Impact of Alternative Nicotine-Delivery Products on Combustible Cigarette Use

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PROTOCOL

"Understanding the real-world impact of the use of three alternate nicotine-delivery products on combustible cigarette use"

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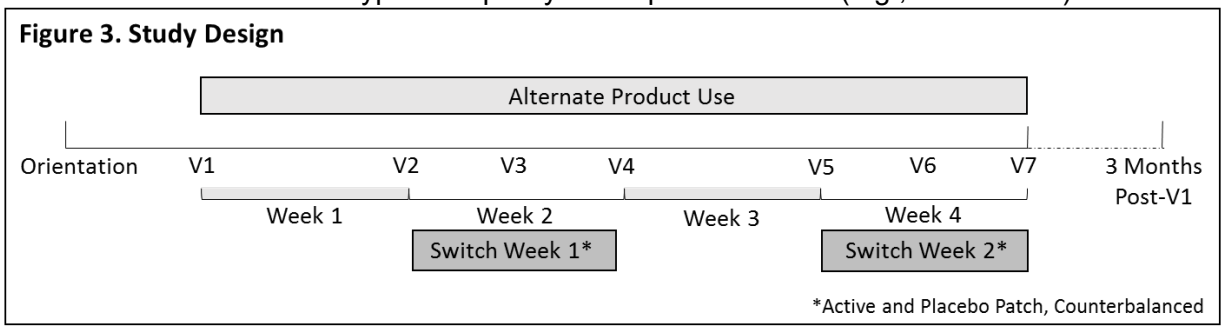
Study Overview and Design

This research will enroll 225 adult smokers in a mixed design study with a within-subjects factor (active nicotine patch vs. placebo patch) and a between-subjects factor (alternative products: VLNCs, Juul e-cigs, or no product). Participants will be randomized to receive either 4 weeks of VLNCs, 4 weeks of Juul e-cigs, or no alternative product. After one week practicing with the alternative product, participants will complete the first of two 7-day switching trials during which they will be asked to refrain from smoking their own cigarettes and encouraged to use the alternative product to which they have been assigned (although the no alternative product group will not have any other products to use). See Figure 3. All participants will be given 8 patches (active nicotine or placebo, in counterbalanced order, with one extra in case of mishaps) to use during the Switch Week. After this first Switch Week, they will smoke normally for one week and then have their second Switch Week using the other type of patch (active or placebo; see Figure 3). We opted to use a 7-day switching phase and only repeat it once to minimize the attrition that was problematic in other studies with longer experimental phases (e.g., three 10-day switching phases produced 45% attrition in the non-step down VLNC group[112]). Participants will complete ecological momentary assessments (EMAs) on smartphones at prior to and during the 4 weeks of product use. EMA targets include own cigarette use, alternative product use, withdrawal symptoms, rewarding value of product use (e.g., taste, buzz), and environmental and affective context of any tobacco product use. We will then conduct a 3-month follow-up to assess own cigarette and e-cig use, risk perceptions, and future use intentions. This design addresses the six critical methodological issues for understanding the impact of alternative products outlined by Villanti et al.[113]: 1) rigorously assesses the key outcome (conventional cigarettes smoked); 2) assesses product use during switching; 3) uses appropriate control/comparison groups; 4) measures product exposure/use that precedes switching; 5) evaluates the dose and duration of the product exposure/use; and 6) has clear evaluation of the type and quality of the products used (e.g., satisfaction).

Figure 3. Study Design



This mixed design study (within-subjects Patch factor: active nicotine and placebo patch; between-subjects Product factor: VLNC, e-cigarette, or no alternative product) will allow us to address key questions identified in the RFA-OD-18-002. Specifically, we will assess the potential "impact of novel and/or potential modified risk tobacco products on tobacco behavior" and provide data that estimates the real-world impact of potential regulatory actions. To address these questions, this research will focus on the following aims:

Primary Aim: Examine the ability of VLNCs and e-cigarettes to substitute for smokers' usual cigarettes compared to each other and to no alternative product use in real-world settings (between-subjects effects) and whether these effects are influenced by active nicotine replacement (interaction with within-subject factor).

Secondary Aims: Examine the main effects of VLNCs and e-cigarette use compared to each other and to no product use as well as their interaction with active vs. placebo patch on: 1) the use of study alternative products, and 2) mechanisms underlying product use (e.g.,

withdrawal alleviation, taste, satisfaction). We will also explore the contexts that promote or inhibit switching from conventional cigarettes to alternative products and whether participants' risk perceptions and key person factors (e.g., gender, race, education, psychiatric comorbidity) influence switching, alternative product use, and the potential mechanisms that drive such use behavior.

Recruitment and Study Entry

Participants from the greater Madison and Milwaukee, WI areas will be recruited via media recruitment methods (i.e., TV, newspaper, and earned media) that have recruited thousands of smokers[86,87]. We will also use Internet/paid Facebook advertisements that have been successful in our recent e-cig studies that recruited 422 smokers willing to provide EMA data during seven 2-week assessment periods over 2 years[101] and 74 dual users willing to reduce combustible cigarette use and switch to using only e-cigs[50]. Specifically, we will place Facebook ads in the Madison and Milwaukee markets, with keywords likely to reach smokers in the general public. Facebook will charge us per click on the ad. We do not plan to target a specific subpopulation beyond smokers in general. Finally, we will use word of mouth referrals from participants. We believe it is feasible to recruit 225 smokers for this study within 18 months.

