collection of breath and urine samples. Subsequent weekly visits will last 30 minutes and consist of self-report measures, distribution of NRT-patches and study cigarettes, and breath and urine samples. If a participant misses a study visit, a research assistant will 1) email the participant that week's questionnaire to complete online and 2) drive to the participant's house to deliver the week's supply of NRT patches and study cigarettes and require a signature of receipt from the participant. If participants miss two consecutive weeks of study visits and nightly questionnaires we will withdraw them from the trial. If participants quit smoking and report abstinence during their study visit, we will provide them with self-help material and NRT-patches, but not research cigarettes for the subsequent week. We will ask participants who quit to continue to complete nightly questionnaires and attend weekly study visits for the duration of the study. If a participant quits and then relapses and requests more research cigarettes during the study period we will provide them with the appropriate study cigarettes to continue with the study.

Nightly questionnaire: All participants' will call a toll free study telephone number on an interactive voice response (IVR) system or complete an online questionnaire nightly to answer a series of questions about their smoking including the number of study and non-study CPD and whether they used the NRT patch. The option to use either the IVR or the online questionnaire is designed for the convenience of participants in order to increase compliance. The IVR and online questionnaire will have the same content. The IVR is a system in which participants call a number which directs them to enter data using the phone keypad. The IVR has many of the assets of computer-assisted telephone interviewing (CATI); e.g., automatic skips, branching options, prohibition of illogical responses and outliers, standardized questioning, and direct data entry. IVR's major assets are the increased confidentiality, the ability to prompt participants to call, and the ability of participants to determine when to call. The IVR system requires a touch-tone land-line or cell phone. However, most (> 95%) of the general population has a touch-tone phone. Those that do not will have the option to answer the same questions in an online questionnaire format.

Participants will begin calling the IVR or completing online questionnaires the same evening after their initial study visit. They will receive instructions for IVR or online questionnaire participation during their first study visit. We will ask the participants what their normal bedtime is. The participant will be able to record one day's answers as late as noon of the day after. To prevent missed calls, the IVR system will make a call or send a text message to the participant at ½ hour before the usual bedtime if the participant has not yet completed the call or online questionnaire for the day. If no response has been received in spite of that evening reminder call or text message, the system will call or text the participant the next day. The reminders are not required and we will ask participants' permission to use reminders. If they decide to use reminders, we will give them the option to receive calls or text messages. The IVR will allow late data entry until 12 noon the next day but not thereafter. In our prior studies, < 5% of completed calls have been on the next day.

Biomarkers: Urine samples will be collected once per week and analyzed for cotinine in our laboratory. Cotinine will be collected as an exploratory measure and used to monitor compliance with NRT as well as transitions to VLNC cigarettes and reductions in CPD. Urine samples from participants' baseline and final study visit will be labeled with participants' ID numbers and stored in a locked freezer in a locked office for future analysis of biomarkers of disease (e.g., NNAL) when more funding is available. Breath samples will be collected once per week in our laboratory and used to measure carbon monoxide (CO) levels.

Follow-up questionnaires: All participants will complete a single online follow up survey during week 9 of the study. The follow up survey will consist of self-report measures similar to those completed during study visits (described below). Participants will not be provided with study cigarettes after week 5 of the study. Participants who decide to quit will be offered a free 4 week supply of 21 mg NRT patches and instructions on how to use them.

Self-report measures: Participants will complete the following measures on a study computer during study visits once per week, at the conclusion of the 5-week study period, and on the Internet during the follow-up at week 9.

1) Nicotine Dependence Syndrome Scale (NDSS)[34] to measure nicotine dependence without CPD as an indicator of dependence.
2) The Glover-Nilsson Behavioral Smoking Questionnaire[43] to measure behavioral dependence.
3) Questionnaire of Smoking Urges – brief scale (QSU)[35] to measure craving and urges to smoke.
4) Minnesota Withdrawal Scale (MNWS)[36] to measure nicotine withdrawal.
5) Perceived Health Risks Rating[6] to measure perceived risk of addiction and harm from smoking.
6) Cigarette Evaluation Scale (CES)[37] to measure responses to cigarette (e.g., reward satisfaction).
7) Cigarette Purchase Task (CPT)[38] to measure the reinforcing effect of cigarettes by asking participants the number of cigarettes they would consume at varying prices.
8) Velicer's self-efficacy scale[44] to measure self-efficacy to quit smoking.
9) DSM 5 Tobacco Use Disorder self-report form to measure whether the participant meets criteria for Tobacco Use Disorder.
10) The quit ladder[45] to measure intention to quit smoking.

