Clinical Outcomes of a Nationwide, Naturalistic E-Cig Trial (CONNECT)

NCT03453385

Protocol Version Date: 11-1-2021

TITLE: CONNECT (Clinical Outcomes of a Nationwide, Naturalistic E-Cig Trial)

ABSTRACT
Electronic (e-)cigarettes are by far the fastest growing segment of the non-combustible tobacco market available to smokers. Most studies of e-cigarettes are 1) lab-based studies of either pharmacokinetics or toxicant exposure 2) cross-sectional studies of prevalence and predictors of use or, more rarely, 3) uncontrolled cohort studies. The three randomized studies to date, all based outside the US, are cessation-focused and thus do not say anything about the natural process by which smokers adopt e-cigarettes, and how such adoption changes smoking behavior. Studies of naturalistic, self-determined used are important to understand real-world impact of e-cigarettes. Many of the existing studies are limited by methodological issues that constrain interpretation: selection bias resulting from comparisons of self-selected users vs. non-users, retrospective or cross-sectional designs that inhibit causal inferences, absence of biomarkers of exposure, and/or insufficient sample size. The absence of prospective, randomized but still ecological studies is a glaring omission in the literature. In fact, there has yet to be a study that a) randomizes smokers to e-cigarettes vs. not, b) is focused on naturalistic outcomes that occur in real time, c) is prospective, with sufficient follow-up duration, d) provides data on nicotine/tobacco exposure, e) is of sufficient sample size, and f) is US-based, an important consideration given upcoming regulatory changes. We know of no published study with even two of these criteria.
We propose a nationwide randomized clinical trial in which smokers (N=660) are randomized to receive samples of e-cigarettes vs. not. Randomization will be 2:1 to increase precision of uptake outcomes (Aim 1). A subset of smokers (n=120) will be recruited locally, to assess the impact of e-cigarette use on biomarkers of exposure (Aim 2). (For this IRB application, we are increasing the total number of study participants by ~10% from 540 to 600 for the national sample and from 120 to 150 for the local sample, for a total of 750 study participants, to account for the ~10% of participants who mail us a consent back but who we never reach for the first study phone call – see section 2.1 Recruitment and Informed Consent on page 18 of this protocol.)
Finally, though ours is not a cessation study, it would be a missed opportunity if we did not track cessation outcomes (Aim 3) or sufficiently power the trial to detect differences if they emerge. Thus, our study is designed and powered to address a comprehensive set of outcomes along three themes: 1) uptake and patterns of use, 2) biomarkers of exposure, and 3) changes in smoking. Importantly, these, dynamic changes will be captured in real time as they naturally unfold.
We believe this will be the best test to date of the naturalistic population impact of e-cigarettes. Methods are strengthened by 1) large sample size (the largest e-cigarette RCT), 2) nationwide recruitment, with 3) locally recruited subset to assess biomarkers, and 4) multiple measures of outcome. The strong investigative team, coupled with our success in prior studies using similar methodology, collectively enhances the probability of success in achieving grant aims. We believe this study will offer an important contribution to the e-cigarette literature, and offer considerable implications for tobacco control, including vital information for regulatory agencies such as the FDA.

Project Narrative
Electronic (e-)cigarettes are the fastest growing non-cigarette product available to smokers, yet the science base to understand these products has not kept pace. This will be among the first prospective, large scale randomized studies of e-cigarette use in the U.S., with aims to examine the naturalistic course of uptake and consequence of e-cigarette use.

SPECIFIC AIMS
E-cigarettes have dramatically altered the tobacco control landscape, and all evidence suggests escalating rates of use among smokers. With the tobacco industry now fully entrenched in this market, prevalence will surely increase further. The e-cigarette literature is predominated by studies of three specific types: a) cross-sectional (usually online) surveys of prevalence and attitudes, b) short-term, lab based studies of nicotine delivery, withdrawal/craving, and toxicant exposure, or c) uncontrolled cohort studies, most of which are retrospective. Only three controlled prospective studies exist. All come from abroad and all are explicit cessation studies of smokers wanting to quit and using e-cigarettes to do so. Collectively, these studies suggest that a) e-cigarettes are likely safer than conventional cigarettes, to both individual users and those around them, and b) use of e-

cigarettes may be associated with quitting, though causal inferences are unclear. There are a number of problems with the existing e-cigarette literature, however. These include i) lack of a control group, ii) crude estimates of use (e.g., ever vs. never), iii) use of self-selected samples of users vs. non-users, iv) limited data on patterns of uptake among new users, including what it means to be a dual user, and v) almost no prospective data on naturalistic changes in smoking. We know essentially nothing with regard to potential uptake among non-treatment seeking smokers naïve to e-cigarette use.

A recurrent theme throughout the literature is a need for stronger methodology; i.e., randomized trials, particularly those that focus on the natural process by which smokers adopt e-cigarettes and its subsequent impact. Our guiding premise is that there has yet to be a study that **a)** randomizes smokers to e-cigarettes vs. not, **b)** focuses on naturalistic outcomes; i.e., non-treatment focused, **c)** is prospective, with sufficient follow-up duration, **d)** provides data on nicotine/tobacco exposure, **e)** is of sufficient sample size, **f)** includes smokers with broad range of motivation to quit, and **g)** is US-based, an important consideration given upcoming FDA regulatory changes. We know of no study with even two of these criteria. Our study group has a strong record of assessing the natural history of product sampling, including large studies of NRT and smokeless tobacco. Our collective expertise and collaborative history makes us the ideal team to do the same with e-cigarettes. The FDA has articulated a clear agenda to understand the uptake and population impact of how smokers use e-cigarettes, and our proposed study offers the most methodologically sound test of these questions.