Interested individuals will be asked to call the study telephone number and leave their name and telephone number, or leave their name and contact information on our secure website link from the Facebook page, to be called for a phone screen. Potential participants who pass the phone screen will be invited to attend a study session at the UW-CTRI Madison or Milwaukee office, where they will learn more about the study, have eligibility confirmed, and provide written informed consent.

Inclusion/Exclusion

Eligibility criteria include: 1) ≥ 21 years old; 2) able to read and write English; 3) no plans to quit smoking in the next 30 days; 4) not currently taking smoking cessation medication; 5) willing and medically able to use nicotine patches, very low nicotine cigarettes, and e-cigarettes; 6) not currently in treatment for psychosis or bipolar disorder; 7) smoking ≥ 5 cigarettes per day for the past 6 months; 8) exhaled carbon monoxide (CO) > 5 ppm; 9) no e-cig use within the last month; and 10) not currently pregnant or breastfeeding. We chose to exclude recent e-cig users to minimize the likelihood that participants would chose to use their own e-cig vs. the study e-cig. We opted not to exclude ever e-cig users to enhance the external validity of these findings. Analyses will examine the influence of prior e-cig use. It should be noted that use of other tobacco products (e.g., cigars, chew, snus) will not be exclusionary to enhance the external validity of the findings, but we will track such use. Incarcerated individuals will not be enrolled in this study. If study staff members learn that a participant is incarcerated at a time point subsequent to enrollment, the participant will be withdrawn.

Study Visits and Phone Contacts

Interested smokers will complete a phone screen to determine initial eligibility. Potentially eligible smokers will attend an Orientation visit where they will receive a detailed description of the study and provide written informed consent. Participants will then provide a breath sample to verify eligibility (CO > 5 ppm). Eligible participants will then be invited to complete the visit and complete baseline assessments. Participants will also be trained to use the smartphone to complete daily assessments, using the training that was effective in our prior research, and will schedule future study visits (see Table 1). At Visit 1, participants will be randomized to receive VLNCs, e-cigs, or no alternative product and will be trained to use the

Table 1. Study Assessments

	Orientation	V1	V2	V3	V4	V5	V6	V7	Call
Day	0	1	8	11	15	22	25	28	
Week	0	1	2	2	3	4	4	5	3 mo
Consent	X								
Demographics	X								
Tobacco use history	X								
Dependence	X								
Psychiatric history	X								
Risks perceptions	X							X	X
Future use intentions	X							X	X
Switching Weeks			Switch Week 1			Switch Week 2			
Alternate product use		X	X	X	X	X	X	X	X
Smoking	X	X	X	X	X	X	X	X	X
Cigarette and product evaluation	X	X	X		X	X		X	
Carbon Monoxide	X	X	X	X	X	X	X	X	
Cotinine		X	X	X	X	X	X	X	
Ecological momentary assessments	X	X	X	X	X	X	X	X	
Adverse health events			X	X	X	X	X	X	

product [if applicable]. The study database will randomize participants, stratified by clinic, gender, and race [White vs. Non-White], to enhance scientific rigor and reproducibility. Participants will use their alternative products as they would like for one week to become comfortable with the product[114]. Participants will also provide a urine sample for cotinine assessment and be given eight study patches to use during Switch Week 1 when all participants will be asked to abstain from using their own cigarettes for the week. At Visit 2, all participants will complete assessments, provide a breath sample for CO assessment and a urine sample for cotinine assessment, receive feedback on their compliance with the smartphone assessments. All participants will then attend a mid-Switch Week visit (Visit 3) and an end-of-Switch Week visit (Visit 4) to assess biomarkers (a breath sample for CO assessment and a urine sample for cotinine). At Visit 4, the end of Switch Week 1, all participants will be told that they can smoke as usual for a week. In addition, all participants will be given the other type of patch (active or placebo) and asked to use these patches at the start of Switch Week 2 (Visit 5) when they are asked to abstain from smoking their own cigarettes for a week. As during the prior Switch Week, all participants will attend visits mid-week and at the end of the week to assess biomarkers (Visits 6 and 7). To enhance reproducibility, we will attempt to schedule appointments at the same time of day (i.e., within a 2-hour window) for each participant so that there is consistent time for product use prior to providing the biological samples across study visits. We opted to use a 7-day switching period to provide a stronger test of the ability of these alternative products to substitute for cigarettes than in our prior study[50] (**A.5.1**), but to minimize the retention problems seen in studies with longer switches[112]. There are also strong theoretical and empirical reasons to suspect that withdrawal and other motivations for cigarette use will be strongest in the first 7 days of switching, and this design will allow sampling of the full range of work/non-work environments for most participants[115]. Participants will complete a follow-up assessment call at 3 months. The baseline visit will last 2 hours, but subsequent visits will last <30 minutes.

Participants will carry a smartphone to complete EMAs from Orientation through all 4 weeks of product use.

After providing consent at the Orientation visit, study staff will ask if the participant gives the study permission to stay in touch with them and send them reminders about upcoming study contacts during the study via email and/or text message. The staff member will remind them that email and text messaging are generally not a secure way to communicate about their health as there are many ways for unauthorized users to access email and text messages. The staff member will also inform them that they do not have to provide their email address or text message number to participate in this study.