Quit attempts will be defined as a self-reported attempt to stop smoking. We will include quit attempts lasting ≥ 24 hours and quit attempts lasting any length of time that are reported on nightly, weekly or follow-up questionnaires as secondary outcomes of this study.

Statistical Considerations: *Delineate the precise outcomes to be measured and analyzed. Describe how these results will be measured and statistically analyzed. Delineate methods used to estimate the required number of subjects. Describe power calculations if the study involves comparisons. Perform this analysis on each of the primary and secondary objectives, if possible.*

Data Analysis Plan

If there is substantial missing data (>10%), then as recommended by the SRNT workgroup, we will conduct additional sensitivity tests using missing data procedures.[46, 47] If participants are missing a single data point (e.g. one nightly call), we will explore imputing this missing data based on the scores before and after the missing data. Our major hypotheses call for comparisons between two conditions and we will only include those participants who have complete data (perhaps including imputations) for both conditions.

Traditionally, "intention-to-treat" analyses in which all participants are included have been thought to produce the more valid results than "per-protocol" analyses that retain only compliant participants. Thus we will use "intention-to-treat" for our primary analyses.

This study is exploratory and is intended to assess feasibility and effectiveness of switching to VLNC cigarettes and reducing CPD. Descriptive statistics and visual representation of the data will be examined for trends that indicate differences in feasibility as well as the relative risks (e.g., craving, withdrawal, and perceived risks) and benefits (e.g., reduced dependence) of switching to VLNC cigarettes with NRT and reducing CPD with NRT. To compare feasibility we will graph retention (e.g., the number of study visits over time) and adherence to study cigarettes (e.g., the number of self-reported non-study cigarettes smoked). Our major dependent variable to assess effectiveness is dependence. NDSS scores will be graphed over time and compared between the two groups. After visual inspection of the data we will run linear and logistic regressions to compare the VLNC vs the CPD group. Outcomes will include number of non-study cigarettes smoked (i.e., compliance), change in dependence scores, number of participants who make a QA, 7-day point-prevalence abstinence at 9 weeks, changes in cotinine, as well as changes in participants' self-report measures. We will begin by examining feasibility (i.e., number of study visits and number of non-study cigarettes) as an indication of the acceptability of switching to VLNC cigarettes vs reducing CPD. Then, if it is possible (i.e., if enough participants attended enough study visits) we will assess changes in dependence as well as our secondary outcomes.

Risks/Benefits: *Describe any potential or known risks. This includes physical, psychological, social, legal or other risks. Estimate the probability that given risk may occur, its severity and potential reversibility. If the study involves a placebo or washout period, the risks related to these must be addressed in both the protocol and consent. Describe the planned procedures for protecting against or minimizing potential risks and assess their likely effectiveness. Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Discuss the potential benefits of the research to the subjects and others. Discuss why the risks to the subjects are reasonable in relation to the anticipated benefits to subjects and others. Discuss the importance of the knowledge gained or to be gained as a result of the proposed research and why the risks are reasonable in relation to the knowledge that reasonably may result. If there are no benefits state so.*

Switching to VLNC Cigarettes

VLNC cigarettes have been obtained through the National Institute on Drug Abuse. The study cigarettes are investigational tobacco products. They are for investigational purposes only and are not available or intended for commercial use. The study cigarettes are not authorized by the FDA for marketing. The study cigarettes will be used for experimental purposes only. The study cigarettes are manufactured in the same way as usual brand cigarettes, but they may contain genetically modified tobacco to reduce the levels of nicotine. There does not appear to be any additional risks associated with genetically modified tobacco.