We propose a nationwide randomized clinical trial in which smokers (N=660) receive samples of cigarette-like e-cigarettes (n=440) vs. not (n=220). Randomization will be 2:1 to increase precision of uptake outcomes, broadly but concretely defined (Aim 1). A subset of smokers (n=120) will be recruited locally, to assess the impact of e-cigarette use on biomarkers of exposure (Aim 2). Finally, though ours is not a cessation study, it would be a missed opportunity if we did not track cessation outcomes (Aim 3) or sufficiently power the trial to detect differences if they emerge. Thus, our study is designed and powered to address a comprehensive set of outcomes along three domains: 1) uptake and patterns of use, 2) biomarkers of exposure, and 3) changes in smoking, all captured during the switching process while it naturally occurs in real time.

Aim1: Describe rates and patterns of naturalistic uptake of e-cigarettes among smokers. We examine a broad set of uptake indicators, including trial, repeat trial, regular use, and purchase, and the time course and predictors for each. Hypothesis 1a: Within the e-cigarette group, we hypothesize that at least 90% of smokers will try the product at least once, 45% will use regularly (at least 4/7 days, at any time during follow-up), 25% will use daily for ≥7 days (at any time during follow-up), 25%/10% will be using at least some/daily at final follow-up, and 20% will independently purchase e-cigarettes. Hyp 1b: Among smokers in the e-cigarette group, 40% will show a minimum of 50% reduction in cigarettes per day, and as a group, e-cigarette users will show greater decreases in cigs/day as compared to control. **Aim2: Assess the impact of e-cigarette use on biomarkers of exposure, to determine if smokers self-titrate to nicotine as they switch products.** Within a subset of locally recruited smokers, we hypothesize (Hyp 2) that use of e-cigarettes will lead to significant short-term (1 month) decreases in CO & NNAL, but no net change in cotinine. **Aim3: Assess concurrent and downstream (over 6 months) effects of e-cigarette use on smoking behavior.** Consistent with most prior research, we hypothesize that provision and use of e-cigarettes (vs. control group) will lead to (Hyp 3a) higher rates of quit attempts, (Hyp 3b) cessation, and (Hyp 3c) increases in motivation/confidence to quit. This is not a cessation trial but is positioned to evaluate important cessation outcomes in a naturalistic setting.

Our methods are strengthened by randomized design, a focus on broad and detailed indicators of naturalistic uptake, nationwide reach but with local recruitment to allow for biomarker assessment. Our success in similar 'sampling' studies, both e-cigarette focused and not, adds further strength. Our multidisciplinary and experienced team is ideally suited to carry out the proposed research, which is strategically aligned with the NIH and FDA's goals to increase knowledge about the impact of e-cigarettes on the behavior of consumers.

RESEARCH PLAN: INTRODUCTION AND SIGNFICANCE

The proliferation of electronic nicotine delivery devices, most commonly referred to as electronic cigarettes or e-cigarettes, has dramatically altered the tobacco control landscape. The FDA classifies e-cigarettes as tobacco products, and has just recently started the process of regulating these products. The three largest U.S. tobacco companies have each entered the e-cigarette market, and market analyses (1, 2) project continued, "disruptive" growth (3), highlighting the potential for the e-cigarette market to ultimately overtake the existing tobacco market. Research on these products has only recently escalated, but has been dominated by basic science and human lab studies. A recent issue of *Tobacco Control*, under the title "FDA E-Cigarettes: Impact on Individual and Population Health" (4) was noticeably devoid of any prospective behavioral research, which is a clear need for this literature (5-7), particularly in light of forthcoming FDA regulation. The public health debate on e-cigarettes endures (8-12), and the science needs to keep pace.

Product Description and Safety

E-cigarettes were originally uniform in design, but have since evolved to span the spectrum from disposable cartridges to highly sophisticated tank systems, including ones that allow the user to control the amount, dose, and power of nicotine delivery. The basic operation of any e-cigarette involves the heating and vaporization of nicotine; there is no combustion, unlike a cigarette. E-cigarettes attenuate craving to varying degree (13-15), but this is likely dependent upon type of e-cigarette product. Though nicotine delivery may be less than from a conventional cigarette (16), this is apt to change as products evolve. Other studies have shown comparable cotinine levels among sustained e-cigarette users vs. regular smokers (17). Along with similar evidence elsewhere (18, 19), this suggests that, after an adjustment period, smokers learn to titrate use to manage cravings, or at least to maintain the psychopharmacological effects previously derived from cigarette smoking.

Growing consensus of expert opinion (5, 20), in concert with most available lab evidence, (15, 21-30), suggests that e-cigarettes are safer than conventional cigarettes. E-cigarettes deliver significantly reduced levels of tobacco-specific nitrosamines, and significantly reduce secondhand smoke exposure to non-smokers (23, 31). Three online surveys of e-cigarette users (32-34), one open label noncomparative study of at-home use (15), and one cross-over study (14) documented mild and tolerable side effects, the most predominant of which are headache, mouth/throat irritation, cough, and nausea. So while there is clear heterogeneity across products, e-cigarettes as a group appear safer than conventional cigarettes.