Assessments

To address the primary aim of examining whether VLNCs and e-cigs serve as effective substitutes for conventional cigarettes, and whether use of these alternative products interacts with nicotine replacement, we will conduct extensive assessments of participants' use of their own cigarettes, their use of their assigned alternative products, use contexts, and potential motivators for such use behavior (e.g., withdrawal, reward value of products, risk perceptions). We will also assess person factors and beliefs that may provide insight into who is able and willing to use these alternative products to substitute for cigarettes and which mechanisms might be more relevant for which smokers. To the extent possible we will use measures from the PhenX Toolkit, a collection of broadly validated measures, to enhance the ability to harmonize data from this study with other studies. See Table 1 for the timing of assessments.

Baseline assessments. At the Orientation visit, participants will complete assessments of basic demographics, motivation and self-efficacy for smoking cessation, and tobacco use history using items from our previous research[86,87,121] and the PhenX Toolkit. This will include a detailed assessment of the timing and use of all non-cigarette tobacco and nicotine products. We will assess lifetime and past year psychiatric comorbidity using a validated self-report instrument[122] as well as psychiatric vulnerability using the validated self-report Anxiety Sensitivity Index-III and the Distress Tolerance Survey. We will also assess alcohol and marijuana use. Participants will complete two validated measures of cigarette dependence, the Fagerström Test of Cigarette Dependence (FTCD[123,124]) and the Brief Wisconsin Inventory of Smoking Dependence Motives (Brief WISDM[125]). We will assess risk perceptions of conventional cigarettes, VLNCs, e-cigs, and patches using items that target the four key constructs identified by the Tobacco Centers of Regulatory Science (TCORS) network: 1) perceptions of benefits, 2) harm perceptions, 3) addiction perceptions, and 4) perceptions of social norms[126]. These assessments will be repeated at Visit 7 and the 3-month follow-up call. We will also assess future intentions to use VLNCs, e-cigs, and the patch.

Visit assessments. At each study visit, participants will complete assessments of affect using the well-validated Positive and Negative Affect Scale (PANAS[127]), withdrawal symptoms using the validated Wisconsin Smoking Withdrawal Scale (WSWS[128]), and craving using the Brief Questionnaire of Smoking Urges (QSU-Brief[129,130]) from the PhenX Toolkit. At Visits 1 through 7 participants will complete the modified Cigarette Evaluation Scale (mCES[71,131,132]) for cigarettes and at Visits 2 through 7 they will complete the mCES for their assigned alternative product based on their reactions in the last 24 hours. The 12 items of the mCES assess product satisfaction, psychological reward, aversion, enjoyment of respiratory tract sensations, and craving reduction. We will use timeline follow-back methods[133,134] to assess daily use of participants' own cigarettes, assigned alternative products, and patch if the visit occurs during a Switch Week. These data will be used to supplement EMA reports in case of missing EMA data. Participants will also be asked at all visits except Visit 1 (when they will not have any study products or medication yet) about any possible adverse events from using VLNCs, e-cigs or the patches[135]. At the final visit (Visit 7), we will again assess acceptability, risk perceptions, and

intentions to use cigarettes, VLNCs, e-cigs, and patches. We will also assess how the Juul e-cig compares to other e-cigs participants have used, including what they like or do not like Juul, using a combination of questionnaires and open-ended questions to provide additional information regarding Juul acceptability among adults.

The primary outcome in this research is the number of their own cigarettes participants smoke during the Switch Weeks, although we will also examine the proportion of cigarettes replaced as a tertiary outcome. We will be clear with participants that we want them to do their best to switch completely from their own cigarettes during the two Switch Weeks, but that it is very important for us to know if, and when, they smoke any of their own cigarettes. Research has shown that self-reports of switching behavior are higher than biochemically confirmed reports of switching[84,136], given the high rates of non-compliance and misreporting[30]. To enhance the validity and scientific rigor of the self-report of smoking their own cigarettes, we will conduct carbon monoxide (CO) and cotinine assays. Participants will be told that these tests are used to reflect conventional cigarette and alternative product use, and we will emphasize the importance of accurate reporting of cigarette and alternative product use.

We cannot biochemically verify abstinence from conventional cigarettes in this research due to the experimental conditions and the clearance rates of CO and cotinine. Specifically, we cannot biochemically verify complete substitution in the VLNC group during the active patch Switch Week because VLNCs still produce CO and cotinine is a nicotine metabolite that cannot distinguish the source of nicotine (i.e., from a combustible cigarette vs. a nicotine replacement product). Further, CO can be used to biochemically verify abstinence only within the last 12-18 hours, given its short half-life (4.5 hours[137]), making it impossible to verify smoking that might have occurred more than one day prior to the assay. Cotinine's half-life is 10-30 hours[138], making it impossible to detect recent abstinence from nicotine products. Therefore, at each visit, participants will provide a breath sample for CO assessment and a urine sample for cotinine assay to evaluate changes in exposure to combustible and nicotine products. Trained study staff at UW-CTRI will collect the participant's urine and follow procedures according to NicAlert directions (see product insert) to get a test reading within the same day. All samples and test results will be labeled with the date of collection and the subject's numerical ID. Urine will be disposed of after cotinine levels are read and recorded.

We will use an exhaled CO < 6 ppm to indicate recent abstinence from combustible products, based on Perkins' cut-off of <5 ppm using a Breathco CO monitor[139], which is similar to the Vitalograph brand, and produces CO values approximately 1-2 ppm lower than the Bedfont Smokerlyzer monitors[140] we will use in this research. Cotinine will be assessed using NicAlert strips, an immunochromatographic assay that uses monoclonal antibody-coated gold particles and a series of avidity traps to quantify cotinine level. We will use the <100 ng/ml cut-off for non-tobacco users recommended by NicAlert to indicate abstinence from nicotine. The NicAlert strips have 91% specificity and 92% sensitivity at this cut-off compared to liquid chromatography-mass spectrometry[141]. To maintain the patch double-blind and enhance the scientific rigor, study staff who have no contact with participants will conduct the urine assays.