All cigarettes are detrimental to a person's health and can lead to cardiovascular disease, respiratory disease, cancer and other health problems. In addition, due to the altered nicotine levels, there could be a change in use of cigarettes including the manner in which the participant inhales the smoke. Smoking the study cigarette does not necessarily provide any less risk than a usual brand of cigarette and could pose increased health risks. For example, using study cigarettes could result in smoking more vigorously, which would increase the health risks associated with study cigarettes. However, recent research suggests switching to VLNC cigarettes could increase the likelihood of quitting smoking.

Reduction in CPD

Participants who reduce CPD may experience withdrawal symptoms; i.e. anxiety, depression, difficulty concentrating, hunger/weight gain, insomnia, irritability and restlessness. NRT patches will decrease nicotine withdrawal for most smokers. There is a small risk that if a participant had a psychiatric problem, it might become worse or return after they reduce CPD. Participants will be encouraged to contact the researchers if they believe any withdrawal symptoms require treatment. A study physician (John Hughes) will be available by phone to discuss any questions about withdrawal symptoms. A potential benefit may include smoking reduction and/or the initiation of a quit attempt. Participants who reduce CPD will also be provided with study cigarettes that are investigational tobacco products and will be used for experimental purposes only. The study cigarettes are not authorized by the FDA for marketing and are not available or intended for commercial use.

NRT Patch

Nicotine replacement therapy (NRT) patch may produce several minor AEs, most of which are skin rash and insomnia. Approximately 10% or less of smokers have to stop NRT patch due to AEs. FDA-defined serious AEs have been very rare and dependence on the NRT patch is very rare. The current labeling on the NRT patch explains that pregnant and breast feeding women, those less than 18 years of age, those using a prescription medication for depression or asthma or a smoking cessation medication, and those with heart disease, recent heart attack, irregular heartbeat, high blood pressure not controlled by medication, stomach ulcers or diabetes should consult a physician before using the patch. It also recommends keeping the medication out of reach of children and pets.

Studies of NRT patch use while smoking cigarettes have not found greater AEs than when the patch is used for cessation. Further, the recommended use for the NRT patch has recently been changed to incorporate use while smoking because “the FDA has determined that there are no significant concerns with using NRT products at the same time as another nicotine-containing product like a cigarette (https://www.nicodermcq.com/faq.html).” A potential benefit from using the NRT patch is an increased likelihood of quitting smoking. If a participant would like to use an NRT patch with less nicotine we will provide them with a 14 mg or 7 mg patch. If a participant

decides to stop using the NRT patch they will be asked to continue participation. This would not have an effect on our primary study outcomes.

Deception

In order to increase the validity of participants' self-report about adherence to study cigarettes, we will 1) inform participants that self-reported noncompliance will not influence their payment or future participation and 2) employ a bogus pipeline technique that has been used in multiple prior studies.[32] Specifically, we will (falsely) tell participants that breath and urine tests will detect any non-study cigarettes that are smoked. In fact, the breath and urine tests will be used to measure CO and cotinine but cannot detect the difference between study and non-study cigarettes. This deception is intended to increase participants' self-report of any non-study cigarettes that they smoke. Knowing the extent to which participants smoke non-study cigarettes is integral to our primary specific aim (determine the relative feasibility of switching to VLNC vs reducing CPD). Participants will be debriefed about this deception and its rationale during the final study visit after the conclusion of the 5-week study period.

Ethical Issues

This study will only include smokers who report that they are not ready to quit in the next month. All participants will be (falsely) told that breath and urine tests will detect non-study cigarettes in order to increase the validity of self-reported noncompliance. Participants will be debriefed about this deception and its rationale at the conclusion of the study.

Therapeutic Alternatives: *List the therapeutic alternatives that are reasonably available that may be of benefit to the potential subject and include in the consent form as well.*

☐ ***Not Applicable***

Usual care for smokers who are not ready to quit is brief advice to quit and education about the dangers of smoking and treatment options. Thus, we will undertake this at the conclusion of the 5 week study period.