Prevalence, Patterns, and Outcomes of Use

Awareness and use of e-cigarettes is quickly growing (35-41). Within the U.S., recent (2013) and nationally representative data (42) indicate 77% awareness of e-cigarettes (89% among smokers), of whom 51% believed them to be less harmful than cigarettes. A separate national survey from 2013 (41) indicate 13% ever use (47% and 54% among nondaily and daily smokers), and 7% current use (34% and 30% among nondaily and daily smokers). More recent, still national data (2014 NHIS) document 13% ever-usage among adults, 4% current usage, and 1% daily usage (43). Some (44) but not all (43) studies suggest that most e-cigarette users are daily users. There are almost no data on the contextual antecedents of use; i.e., whether use is bound specifically to smoking restricted environments, or whether situational cues (e.g., other smokers, mood, stress) drive e-cigarette use in ways similar to smoking. Motives for e-cigarettes use are also unclear. Based on our data from the International Tobacco Control (ITC) cohort, wherein 15% of all U.S. smokers have tried e-cigarettes, and 37% of ever-triers were current users (45), the most common reasons for use were 1) use in smokefree settings, 2) facilitate reduction, 3) perceptions of reduced harm, and 4) to quit smoking. While follow-up data from this cohort showed greater reduction in smoking among users vs. non-users, there were no differences in quitting. Another cohort study from Italy (46, 47) provided e-cigarettes for ad libitum use to 40 smokers not wanting to quit, of whom 1/3rd reduced smoking by half, and 23% were continuously quit after six months. Another cohort study from the same group but within smokers with schizophrenia found 64% of e-cigarette users to be either quit or have significantly reduced smoking (48). More recent cohort studies further document a positive association between e-cigarette use and subsequent quitting (49, 50), particularly when e-cigarettes are used regularly (51-53). As uncontrolled studies, causal effects on quitting are unclear, but these data are consistent with a number of other studies, almost all cross-sectional, that suggest that e-cigarette use is associated with motivation to quit (54) or increased abstinence (32, 33, 55-58). Even in the absence of cessation, use of e-

cigarettes can reduce smoking, both over the short (15) and long term (59). It is also worth noting that at least three studies (60-62) and one review paper (63) show lower (either numerically or statistically) quit rates among self-selected user vs. non-users. On the whole however, and as the most recent review noted (64), the literature suggests a positive link between e-cigarette use and reduction/quitting, though this same review cites **the need for well designed randomized trials to address** this issue directly.

A universal theme in the literature is a need for controlled trials. Only three such trials exist (65-67), one is pending (68) and none are within the U.S. The first published trial is a study of Italian smokers (66) sponsored by an e-cigarette manufacturer. Smokers (N=300) were randomized to high (7.2mg cartridge), moderate (4.8mg) or placebo (0mg) e-cigarettes. Rates of abstinence after 3 months (11%, 17%, 4% in each group respectively) and 12 months (13%, 9%, 4%) suggested higher quit rates among active e-cigarette groups. The second study, a non-inferiority, cessation-focused trial (N=657), came from New Zealand (67, 69). Smokers were randomized to receive 1) e-cigarettes, 2) transdermal patch, or 3) placebo e-cigarettes. Abstinence rates numerically but not statistically favored e-cigarettes over both patch and placebo. The last study was a small scale (N=48), randomized trial from Belgium that showed short term (2-month) increases in quitting as a function of e-cigarettes (65). All three trials focused on prescribed and/or structured e-cigarette use, which is entirely different from real-world uptake. The lack of trials within the U.S., or those with a focus on naturalistic outcomes, is surprising, particularly given FDA interest in these products. Indeed, a recent Cochrane review cautioned against over-interpretation of these trials, and cited a "low" grade of overall evidence (70).

The Glaring Literature Gap

Most e-cigarette studies are 1) lab-based measures of pharmacokinetics or toxicant exposure 2) cross-sectional studies of prevalence and predictors of use or 3) uncontrolled cohort studies. The two big remaining questions are uptake among non-smokers (not addressed here), and the impact of e-cigarette use among smokers. This latter question is important to the ongoing public health debate about where these products fit within tobacco control. **E-cigarettes may lower *individual* health risk, but this may or may not translate to reduced *population* risk**. Four limitations exist within the literature. First, most studies lack a control group and as such they are merely descriptive in nature. Second, when studies do include a comparison group, they are almost invariably based on groups of self-selected users vs. non-users, which are inherently biased and limit ability to draw causal inferences. Third, these studies describe attitudes and patterns of use among established users, but say nothing about uptake, trial, and adoption of e-cigarettes among smokers who newly use these products, assessed concurrent in real time. Fourth, these studies provide minimal data (with appropriate control comparisons) on concurrent and downstream effects on behavior. There is strong need for randomized trials to assess these outcomes. Our **guiding PREMISE** is that **there has yet to be a study that a) randomizes smokers to e-cigarettes vs. not, b) is focused on naturalistic outcomes; i.e., not cessation focused, c) is prospective, with sufficient follow-up duration, d) provides data on nicotine/tobacco exposure, e) is of sufficient sample size, and f) is US-based, an important consideration given upcoming regulation.** We *know of no study that meets even two of these criteria*.