Ecological momentary assessments. We will assess cigarette and alternative product use in real time in the real-world environment (i.e., ecological momentary assessment [EMA]) using a smartphone app we have used in our prior research. Participants can choose to have the app downloaded on their own smartphone or they will be given a smartphone at the Orientation visit and will be trained to press a button marked "Cigarette" every time they start a new cigarette and to press one marked "JUUL" or "Study Cigarette" every time they use a VLNC or e-cig (which they will be able to use after Visit 1). Participants randomized to receive no alternative product will just record their cigarette use. Daily, each time someone presses a product use button (either to say they used the alternative product or to say they smoked their

own cigarette), there is approximately a 30% chance a more comprehensive assessment (3 minutes) will be triggered that will include: 1) time since prior use of cigarette/alternative product), 2) use context (e.g., smoking prohibited, others vaping/smoking, home, work), activity, and withdrawal symptoms and affect prior to use, and 3) individual items from the mCES that tap potential mechanisms (e.g., product satisfaction, psychological reward, aversion, enjoyment of respiratory tract sensations, and craving reduction). The comprehensive assessments will be specific for each type of use event (i.e., cigarettes, VLNCs, and e-cigs). All participants will complete an evening assessment prior to going to bed. Evening reports (5 minutes) will assess: affect, withdrawal, use of cigarettes and alternative products, overall satisfaction with cigarettes/alternative products, use of patch during Switch Weeks, smoking cues, stressors, and pleasure in daily activities. Participants will spend less than 25 minutes each day recording use events and answering questions, eliminating the problems of recall bias or participants prefilling or back-filling a traditional daily diary. This approach is more rigorous than relying on participants to document their use of non-experimental products using a paper and pencil log[142]. We have conducted numerous EMA studies and will use the strategies that have been successful in our earlier work: training in assessments, ability to briefly postpone assessments, use of counters, etc.[50,86,143]. This frequency of assessment is of moderate intensity relative to protocols used in our prior work[86].

Follow-up assessment call. Three months after Visit 1, participants will complete a brief follow-up assessment call to assess current smoking, use of any alternative products, motivation and self-efficacy for smoking cessation, risk perceptions, and future plans to use VLNCs, e-cigs, and patches.

Participants who are interested in quitting smoking after Visit 7 will be offered the Wisconsin Tobacco Quit Line toll-free number? (1-800-QUIT-NOW 784-8669) and the phone number(s) for smoking cessation studies being conducted at our Center.

Alternative Products and the Nicotine Patch

The goal of this research is to examine the potential impact of alternative tobacco products on the use of conventional cigarettes, alone and in combination with nicotine replacement, to simulate a potential regulatory scenario in which a variety of tobacco and nicotine products are available that vary in degree of risk, similarity to cigarettes, and acceptability. Therefore, we opted to use two products that have shown potential to substitute for traditional cigarettes: very low nicotine content cigarettes (VLNCs) and the Juul e-cig.

VLNCs. Participants randomized to receive VLNCs will receive NIDA's reduced nicotine cigarettes with 0.03 (±0.01) mg of nicotine with a tar yield of 9±1.5 via NIDA's Drug Supply Program (NOT-DA-14-004). These cigarettes have been characterized by Richter and colleagues[116]. Participants will be able to choose either menthol or non-menthol VLNC's consistent with prior research (e.g., [100]) and to enhance the external validity of these findings. Participants will be instructed to smoke the VLNCs the same way they would their own cigarettes and will be given enough VLNCs to completely substitute for their own cigarettes during the Switch Weeks (i.e., if they smoke 20 cigarettes per day, they will receive enough VLNCs to be able to smoke 20 VLNCs per day).

One real-world safety concern with VLNC use is that it might result in compensatory smoking or oversmoking and increased exposure to carcinogens[117]. However, many studies have shown that smokers engage in minimal or no compensatory smoking[73,82,83,102,118]. If participants in this condition need more VLNCs, they will be provided with additional VLNCs at subsequent study visits. However, we will monitor compensatory smoking by examining both VLNCs smoked/day as well as carbon monoxide (CO) levels. Participants found to be smoking more than twice their usual cigarettes/day or who demonstrate a CO ≥100 ppm will be

discontinued from the study protocol. Research has also shown that there is no increased risk with respect to cardiovascular biomarkers or exposure to toxicants among smokers using VLNCs[67,97,119,120] and this study will produce a very brief exposure (i.e., only 4 weeks, which is less than the 6 weeks used by other studies[67,83,97]).

E-cigarettes. Participants randomized to receive e-cigs will receive a Juul e-cig and 4 weeks of pods. Each Juul pod of e-liquid contains 0.7ml nicotine by volume / 5% nicotine by weight. Participants will be given a choice of four flavors: tobacco and menthol. To enhance external validity, participants will be allowed to choose different flavors at each study visit if they wish. Each pod is considered to be the equivalent of 1 pack of cigarettes. Therefore, participants will be provided enough pods to match their daily cigarette use. As with the VLNCs, if participants assigned to this condition need more pods, they will be given more pods at the subsequent study visits. Participants will be instructed in how to use the Juul at Visit 1, and encouraged to practice using the Juul during the first week so that they feel comfortable using it during the Switch Weeks and are able to titrate their nicotine consumption.