Data Safety and Monitoring: *The specific design of a Data and Safety Monitoring Plan (DSMP) for a protocol may vary extensively depending on the potential risks, size, and complexity of the research study. For a minimal risk study, a DSMP could be as simple as a description of the Principal Investigator's plan for monitoring the data and performance of safety reviews or it could be as complex as the initiation of an external, independent Data Safety and Monitoring Board (DSMB). The UVM/UVM Medical Center process for review of adverse events should be included in the DSMP.*

Safety

The study will be managed from the Vermont Center on Behavior & Health at the University of Vermont. At each study visit participants will be asked to report any AEs using the standard open-ended question: "have you had any problems that might be related to your use of NRT or the study cigarettes?"[48] We will consider a marked increase in smoking an AE. A marked increase in smoking will be defined as the combination of a self-report 100% increase in CPD and a 100% increase in expired breath carbon monoxide for two consecutive weeks. If we determine that a participant has had an AE or if a participant reports that they have had an AE, an RA will ask the participant about the specific problem, date of its onset and offset, severity (mild, moderate or severe), judgment of its relation to NRT or study cigarettes (not related, unlikely, possibly, probably and likely related), whether it caused discontinuation of NRT or study cigarettes, dropout, and whether it met FDA definition of a "serious event." The RA will pass this information to the physician on call (John Hughes) to make a decision on further action. If the physician agrees it is safe to let the participant continue, we will monitor severe AEs during study visits until it resolves or the study ends. All unexpected, FDA-defined "serious" and possibly-related AEs will be reported within 24 hours to our IRB as well as NIDA and the Center for Tobacco Products. Potential conflicts of interest will be reported using the SRNT rules for disclosure (www.srnt.org).

Participants will be informed about possible AEs in the consent. At study onset, participants will be provided with a phone number and email to report AEs that are urgent. We will withdraw participants who have an FDA-defined serious AE that are likely or probably related to the study products as well as participants who become pregnant or begin breast feeding.

The above traditional methods of collecting AEs can be insensitive; thus, we will in addition, have participants complete a 0-3 Likert scale (none, mild, moderate and severe) of the typical symptoms of nicotine intoxication of nausea, dizziness, headache, and stomachache once per week at study visits during the study period. Participants will be encouraged to contact us and follow-up with their physician if they experience an AE during the 4 week follow-up period.

Data Monitoring

Results from the computerized surveys and nightly questionnaires will be sent directly into study database spreadsheets. Carbon monoxide and cotinine levels will be entered by hand into study database spreadsheets. The PI (EK) will have weekly meetings with RAs to discuss qualitative comments received during data collection and any problems with data collection. Further the statistician (PC) will periodically examine the database to look for irregularities. The statistician will have no contact with participants or the randomization code. Consensus of the PI (EK), the statistician (PC), and the faculty sponsor (JH) are necessary to break the randomization code; e.g., in the event of an FDA defined serious AE.

All data will be stored in an encrypted database on a password-protected computer in a locked office in the Vermont Center on Behavior & Health in the University Health Center building.

Confidentiality

We will use the participant's name only on the screening and informed consent documents and these and a sheet describing each participant's ID number will be kept in a locked room in a locked file. No other data sets will have identifying information. Data will be entered directly from computerized surveys and the IVR system into our password-protected database. Access to the database, urine samples and paper files will be granted only to those approved by the PI. We will instruct the RAs that they cannot reveal if the participant is in the study without the participant's permission, except in emergency situations. We will instruct RAs that they cannot use names in discussing participants, but must use participant numbers.

Adverse Event and Unanticipated Problem (UAP) Reporting: *Describe how events and UAPs will be evaluated and reported to the IRB. All protocols should specify that, in the absence of more stringent reporting requirements, the guidelines established in the Committees on Human Research "Adverse Event and Unanticipated Problems Reporting Policy" will be followed. The UVM/UVM Medical Center process for review of adverse events and UAPs to subjects or others should be included in the DSMP.*

The guidelines established in the Committees on Human Research "Adverse Event and Unanticipated Problems Reporting Policy" will be followed.

Withdrawal Procedures: *Define the precise criteria for withdrawing subjects from the study. Include a description of study requirements for when a subject withdraws him or herself from the study (if applicable).*

Participants who miss several visits such that their data will not be useful may be terminated.

Sources of Materials: *Identify sources of research material obtained from individually identifiable human subjects in the form of specimens, records or data. Indicate whether the material or data will be obtained specifically for research purposes or whether use will be made of existing specimens, records or data.*

Computerized surveys, paper forms and data from the nightly phone calls will be obtained specifically for research purposes.