INNOVATION

There is strong need for prospective randomized studies that examine both uptake (trial, adoption, patterns of use) and consequences (dual use, quit attempts, abstinence) of e-cigarettes among smokers in the U.S. We searched for similar studies, either ongoing or recent, on NIH RePORTER. We found none, with the possible exception of forthcoming research from the VCU TCORS P50 (Project 3: *Randomized Control Trial Methods for MRTP Evaluation*), in which 520 smokers are to be randomized into one of four groups (n=130 each): a) high dose e-cigarette, b) mid-dose e-cigarette, c) placebo e-cigarette, or d) non-combusted, non-nicotine cigarette substitute (71). Participants will be given e-cigarettes with advice to reduce smoking by at least 50%, and thus is not naturalistic. That study is primarily focused on toxicant outcomes, and secondarily on behavioral outcomes. Another recently funded study (R01 CA184681) does capture longitudinal patterns of e-cigarette use through ecological momentary assessment (EMA), but does so seemingly among self-selected users, without a control group. These are clearly strong studies, and ours is similar in some ways. However, our study will: a) be somewhat larger and nationwide, b) include randomized, controlled design, c) capture broad set of uptake data dynamically in real time, and d) be inclusive and powered on the most stringent behavioral outcomes. In

fact, ours **would be the largest randomized trial of e-cigarette use in the U.S**. The importance of a randomized design is critical in that it minimizes self-selection bias, distributing the effects of self-selection equally across groups. Selection bias is well documented in the literature, which explains in part the divergent findings as to how e-cigarette use relates to behavior (72). We have shown the value of randomized designs to test naturalistic outcomes of alternative tobacco products (see below), demonstrating the need and importance of large, randomized trials that may contradict prevailing indirect evidence.

Second, our study collects a **rich history of patterns of (dual) use,** broadly but concretely assessed and operationally defined. Most studies of e-cigarettes describe dual use in binary fashion (use vs. non-use). A few more recent studies do provide broad data on contextual use (32-34, 56), but these studies are all cross-sectional and specific to online surveys of established users. The existing literature generally fails to capture the finer details of amount, frequency, context, and purpose of novel product use, and how these patterns naturally evolve over time. Moreover, there is a growing sense that some smokers use e-cigarettes for purposeful use, to quit or cut down cigarettes, or to circumvent smoking restrictions. Many other smokers experiment with e-cigarettes but never progress. We do not know how many smokers fall into each of these "purpose buckets." Only a randomized trial will answer this question. The three RCTs above provided some information on patterns of use (65-67), but were based on prescribed e-cigarette use. Our focus is on the switching process while it naturally occurs, in real time. Through collection of rich diary data, we have the ability to examine typologies of use, through such means as latent class analysis. Within our recently completed snus trial, we are in the process of analyzing use data using these methods, which will allow us to understand the varying types of dual use, predictors of dual user types, and how these types vary over time.

Third, we believe this study would provide **strong prospective data on biomarkers of use:** carbon monoxide & NNAL, and cotinine. We expect both CO and NNAL to vary directly with e-cigarette use, but no overall net difference in cotinine. The existing literature is predominated by cross-sectional, usually online surveys. We do not assess other specific carcinogens, as any results herein would be specific to our e-cigarette of choice. Here we use NNAL as yet another marker to discriminate between smoking vs. vaping, not as a stand-alone carcinogen to describe our choice of product.

Fourth, this study will provide what we believe are the strongest data on **how e-cigarettes alter smoking behavior**, including smoking reduction, quit attempts, and cessation. The three strongest studies to date are cessation studies, and do not provide information on naturalistic impact of e-cigarettes on quitting. They are based outside the U.S., which leaves a gap in the domestic science that is so needed to inform regulatory policy. We emphasize that, though this study is powered to detect differences in abstinence, this is not a cessation study. We are not specifically testing if e-cigarettes can help people quit, but will be positioned to evaluate this as a potential naturalistic outcome.

A note on PATH: The Population Assessment of Tobacco and Health (PATH) study (73) is similar in some respects to this proposed work. PATH will provide population-based surveillance of tobacco use and dual use. However, at its core, it is a cohort study and is limited by the same challenges noted above. Furthermore, PATH has annual assessments only, with a limited scope of measurement. We assess patterns of use in a much more fine grained and detailed manner, within a randomized design.

Our study will add to the ongoing literature base that is slowly establishing a whole new lexicon for non-cigarette use, and particularly e-cigarettes. For example, cigarettes per day is one of the most common outcome measures within cigarette-focused studies, but this does not translate to e-cigarettes (puffs per day? puffing

Table 1: Key Research Gaps (77) Addressed by Current Study
• How are e-cigarettes used by current, [former, and never-] smokers? Is conventional cigarette use affected?
• Do e-cigarettes delay or facilitate cessation? What characteristics influence cessation?
• How is dual use defined? What are the patterns of and reasons for dual use? What are the attitudes, knowledge, and beliefs about e-cigarettes? How do they affect behavior?
• Is it possible to encourage users of conventional cigarettes to transition to e-cigarettes?
• Who are the best candidates for cessation or conventional cigarette reduction intervention with e-cigarettes?

episodes per day? cartridges per day?). Should abstinence definitions include or exclude e-cigarettes? What are the implications for either? These are unsettled questions, and the SRNT listserv has been filled with debate on these issues. We will capture the necessary information to guide the discussion of e-cigarette assessment, which we think will offer a significant advance upon the literature. Smaller studies can do this, but only a large prospective study can do it well. In summary, we do not believe there has yet been a study that offers the same innovation as ours. This study will move the literature forward in significant ways, and is highly attentive to recommended NIH research agenda on e-cigarettes (74)(see Table 1 below).