Nicotine patches. During the Switch Weeks, all participants will receive 8 patches (7 days' worth plus one extra in case of mishaps), placebo patches for one Switch Week and active patches for the other, in counterbalanced order. Both staff and participants will be blind to patch type. Active patch dosing will be based on the package insert: >10 cigs/day = 21 mg patch and ≤10 cigs/day = 14 mg patches. We opted to use a placebo control, rather than a no-patch control, to ensure that the NRT effects were due to nicotine replacement *per se* rather than expectancies. Using nicotine patches will provide critical information regarding whether a steady-state nicotine replacement interacts with an *ad lib* alternative product's ability to replace conventional cigarettes. We opted to use the highest dose of nicotine patch appropriate based on daily smoking to maximize the potential effect of nicotine replacement. However, if participants experience symptoms of nicotine overdose (e.g., nausea, dizziness), they will be told to remove the patch. Our prior research suggests that the majority of smokers are able to tolerate both a 21 mg patch and *ad lib* use of other nicotine replacement[86,87]. We are currently conducting a study with active and placebo patches, and the two types of patches are visually identical. We will use the same vendor for this research.

All study products (nicotine and placebo patches, JUUL e-cigarettes, and very low nicotine cigarettes) will be received from vendors at the Center for Tobacco Research and Intervention Madison office. Products stored in a locked room or cabinet at the Madison and Milwaukee research sites until processed and portioned for dispensing. Dissemination bags containing processed study product will be labeled with Study ID and participant initials and stored in secure, locked cabinets, closets or rooms in Madison and Milwaukee. Study staff with no contact with participants will process and portion out the study products to maintain the double-blind on the patches. Participants will be asked to return all unused patches, VLNCs and JUUL pods as well as the JUUL device at the end of the study. Participants in the JUUL condition will also be asked to return used JUUL pods at each study visit.

Promoting Continued Experimental Participation

We will promote participation and adherence to study procedures using strategies that were effective in our prior research. We will: 1) allow flexibility in scheduling[144-146]; 2) provide participants with a single, consistent liaison[144,147,148]; 3) ensure that research staff are culturally sensitive[149,150]; 4) send reminder letters prior to the Month 3 follow-up call and make reminder calls to remind participants about their Orientation Visit and Visits 1, 2 and 5; and 5) compensate participants for their time[147]. Specifically, participants will be paid $20 for completing each of the 8 study visits and the 3-month follow-up call (up to $180), and $200 for completing 80% of the EMA prompts or $150 for completing 75% of the EMA prompts.

Participants may receive up to $380 in total compensation. Finally, participants will be invited to share their email or mailing address to receive a copy of the final research results.

Analytic Plan

The primary aim of this research is to examine the ability of VLNCs and e-cigs to substitute for smokers' usual cigarettes compared to each other and to no alternative product use (Product between-subjects effects) and whether these effects are influenced by steady-state nicotine (Patch within-subjects factor: active vs. placebo patch). The primary analysis model will consist of a mixed analysis of variance (ANOVA) with three levels of the Product between-subjects factor (VLNCs, e-cigs, no alternative product) and two levels of the Patch within-subjects factor (active nicotine patch, placebo patch). To address the primary aim, we will explore statistically significant main or interaction effects in the mixed ANOVA by means of unadjusted simple main effects, interaction contrasts, and pairwise comparisons[156,157]. Specifically, we will examine the main effect of Product to evaluate the hypothesis that participants who do not have an alternative product will report smoking significantly more of their own cigarettes during the Switch Weeks compared to those who have VLNCs or e-cigs. We will also conduct a pairwise comparison to explore whether there is a significant difference in the number of conventional cigarettes smoked in the VLNC vs. e-cig conditions. We will use the main effect of Patch (active vs. placebo) to evaluate the hypothesis that participants will report smoking fewer of their own cigarettes during Switch Weeks when they receive active nicotine patches compared to placebo patches. We will also test the Patch x Product interaction, with follow-up pairwise comparisons, to examine whether steady-state nicotine produces a differential effect on the number of conventional cigarettes smoked, based on which alternative product a participant was assigned to receive.

The primary outcome is the number of conventional cigarettes smoked during each Switch Week. Based on the literature and our own research, it is possible this outcome will not be normally distributed (i.e., a substantive proportion of participants may smoke no conventional cigarettes during a Switch Week). Therefore, prior to conducting main analyses, we will examine the distributional characteristics of the primary outcome to determine if a transformation is needed (e.g., if the distribution substantially deviates from a normal distribution).

The secondary outcome is number of VLNCs or JUUL pods used during each switch week. This research will also examine the main effects for Product and Patch and the Product X Patch interaction effect on other exploratory outcomes: 1) the proportion of conventional cigarettes replaced; 2) the use of alternative tobacco products; 3) use contexts; and 4) potential mechanisms such as rewarding value of the alternative products and conventional cigarettes, alleviation of withdrawal symptoms, and taste. We will also explore the impact of person factors (e.g., sex, education, psychiatric comorbidity, dependence) and risk perceptions on the primary, secondary, and exploratory outcomes. We will include these variables as covariates in the analyses, and we will include covariate interaction terms with the between- and within-subjects factors (e.g., sex x Product; sex x Product x Patch) to determine whether these individual difference variables moderate the ability of the alternative products to substitute for conventional cigarettes. To examine use contexts and putative mechanisms driving alternative product use and substitution for conventional cigarettes, we will use the daily EMA data from the evening reports as well as data from the quasi-random daily assessments that will be collected during the Switch Weeks as described above as the exploratory outcome variables. One set of analyses will test summary versions of the outcomes (e.g., means or counts across the Switch Weeks); another set of more fine-grained analyses will preserve the intensive longitudinal data (ILD) aspect of the EMA data collected during each of the 7 days of the Switch Weeks. For the summary versions of the outcomes, the alternative product use outcome will consist of the mean alternative product use events per day reported during the Switch Weeks and the context