DRUG AND DEVICE INFORMATION

The FDA has stated that an IND is not necessary for the very low nicotine content (VLNC) cigarettes in this study. However, VLNC cigarettes are an Investigational Tobacco Product (ITP). An ITP is a tobacco product that is a new or modified-risk tobacco product that is not legally marketed, or a tobacco product that is required to comply with a tobacco product standard that does not conform in all respects to the marketed standards and is intended for investigational use. Our Program Project Grant (1 P50 DA036114) currently has an approved ITP plan that includes the VLNC cigarettes that will be used in this study (see the included Letter of Acknowledgement from the

FDA). All research cigarettes will be ordered via NIDA and will be stored in UHC in a locked office in a locked freezer between -25 and -15 degrees Celsius.

Investigators are encouraged to consult the UVM Medical Center Investigational Pharmacy Drug Service (847-4863) prior to finalizing study drug/substance procedures.

Drug (s) [X] ***Not applicable***

Drug name – generic followed by brand name and common abbreviations. Availability – Source and pharmacology; vial or product sizes and supplier. If a placebo will be used, identify its contents and source. (attach investigational drug brochure)

Preparation: Reconstitution instructions; preparation of a sterile product, compounded dosage form; mixing guidelines, including fluid and volume required. Identify who will prepare.

Storage and stability – for both intact and mixed products.

Administration – Describe acceptable routes and methods of administration and any associated risks of administration.

Toxicity – Accurate but concise listings of major toxicities. Rare toxicities, which may be severe, should be included by indicated incidence. Also adverse interactions with other drugs used in the protocol regimen as well as specific foods should be noted. Address significant drug or drug/food interactions in the consent form as well. List all with above details.

Is it FDA approved: (include FDA IND Number)

1. *in the dosage form specified? If no, provide justification for proposed use and source of the study drug in that form.*
2. *for the route of administration specified? If no, provide justification for route and describe the method to accomplish.*
3. *for the intended action?*

Device (s) [X] ***Not applicable***

Device name and indications (attach investigational device brochure)

Is it FDA approved: (include FDA IDE Number)

1. *for indication specified? If no, provide justification for proposed use and source of the device.*

Risk assessment (non-significant/significant risk) - PI or sponsor needs to assess risk of a device based upon the use of the device with human subjects in a research environment.

SUBJECT CHARACTERISTICS, IDENTIFICATION AND RECRUITMENT

Subject Selection: *Provide rationale for subject selection in terms of the scientific objectives and proposed study design.*

Participants will be current smokers who do not plan to quit in the near future; i.e., about 70% of all smokers, because the purpose of our study is to examine methods to reduce dependence among ambivalent smokers.

[X] ***Not applicable***

Number of Subjects: *What is the anticipated number of subjects to be enrolled at UVM/UVM Medical Center and in the case of a multi-center study, with UVM/UVM Medical Center as the lead, the total number of subjects for the entire study.*

We have selected a sample size of 32 subjects per group in order to have 80% power with a two sided alpha of 0.05 to detect a group by time interaction in NDSS scores across the 5 week study duration if the final difference in NDSS scores is 0.5 units (i.e., 10% change). Thus we will enroll a total of 74 participants in an effort to have at least 64 complete at least two weeks of the study.

Inclusion/Exclusion Criteria: *Eligibility and ineligibility criteria should be specific. Describe how eligibility will be determined and by whom. Changes to the eligibility criteria at a later phase of the research have the potential to invalidate the research.*

Participants will be asked all of the inclusion criteria over the phone or on an online survey. Those who are eligible after the screening process will be invited in for the baseline visit. This study will consent 74 smokers who are not ready to quit in the near future. Inclusion criteria will be a) ≥ 18 years old, b) smoke ≥10 CPD seven days per week c) have no plans to stop smoking in the next 30 days d) is willing to use NRT-patch and has no contraindications to