METHODS

Relevant Experience / Preliminary Data

Four trials of sampling NRT, including two large nationwide trials and two statewide trials

While the current study is not a cessation trial, we briefly show our experience in conducting similar "sampling" studies. Dr. Carpenter led a large, nationwide trial of smoking reduction among smokers not motivated to quit (N=616), demonstrating that NRT-assisted reduction leads to subsequent cessation (75). We then led another large (N=849), nationwide study of NRT sampling, with less structured use of NRT (76). We demonstrated clinical benefits of sampling NRT, without pressure to quit. Evidence of successful recruitment and retention across both studies is in Table 2. A third trial, again of NRT sampling (77), was smaller (N=150) and managed statewide. This was a programmatic extension of our prior study, and again mailed NRT to smokers and again benefited from high recruitment and retention. Lastly, we have an ongoing cluster randomized clinical trial of smokers (N=1160, current n=905) across 20 primary care sites in South Carolina, now testing the pragmatic concept of NRT sampling in real-world settings.

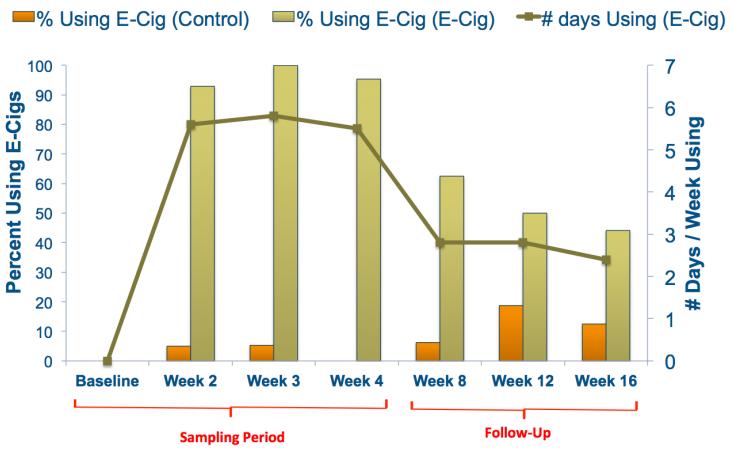
Table 2: Single-Site, Mail/Phone-Based, Nationwide RCT experience

Study (citation #)	Sample Size	Recruited in ____ days	% of scheduled calls completed
Smoking reduction (69)	616	230	95% [thru 26 wks]
NRT sampling (70)	849	400	90% [thru 26 wks]
Snus sampling	1236	630	88% [thru 52 wks]

Three studies of alternative tobacco products (not e-cigarettes), including one large nationwide trial

Our group has strong experience in the assessment of novel products purported to reduce individual harm. Dr. Carpenter has led two small studies and one large trial, all very similar to the current design. The first two studies were small controlled pilot studies of Ariva/Stonewall (compressed nicotine lozenge) (78) and snus (79), which generally showed reductions in smoking and increases in motivation to quit compared to control groups. The third trial was a large randomized study of smokers across the U.S. who either received Camel Snus or not (N=1236). This was the largest, longest, and most direct test of snus ever conducted in the U.S., and parallels our intentions herein. We provided minimal instructions on snus use, much like the current study, and smokers could use as much or as little as they wish. Outcomes during the sampling period focused on uptake: trial, adoption, patterns of use, after which smokers were followed for one year, in which naturalistic outcomes include quit attempts, cessation, and additional non-cigarette use. These outcomes parallel those within the current study, and document our fine-tuned experience with these methods, inclusive of mailing product to individual participants. Recruitment and retention are very strong; see Table 2. Results from our snus trial are now in, and several manuscripts are now published (80, 81). In contrast to prevailing literature (mostly indirect studies), we were the first randomized study to demonstrate a negative impact of snus on quit attempts (no effect on cessation). We mention results here only to **demonstrate the value and importance of randomized trials over indirect studies to test alternative products**.

Figure 1: E-Cigarette Use Within R21 (randomized, naturalistic design)



Ongoing / Recent studies of e-cigarettes Dr. Carpenter recently completed a small pilot study, internally funded, to examine short term (1wk) behavioral effects of active vs. placebo e-cigarettes (BluCig), using a double-blinded cross-over design (N=24). Findings were recently published (82),