and mechanisms variables will be based on means across the 7 days of the Switch Weeks. For these summary outcomes, we will use statistical models similar to the analyses described above for the primary outcome. For the ILD outcomes, we will create one set of outcomes based on the evening report that assesses experiences across the full day and another set based on the 3 quasi-random comprehensive assessments that occur during the day. For the ILD versions of the outcomes, we will use conditional growth curve models that permit slope and intercept parameters to be evaluated across the 7 days of the Switch Weeks as a function of group; these models also permit examination of other forms of change over time (e.g., linear, quadratic, cubic). We will explore two main approaches to growth curve modeling: a multilevel modeling (MLM) approach[158] and a structural equation modeling (SEM) approach[159]. Although similar, each of these modeling approaches has advantages and disadvantages[160] that we will exploit in exploratory analyses. While we are not powered to detect mediation due to funding limitations, we will conduct exploratory mediation analyses to provide information for future research on whether these mechanisms mediate the effects of alternative product use on the use of conventional cigarettes.

Power for Primary Aim Hypotheses

With attrition-adjusted n=54 per group for a between-subjects pairwise comparison, the study is powered to detect a difference of 3.3 cigarettes (SD=6); a corresponding within-subjects pairwise comparison (SD=6, correlation=0.5) is powered to detect a difference of 2.8 cigarettes. Thus, we feel that a total N=225 provides adequate power to detect predicted effects.

Protection of Human Subjects

Human Subjects Involvement and Characteristics. A total of 225 participants smokers will be recruited to participate in the proposed research. Specific eligibility requirements are: 1) ≥ 21 years old; 2) able to read and write English; 3) no plans to quit smoking in the next 30 days; 4) not currently taking smoking cessation medication; 5) willing and medically able to use nicotine patches; 6) not currently in treatment for psychosis or bipolar disorder; 7) smoking ≥ 5 cigarettes per day for the past 6 months; 8) exhaled carbon monoxide (CO) > 5 ppm; 9) no e-cig use within the last month; and 10) not currently pregnant or breastfeeding. Use of other tobacco products (e.g., cigars, chew, *snus*) will not be exclusionary, but we will track such use. Vulnerable populations (e.g., children under 18, prisoners) will not be included in the proposed research.

Sources of Materials. Participants in this study will provide data for the express purpose of research. Data collected from participants in this research will consist of: 1) answers to questionnaires and interviews assessing tobacco use history, demographics, nicotine dependence, affect and psychiatric history, and risk perceptions of cigarettes and alternative products; 2) recording of their own cigarette use and alternative product use and responses to ecological momentary assessment (EMA) prompts on a smartphone; 3) breath samples to permit determination of carbon monoxide, which reflects smoking status; and 4) urine samples to assess biomarkers of exposure to nicotine. All data are retained in the study database. The study database access is limited by physical and password protection to those staff members and investigators directly involved in the study and under the supervision of the UW IRB.

Potential Risks. Risks associated with this research are judged to be minimal. None of the physiological, self-report, or behavioral measures constitute a significant risk. Withdrawal for the Switch Weeks is associated with a number of unpleasant symptoms such as sleep

disturbance, hunger, craving, and negative mood. These symptoms are quickly reversed once the participant smokes their own cigarettes. These symptoms will also be alleviated to some degree by the alternative products and the active nicotine patches. Most smokers have tried to quit in the past and are familiar with these phenomena. Participants will be informed about the likely effects of smoking withdrawal. The risks of VLNCs are no greater than the risks of smoking their own cigarettes, although there is the potential for compensatory smoking or oversmoking. The risks of using e-cigarettes have been deemed to be less than smoking a conventional cigarette (National Academy of Sciences, 2018). However, participants may experience sore throat or dry mouth. Recently the FDA has reported that users of e-cigarettes have experienced seizures, mostly among adolescent and young adult users. The risks associated with the nicotine patch are sufficiently minimal that they are available over the counter. The nicotine patch is generally well tolerated, but up to 50% of participants may have a local skin reaction, and rarely, individuals may have a more systemic allergic reaction. Although most smokers have tolerance to nicotine, symptoms of acute nicotine toxicity (nausea and vomiting) are possible, especially in conditions where participants receive e-cigarettes and the active nicotine patch.

Finally, there is a small risk of loss of confidentiality. This could occur through a number of possible avenues, all highly unlikely due to the data security measures in place. The University of Wisconsin's Center for Tobacco Resesarch and Intervention (UW-CTRI) computer system is linked to the UW network through a firewall, which is managed by the School of Medicine and Public Health network team, via a fiber link which is maintained by the UW Division of Information Technology. No data are stored on individual computer hard drives. All data are transmitted from the point of collection to the UW-CTRI server through secure, encrypted web connection. There are rare occasions when, due to a loss of internet access or computer hardware failure, data are collected in paper forms, which could be taken or lost. In addition, consent forms are obtained in paper copy; these forms contain the participant name and signature. Finally, the University of Wisconsin and the National Cancer Institute may inspect the signed consent forms. Because of this possible need to release information to these parties, we cannot guarantee absolute confidentiality.