patch use (see below), e) have not used non-tobacco nicotine products (e.g., electronic cigarettes) or non-cigarette tobacco (e.g., smokeless) regularly in the past month, f) has not used nicotine replacement medications, varenicline, or bupropion or received smoking cessation counseling in the last month, g) has not reduced CPD by ≥ 25% in the last month, h) meets DSM 5 criteria for Tobacco Use Disorder, i) is currently or has previously been a menthol smoker, j) is not prescribed or currently taking methadone or buprenorphine, k) lives within a 1.5 hour drive of the University of Vermont, l) has been smoking cigarettes daily for ≥ 1 year, m) has access to a telephone on a daily basis, o) typically goes to sleep between 8:00 PM and 2:00 AM (to maintain a consistent schedule for nightly phone calls) p) is a US citizen or a permanent resident alien with a green card, q) is comfortable reading and writing in English and demonstrates comfort speaking in English, r) is not currently participating in another study that affects the way they smoke cigarettes, and s) is not currently breastfeeding or planning to breastfeed in the next 3 months. If a participant is female she will be excluded if she is pregnant, planning to become pregnant in the next 3 months, or of reproductive potential, sexually active and not using protection or on birth control. All females who are of reproductive potential will also complete a pregnancy test, whether they report that they are sexually active or not, to verify that they are not pregnant. Smokers who have tried to reduce CPD in the past but not in the last month will be included.

Potential participants who have a contraindication to nicotine patch use will be identified during the initial screening. Specifically, individuals who indicate they have any of the following health conditions will be excluded from the study: a) recent heart attack; b) heart disease that is untreated; c) arrhythmia or irregular heartbeat; d) high blood pressure not controlled by medications; e) an allergy to adhesive tape; f) skin problems that require treatment.

Inclusion of Minorities and Women: *Describe efforts to include minorities and women. If either minorities or women are excluded, include a justification for the exclusion.*

We will not exclude minorities or women from this study. However, we will use a convenience sample that is likely to not be representative of minority smokers because Burlington, VT has few minorities (<3%). Two of our lab's recent studies that recruited smokers from the Burlington area had 71% and 54% women. Although both genders are included and we plan post-hoc analyses of gender differences, we will likely not have sufficient power to detect statistically significant differences. The data from this study will be used to design a future trial with a nationally representative sample including minority populations who smoke cigarettes.

Inclusion of Children: *Describe efforts to include children. Inclusion is required unless a clear and compelling rationale shows that inclusion is inappropriate with respect to the health of the subjects or that inclusion is inappropriate for the purpose of the study. If children are included, the description of the plan should include a rationale for selecting or excluding a specific age range of children. When included, the plan must also describe the expertise of the investigative team in working with children, the appropriateness of the available facilities to accommodate children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study.* ***If children are excluded*** *then provide appropriate justification. Provide target accrual for this population.*

Children under the age of 18 will be excluded because purchase of tobacco in this age group is illegal in the United States.

For protocols including the use of an investigational drug, indicate whether women of childbearing potential have been included and, if not, include appropriate justification.

If a participant is female she will be excluded if she is pregnant, planning to become pregnant in the next 3 months, or of reproductive potential, sexually active and not using protection or on birth control. All females who are of reproductive potential will also complete a pregnancy test, whether they report that they are sexually active or not, to verify that they are not pregnant.

Pregnancy tests will only be conducted at the initial study visit, prior to consent, for females who are reproductive potential. Approved study personnel will be trained by the principal investigator to conduct pregnancy tests according to the test instructions. If a pregnancy test yields a positive result a second test will be conducted. If the second test is also positive then the study personnel will inform the individual that our pregnancy test indicates that she is pregnant, provide her with a list of women's health services and inform her that she is not eligible for this study. If the first pregnancy test yields a positive result but the second test yields a negative result, the study personnel will inform the individual that our pregnancy tests were inconclusive, provide her with a list of women's health services and inform her that she is not eligible for this study.

If HIV testing is included specifically for research purposes explain how the test results will be protected against unauthorized disclosure. Include if the subjects are to be informed of the test results. If yes, include the process and provision for counseling. If no, a rationale for not informing the subjects should be included.

X | ***Not applicable***

Recruitment: *Describe plans for identifying and recruitment of subjects. All recruitment materials (flyers, ads, letters, etc) need to be IRB approved prior to use.*

Recruitment will occur at the University of Vermont in Burlington, VT via a) Facebook ads posted to relevant groups and conversations, b) Craigslist ads, c) flyers posted in the Burlington area, d) study participants who refer others to the study, e) tables/booths in indoor and outdoor malls, and f) emailing and calling individuals who screen for other smoking studies in our center and consent to have their information shared with other studies for which they may be eligible.