suggesting: a) strong initial uptake of e-cigarette, b) favorable liking/satisfaction/withdrawal relief, and c) that these effects are not nicotine specific (few differences between active vs. placebo). We also just completed a R21 that is thematically very similar to the current trial: 68 participants randomized to receive e-cigarettes (again, BluCig) or not, with a naturalistic sampling period and prospective follow-up. The R21 used ecological momentary assessment (EMA) methods to capture uptake patterns among smokers who are provided an e-cigarette. The study included a control group (Total N=68) that allows us to compare prospective changes in smoking behavior as compared to smokers who do not receive an e-cigarette (BluCig). Manuscript is in preparation and results are to be presented at SRNT 2017. Figure 1 shows uptake and amount of usage of e-cigarettes, during and following the sampling period. General uptake during the 3-wk sampling period was strong: 100% of those receiving BluCig used at least once, 71% reported regular use during at least 1 of the 3 sampling weeks, and 63% used daily during at least 1 week. Smokers in the e-cigarette group were 2.9x more likely (41 vs. 14%) to independently purchase their own e-cigarette, 1.6x more likely (44% vs. 27%) to make a quit attempt, and 3x more likely (15% vs. 5%) to achieve "floating abstinence" (any 7-day period of non-smoking, ever within study). Cessation-related outcomes were non-significant for this small study, and we caution against over-interpretation since confidence intervals (not shown here) are wide. We found significant reductions in both CPD and CO/NNAL, but no changes in cotinine. EMA data suggested clear contextual differences for e- vs. conventional cigarettes. EMA compliance was strong: 80% of participants completed at least 12 diaries in 3 weeks (most comparable to herein) and 78% completed at least 3 diaries/week. These early results show: a) general congruence of outcomes to those we hypothesize for the proposed larger trial, b) palatability of product, c) uptake/use even without structured instructions to do so, and d) our strong experience in methods: recruitment, sampling product, EMA, biomarkers, and product evaluation. The general methods and measures from these studies guide our current trial, though we now turn to a 2nd generation device, which should have even fewer barriers to uptake and/or substitution.

Dr. Goniewicz (co-I) has published extensively on nicotine delivery of e-cigarettes, their potential toxicity, and patterns of use (16, 23, 28, 31, 32, 74, 83-92). His expertise in this area is well known. As just one example, he has completed a short-term observational study (84), in which 20 smokers were provided e-cigarettes for ad libitum use over a 2-week period; i.e., a study very similar to current proposal. Data demonstrate that increases in e-cigarette use occurred in direct proportion with decreases in cigarette smoked, resulting in a non-significant net decrease in nicotine. Thus, smokers who engage in dual use are likely to NOT increase total nicotine intake.

Dr. Wagener (co-I) has published several studies/reviews on e-cigarettes (8, 9, 59, 93-98). Three studies are most relevant to this proposal. The first is a pilot study similarly themed to current application (94), in which smokers sampled three separate e-cigarettes within the lab, after which they selected one for 1 week of ad libitum use. E-cigarette use during the ad-libitum phase did not substantively increase total tobacco consumed, as there was a 44% reduction in cigarettes smoked per day. Readiness and confidence to quit increased significantly over the study period. He next conducted a lab study (95) that compared 2nd vs. 3rd generation devices, finding that both deliver cigarette-like amounts of nicotine and reduced carcinogens. Third, he has a newly funded R01 to examine 1st vs. 2nd generation e-cigarettes vs. conventional cigarettes, in terms of substitution, biomarkers and changes in nicotine dependence. This will be a large study (N=453) but still smaller than proposed herein and local to Oklahoma (vs. national herein). Nonetheless, we see great opportunity to leverage our studies together, using common assessments where possible for downstream secondary analyses. All tolled, he has extensive knowledge of e-cigarette devices and relevant literature.

Overlap of Prior/Proposed Studies? The R21 was designed solely as a pilot study (N=68) in advance of a larger trial. The main intent of the R21 was to identify the best strategies to track the clinically relevant behaviors of use and dual use; i.e., to determine what questions we should be asking. Our intent within this R01 is to do this on a larger scale, with longer follow-up, and with a sizable sample that will ensure adequate power for hypothesis testing related to a broader array of outcomes. We believe innovation is high.

Summary of Preliminary Studies

Across all studies described above, we have set the stage for next obvious step, i.e., to conduct a large scale, prospective, naturalistic study of e-cigarettes, to assess uptake/patterns of use including dual use, and to

rigorously determine the ultimate impact on smoking behavior. We have established all methods to a) recruit large numbers of participants, b) retain effectively, c) mail product to participants with minimal instructions to maintain naturalistic intent, and d) assess a broad range of outcomes, including multiple measures of non-cigarette tobacco use. If a study like this is to be done, we are the ones to do it.

Roles

Each investigator offers a strong, unique role. Dr. Carpenter is a clinical psychologist with an extensive history of conducting local and nationwide clinical trials that test alternative products and their impact on smoking behavior. Dr. Gray is a psychiatrist with strong experience in clinical trials for smoking and smoking cessation; in addition to his RCT experience, he offers primary medical oversight for the trial. Dr. Cummings is an internationally respected policy expert with extensive experience in product regulation. He leads the ITC cohort study, which recently reported on e-cigarette use in the U.S. and abroad, briefly noted above (45), and has a pending P01 that focuses specifically on e-cigarettes (of which Dr. Carpenter is Co-I). Drs. Warren (radiation oncologist with a strong understanding of e-cigarettes, biomarkers, & nicotine health effects) and Cummings have extensive knowledge of e-cigarettes, each having led or co-authored policy statements for national organizations (87, 99). Dr. Warren is current or previous chair/member of tobacco-specific sub-committees at national level (ASCO, AACR, IASLC). Dr. Goniewicz is a pharmacologist and toxicologist with expertise in e-cigarette testing and nicotine pharmacology. He has many prior/ongoing studies or reviews that focus on e-cigarette safety (16, 23, 28, 32, 84, 86-88, 90). Dr. Wagener is a clinical psychologist who also has extensive experience conducting e-cigarette (9, 59, 93, 94, 97), secondhand smoke exposure, and other non-cigarette tobacco research, including impact on smoking. Together, our outside co-investigators are intimately familiar with product design and evolution, including inside knowledge of products soon to come to market. In all, our group is interdisciplinary, transdisciplinary, and highly versed in both content and methods.