Participants will be informed about all of these risks prior to providing written informed consent.

Adequacy of Protection Against Risks

Recruitment and Informed Consent. Participants will be recruited from the greater Madison and Milwaukee, WI areas via the media recruitment methods (i.e., TV, newspaper, and earned media) that have recruited thousands of smokers. We will also use Internet/Facebook advertisements that have been successful in our recent e-cig studies. Interested potential participants will contact the study via phone. Study staff will call interested potential participants within 48-72 hours to introduce the study, assess interest and screen for eligibility. If the person is interested and eligible, an in-person Orientation Visit will be scheduled. At this visit, the smoker will learn about general requirements for participation (e.g., need to switch from using their own cigarettes for 2 7-day Switch Weeks, participation in assessments) as well as risks associated with nicotine withdrawal, alternate product use, patch use, and the possible loss of confidentiality. Study staff will then provide each study candidate with an IRB-approved

informed consent document. Study candidates will read the informed consent document and will be given an opportunity to ask any questions regarding study participation. A research staff member will read the consent form to the study candidate if needed or desired. The consent form will include necessary HIPAA language. Participants will be required to sign the consent form and will then be given a copy of the consent form.

Protection Against Risk. Risks related to alternative products and the nicotine patch will be minimized through close monitoring. The PI will be responsible for routine monitoring of unanticipated health events. This risk protection includes procedures for monitoring of all events through scheduled biweekly meetings with study staff and review of written documentation. Unanticipated health event assessment, recording, reporting and investigation will be accomplished through staff training, structured/standardized assessments of untoward occurrences/events, and regular monitoring the PI. The PI has ultimate responsibility for ensuring that unanticipated health events are detected and reported in a timely manner. Health events that raise concerns (e.g., allergic reaction, symptoms suggestive of nicotine toxicity) will be immediately reported to the PI who will determine an appropriate course of action.

The U.S. Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) are investigating recent reports of serious lung disease associated with the use of vaping/e-cigarette devices. Many of the illnesses are related to vaping THC products. The FDA has advised people to avoid buying vaping products on the street, to refrain from vaping THC or other oils, and to not modify or add any substance to vaping products purchased at stores. We will tell all participants that if they use a vaping device/e-cigarette products, they should watch for symptoms such as cough, shortness of breath, chest pain, nausea, vomiting, diarrhea, abdominal pain, fatigue, fever, and weight loss, and get medical attention right away for any health concerns. They can also call their local poison control center at 1-800-222-1222.

To facilitate safety, participants who are not be medically appropriate to use the nicotine patch will not be included in the study (e.g., no previous allergic reactions). Once enrolled, study protocols will assess side effects and unanticipated health events at all study visits and follow-up contacts. We will recommend using a lower dose patch or no patch if the participant experiences symptoms of nicotine toxicity or other troublesome side effects during their Switch Weeks. If participants in the VLNC condition are found to be smoking more than twice their usual cigarettes/day or have an exhaled CO ≥ 100 ppm, they will be discontinued from the study protocol. We will refer participants their primary care provider as needed. Should excessive risk to study participants be determined, the study will be stopped and all participants notified in a manner appropriate to the nature of the risk.

Confidentiality of participant data and information will be accomplished by using participant ID numbers as unique identifiers, allowing us to keep participant data separate from identifying information. The UW-CTRI Information Technology Administrator, Jonah Stankovsky, manages the hardware, data, security, and infrastructure below the firewall. Access to the network is limited to only UW-CTRI owned and actively managed devices. All devices automatically lock and are password protected after 15 minutes of inactivity. All portable devices are encrypted for data security and no PHI is stored on local devices. All data stored on the network file server is limited by the principle of least privilege. With respect to the study smartphones, to provide confidentiality and HIPAA compliance, UW-CTRI uses MDM software (mobile device management software) in said study to protect and collect subject data. All

mobile devices that are provided to subjects are deployed with password protection, MDM software, encryption, and other lockdown features. Each device returned to UW-CTRI from subjects are wiped and factory reset, then redeployed with the above features and then minimal features to complete data collection per study design. The minimal features that are enabled on each device are phone, text messenger and data collection app. There will be no data stored on the UW-CTRI mobile devices, it will be directly transferred from the app to a secure UW-CTRI server.

As stated above, no data are stored on individual computer hard drives. All data are transmitted from the point of collection to the UW-CTRI server through secure, encrypted web connection. On those rare occasions when, due to a loss of internet access or computer hardware failure, data are collected in paper forms, these forms will be stored securely at UW-CTRI until the data are able to be entered into the database and the paper document will then be disposed of securely. No identifying data other than a participant ID number is entered on any data form. Consent forms are obtained in paper copy; these forms contain the participant name and signature. These are retained in secure files at the clinic where they are collected and then transported to the UW-CTRI office, where they are securely stored.

Finally, no publications or presentations resulting from this research program will contain any identifying information about individual participants.

Potential Benefits of the Proposed Research to the Participants and Others

There are no specific benefits for smokers participating in this study, beyond the benefit of helping inform scientists and FDA regulators about the ability of these alternative products to serve as substitutes for conventional cigarettes and whether this is influenced by the presence of steady-state nicotine.

Importance of the Knowledge to be Gained

The results from this research will provide important insight into how well very low nicotine cigarettes and e-cigarettes serve as a substitute for conventional cigarettes and how this is influenced by the presence of steady-state nicotine. Further, these data will inform scientists and regulators about the potential mechanisms that may support the use of alternative products. This information will aid scientists and regulatory bodies in understanding the real-world impact of potential regulatory policies regarding access to safer nicotine sources and reducing the addiction potential of combustible tobacco products.