FINANCIAL CONSIDERATIONS

Expense to Subject: *If the investigation involves the possibility of added expense to the subject (longer hospitalization, extra studies, etc.) indicate in detail how this will be handled. In cases where the FDA has authorized the drug or device company to charge the patient for the experimental drug or device,* ***a copy of the authorization letter from the FDA or sponsor must accompany the application. Final approval will not be granted until the IRB receives this documentation.***
There are very limited circumstances under which study participants may be responsible (either directly or via their insurance) for covering some study-related expenses. If the study participant or their insurer(s) will be billed for any portion of the research study, provide a justification as to why this is appropriate and acceptable. For example, if the study involves treatment that is documented standard of care and not investigational, state so. In these cases, the protocol and the consent should clearly define what is standard of care and what is research.

None.

Payment for participation: *Describe all plans to pay subjects, either in cash, a gift or gift certificate. Please note that all payments must be prorated throughout the life of the study. The IRB will not approve a study where there is only a lump sum payment at the end of the study because this can be considered coercive. The amount of payment must be justified. Clarify if subjects will be reimbursed for travel or other expenses.*

| | ***Not applicable***

Participants will earn $15 for each study visit, $5 for completing each weekly questionnaire, $2 per nightly call, and an additional $20 weekly bonus for completing all calls and visits. Participants will also earn $10 for completing the follow-up survey at week 9 of the study. Thus the total compensation for the study and follow-ups for a fully compliant participant is $300. Participants will be paid at weekly study visits in cash and/or gift cards during the study period. Participants will be mailed a $10 gift card for completing the follow-up survey.

Collaborating Sites*. When research involving human subjects will take place at collaborating sites or other performance sites when UVM/UVM Medical Center is the lead site, the principal investigator must provide in this section a list of the collaborating sites and their Federalwide Assurance numbers when applicable. (agreements may be necessary)*

X | ***Not applicable***

INFORMED CONSENT

Consent Procedures*: Describe the consent procedures to be followed, including the circumstances under which consent will be obtained, who will seek it, and the methods of documenting consent. Specify the form(s) that will be used e.g. consent (if multiple forms explain and place identifier on each form), assent form and/or HIPAA authorization (if PHI is included). These form(s) must accompany the protocol as an appendix or attachment.*

<u>Note</u>: Only those individuals authorized to solicit consent may sign the consent form confirming that the prospective subject was provided the necessary information and that any questions asked were answered.

Potential participants will give verbal or written consent to initial screening. If eligible and interested the study will be described to potential participants by phone or in writing and they will be encouraged to ask questions. If they remain interested in the study, they will be asked to come to our laboratory to provide written consent. The consent will emphasize that this is not a treatment study and that all study cigarettes are for investigational purposes only and are not available or intended for commercial use. Potential participants will be encouraged to

ask questions. The RA will conduct a brief test that asks participants to describe the study procedures to make sure they understand the study and to correct misperceptions. Participants will then be asked to sign the consent if they are interested in being in the study.

Information Withheld From Subjects: *Will any information about the research purpose and design be withheld from potential or participating subjects? If so, explain and justify the non-disclosure and describe plans for post-study debriefing.*

☐ ***Not applicable***

In order to increase the validity of participants' self-report about adherence to study cigarettes, we will 1) inform participants that self-reported noncompliance will not influence their payment or future participation and 2) employ a bogus pipeline technique that has been used in multiple prior studies.[32] Specifically, we will (falsely) tell participants that breath and urine tests will detect any non-study cigarettes that are smoked. In fact, the breath and urine tests will be used to measure CO and cotinine but cannot detect the difference between study and non-study cigarettes. This deception is intended to increase participants' self-report of any non-study cigarettes that they smoke. Knowing the extent to which participants smoke non-study cigarettes is integral to our primary specific aim (determine the relative feasibility of switching to VLNC vs reducing CPD). Participants will be debriefed about this deception and its rationale at the final study visit after the conclusion of the 5-week study period.

Attach full grant application, including budget information and/or any contract or draft contract associated with this application.