Design Overview

Eligible smokers, once consented, will be randomized to receive a sample of e-cigarettes (NJoy Pre-Filled Tank; n=440) or not (n=220). E-cigarette samples are inclusive of a battery and self-contained tanks of assorted flavors to last up to 4 weeks. Participants will be recruited nationally, but a subset (N=120) will be recruited locally to allow for biomarker collection (locally recruited participants will be managed via phone/mail as are all other participants; details below). Beginning in November 2021, ***all*** participants will be asked to complete a carbon monoxide breathalyzer remotely (rationale below) and send us the results. All smokers will be asked to provide smoking diary data, captured electronically, daily for 4 weeks. More substantive phone assessment will track smoking and related behaviors at baseline (Day 0) and +10, +17, and +24 days (weekly during initial 3 weeks, following brief lag for delays in product mailing), and at +1, +3, and +6 months. We will not accept support from the e-cigarette industry and believe this independence is an additional strength.

Naturalistic and Observational, But Randomized? Is this a cessation trial in disguise?

Our study is not purely naturalistic, but it comes close. We provide product for free, mailed directly to participants. This allows us to examine uptake in the absence of cost/access barriers. Asking smokers to pay for e-cigarettes might provide a truly real world test of uptake, but without large numbers of participants, does not allow for assessment of uptake and impact on smoking. We have very little interaction with participants other than through assessments, and never instruct on cigarette or e-cigarette use. We provide referrals to cessation support (quitlines) for those who wish it. This is not a cessation trial, but rather an observational study of smokers over time, some of whom are randomized to receive e-cigarettes to use however they wish, or not at all. Randomization removes self-selection bias that is so common in the existing literature. It also allows for prospective analysis of uptake, use, trial, and adoption among smokers exposed/offered a product, with needed comparison to those who are not given product. Smokers both wanting to quit and not will be enrolled. Our primary focus in this study is the impact of e-cigarette use upon smoking behavior, with emphasis on uptake/usage/adoption, as well changes in smoking. However, with such a large study, among the first of its kind in the U.S., we believe that omission of cessation/quit attempt outcomes in this study would be a significant lost opportunity. Furthermore, if there are group differences in cessation, we believe it would be another lost opportunity to be underpowered to detect them. Thus, our trial is powered on naturalistic rates of point prevalence

abstinence at six-month follow-up, but we again emphasize that we are not promoting or testing e-cigarettes as a cessation intervention.

Regulatory Issues
FDA regulation of e-cigarettes is now upon us, but regulations, for now, are in regards to manufacturing, packaging, warnings (e.g., this product contains nicotine. Nicotine is addictive), and retail sales (protections against sales to minors). These are all consistent with the earlier (2014) notice from FDA that proposed regulations that would: a) ban sale of e-cigarettes to minors, b) ban vending machine sales, c) require warnings that e-cigarettes contain nicotine, d) require disclosure of ingredients, and e) prohibit distribution of free- samples, but with exemptions for research purposes. We welcome e-cigarette regulation and do not believe forthcoming changes will undermine our study.

The possibility of needing an IND or ITP (investigational new device; tobacco product) weighs over investigators. An IND/ITP would definitely be necessary for any trial in which e-cigarettes are presented as a method to quit. Our study is naturalistic. We contend that any need for an IND for a study like ours would have the immediate effect of extinguishing all such studies, or at least those that are independent from the e-cigarette industry. Our study is methodologically very similar to our previous snus RCT, with similar outcomes. For that study, we were initially told that we needed at IND, but after a discussion with the FDA in which we emphasized the naturalistic nature of our study, we were granted an IND exemption. Herein, our purpose and methods are very similar: 1) we do not promote e-cigarettes as a cessation strategy, 2) there is no therapeutic intent, 3) we do not require any level of e-cigarette use (non-use is an outcome), and 4) we are primarily focused on the patterns of use during the sampling period, with 2:1 randomization to increase precision.

Participant Eligibility, Consenting Process, Recruitment Feasibility, and Retention
We will advertise nationally but in select number of cities, with separate localized recruitment of a subset of smokers. We will choose cities on the basis of exceeding national rates for minority and/or Hispanic populations; see Table 3 for *potential* cities, which have the added benefit to allow for geographic diversity. Advertisements will be spread across various media outlets (newspapers, radio, Facebook, craigslist). We will now also utilize a respondent-driven (i.e., RDS, referral) sampling program. The RDS sampling methodology is based on recruiting the eligible friends and acquaintances of each participant so that the sample "snowballs". Participants will be told that they can tell friends or acquaintances that they think would be interested in the study about the study. Participants will be compensated $30 for every person who enrolls (completes week 0 phone call) into the study. Individuals referred to the study may not reside in the same household as the study participant while the study participant is enrolled. All comers, both motivated to quit and not, will be eligible to participate. Eligibility criteria include: a) age 21+, b) current smoker of ≥5 cigarettes per day for ≥1 year, c) no recent history of cardiovascular distress (arrhythmia, heart attack in past 3 months; uncontrolled hypertension) or renal disease (e.g., dialysis) that would interfere with urinary biomarker assessment, d) neither pregnant nor breastfeeding, e) at least some concern for health effects of smoking (>none at all on a Likert scale), f) no current use of cessation medication, and g) have not purchased in the past 6 months or ever regularly used (daily or weekly) a tank system, mechanical mod, or advanced personal vaporizer e-cigarettes (though previous use of cig-a-like devices will be allowed), h) no regular use (daily or weekly) of any e-cigarette (including cig-a-like devices) in the last 6 months, i) and no current use of other tobacco products, j) mobile device with capacity to receive SMS text and internet access (for purposes of diary completion and remote carbon monoxide breathalyzer using the mobile device; see below) k) no other household members are enrolled in the study, and l) no history of seizure disorder. We restrict the sample to smokers with at least some concern