As outlined above, the risks of this study are minimal and limited to the discomfort of withdrawal, the use of alternate products and the nicotine patch, and the small risk of breach of confidentiality. The potential study impact on informing the science and policy debate over nicotine regulation far outweigh these risks.

Data and Safety and Monitoring Plan

***Monitoring study progress and the safety of participants*.** The Principal Investigator is responsible for routine monitoring of the progress of this research. This includes scheduled biweekly meetings with study staff and review of written documentation. Data reviewed at these meetings will include the number and type of participants enrolled, the number and reasons for exclusions from enrollment, the number treated and the stage of intervention, summary of

adverse events (AEs), and individual review of serious adverse events (SAEs) and study participation. In addition, SAEs or AEs that raise concerns (e.g., allergic reaction, significant change in mood or suicidality) will be immediately reported to the study physician who will determine an appropriate course of action, which may include discontinuation of study products. As data become available, the Principal Investigator will review the data on a regularly scheduled basis (initially weekly and later monthly) to determine progress. To facilitate participant safety, study participants must meet study inclusion and exclusion criteria. Once enrolled, study protocols will assess the presence of AEs and SAEs at all study contacts, with the exception of the final assessment call 3 months after the use of study products. Should either excessive risk to study participants be determined, the study will be stopped and all participants notified in a manner appropriate to the nature of the risk and/or lack of benefit. When taking that step the Principal Investigator will consult with the IRB and NCI.

***Plans for the reporting of unanticipated health events*.** This DSMP requires that the Principal Investigator notify NIH and the University of Wisconsin IRB in a timely manner (consistent with IRB and NIH policies) of the occurrence of any SAE or any AE that is severe, unexpected, and possibly related to study products or protocol. Because this study involves a pharmaceutical agent, if an SAE might be related to study patch use, both the Food and Drug Administration (FDA) and the manufacturer will also be notified within five days of investigators becoming aware of the event. Examples of SAE would be untoward medical or intervention occurrences that result in death, are life-threatening, require hospitalization or prolonging of existing hospitalization, create persistent or significant disability/incapacity, or involve congenital abnormality/birth defects. Unanticipated problems will be monitored and reported to the DSMC. These are events that meet the following criteria: 1) suggest the research places subjects or others at increased risk of harm, 2) are unexpected (in terms of nature, severity or frequency) given the research procedures that are described in the study-related documents, and 3) possibly related to study participation. Any SAE will be queried and reported if it meets the definition of unanticipated problem. The Principal Investigator will also be responsible for the accurate documentation, investigation and follow-up of all study-related adverse events.

Adverse event assessment, recording, reporting, and investigation will be accomplished through staff training, structured/standardized assessments of untoward occurrences/events, and regular monitoring by the Principal Investigator and study physician. The Principal Investigator has ultimate responsibility for ensuring that SAEs are detected and reported in a timely manner. Additionally, the IRB will receive an annual report of all SAEs and AEs meeting the criteria listed above.

Plans for assuring that any action resulting in a temporary or permanent suspension of an NIH-funded research is reported to the NIH grant program director responsible for the grant. The NIH grant program director will be notified within five days if the Principal Investigator deems it necessary to suspend this research. In the case of a temporary suspension, the Principal Investigator will develop a plan for continuation of the project and discuss this plan with the NIH grant program director in a reasonable time frame.

Plans for assuring data accuracy and confidentiality and protocol compliance. The Principal Investigator, supported by CTRI analysis staff will develop plans for assuring data accuracy and protocol compliance. Such plans will include data verification and protocol

compliance checks. The Data Manager and IT Manager shall be responsible for ensuring that the data for the project are securely stored, that storage is in compliance with University and federal regulations and that no unauthorized persons have access (electronic or physical) to any participant-identifiable data. All HIPAA regulations and guidelines will be followed, and all study staff must complete approved human subjects and HIPAA training programs.

Data and Safety Monitoring Committee

In addition to the protections outlined in the DSMP (above), this research project will have an independent Data Safety and Monitoring Committee (DSMC). The DSMP specifies overall monitoring that will be conducted by Principal Investigator, including timely reporting of AEs and SAEs. Every six months, the DSMC will convene to review the overall safety data, as well as data on safety summarized by treatment condition. As per NIH guidelines, the objective of these reviews will be to determine whether continued conduct of the research poses any undue risk for participants.

The existing DSMC is chaired by Dr. James Cleary, leader of the Cancer Control Program of the UW Comprehensive Cancer Center. Dr. Cleary is an experienced physician and clinical trial researcher with no involvement in any of this project's research activities. Dr. Cleary is joined on the DSMC by Dr. James Sosman and Dr. Burke Richmond. Dr. Sosman is Associate Professor of Medicine and Medical Director of the HIV/AIDS Comprehensive Care Program at UW Hospital and Clinics who has previously collaborated on a clinical trial of smoking cessation with UW-CTRI. Dr. Richmond is an otolaryngologist who has served on independent DSMBCs for Phase II and III trials involving a nicotine vaccine. Neither has direct involvement with any of the proposed research. The Principal Investigators will report to the DSMC; the three DSMC members will make the final determinations as to study continuation.

ClinicalTrials.gov Requirements

This research project will be registered with clinical trials.gov prior to the enrollment of the first subject. Final data (including outcomes and adverse events) will be reported to clinicaltrials.gov within 1 year of the conclusion of the trial.

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