Table 3: Potential Recruiting Cities (US Census Data)

	Population	% Minority [a]	% Hispanic
Aurora CO	339,030	27.1%	28.7%
Baton Rouge LA	230,058	29.3%	3.3%
Bellevue WA	126,439	34.4%	7%
Grand Rapids MI	190,411	27.8%	15.6%
Odessa TX	106,102	10.4%	50.6%
Orlando FL	249,562	35.8%	25.4%
Sacramento CA	475,516	42.5%	26.9%
Savannah GA	142,022	59.9%	4.7%
Syracuse NY	144,170	41.2%	8.3%
Tempe AZ	166,843	18.8%	21.1%
Charleston County SC [b]	372,803	32.9%	5.3%
National Average		**22%**	**16.9%**

[a] African American, American Indian, Asian, Hawaiian/Pacific, Multiracial
[b] locally recruited subset

of heath, since this is likely the target population for e-cigarettes. We considered but rejected eligibility to be restricted to those with e-cigarette interest, as we believe that would artificially inflate use. Nonetheless there is a potential for a selection bias in that smokers interested in ecig use would be more willing to enroll. This is an issue of representativeness to general population (as within any smoking study), but any level of ecig interest will be randomized equally across groups. We restrict our sample to smokers who have minimal use of e-cigarettes in the past, and follow the precedent of our colleague Dr. Wagener in his ongoing R01. We recognize that e-cigarette use is escalating rapidly, yet the most recent, large N survey indicates 54% ever use and 30% current use among daily smokers (41). We are confident in our recruitment capacity but see below for contingency planning. data collection. We hope to minimize a digital divide but recognize that it may still exist. Over 84% of Americans have an internet connection, and almost 70% of Americans have a smartphone (Pew Poll 2015). Even so, the digital divide affects the representativeness of those enrolled; it is unlikely to alter internal validity (i.e., cause/effect between group assignment and outcome) (100).

In our prior studies, recruitment from national sources was based on mail-based return of consent form. That is, after determination of eligibility, we mailed a consent form (2 copies) and asked the participant to sign one copy and return to us in a pre-addressed, pre-stamped envelope. Receipt on our end is the start of official consent, and official enrollment begins with first phone call. While this process generally worked, it was terribly inefficient. For one, mailing delays often meant a lag between the person expressing interest and when s/he was officially enrolled. Second, there are occasional instances where the person does not fully complete the consent form (e.g., missing date), or does not return all necessary pages, and the process repeats itself (back and forth mailing) until we get all forms in full. Third, a large number (~55%) of the consent forms go un-returned, for any number of reasons. Thus if we want 660 participants we would need to identify ~1460 who would be eligible and interested. Loss of interest in the study is a possibility (which we abide by) but we also believe that consents get lost, thrown away, regarded as junk mail (particularly if seen by someone else), etc. For this study, we will continue with this procedure of mail-based consenting, but add three new design features intended to address this inefficiency, described below: 1) real time, personalized online consent through doxy.me (i.e, teleconsent), 2) electronic consent (e-consent) via REDCAp and 3) nominal pre-payment sent along with mailed consent package.

First, we will provide participants with the option to complete consent via MUSC's doxy.me system (teleconsent). After the initial determination of study eligibility, assessed online in our secure survey, participants will be asked about their capacity for doxy.me procedures, including access to a computer with or without a webcam and speakers, and compatible internet browser (doxy.me is currently optimized for Google Chrome & Firefox, with planned expansion to additional browsers). For those who have the required hardware and software for doxy.me, we will then describe the basic mechanics of the teleconsent process and ask for their preference for mode of consent. Participants can choose their preferred method of consent, and none of this is an eligibility requirement. Participants who do not meet doxy.me or REDCap requirements will be mailed a consent form following standard procedures. Thus, we are simply offering other, more immediate options for study consent that may be preferable for some participants.

For those who elect teleconsent, we will follow procedures as per precedent (101) and through consultation with MUSC researchers (Dr. Brandon Welch). We have consulted with 3 other MUSC investigators who are currently using doxy.me and their favorable impression guides our decision here. All doxy.me signed consent forms will be saved as pdf files within our study records. Research staff will then have the participant complete the baseline questionnaire (that would otherwise be sent with mailed questionnaire; see below). We anticipate that 10-20% of study participants might enroll through this method. Signatures on the consent form may be electronically via REDCap/doxy.me. Participants who do not have access to the required technology to complete consent remotely via REDCap or doxy.me will sent a consent packet by mail.

For those opting to receive consent packet through the mail, we will follow our prior procedures, sending a packet inclusive of two copies of the consent, a baseline questionnaire, and a pre-addressed, pre-stamped return envelope. Participants will sign and return one consent and their completed baseline questionnaire. We have a toll-free phone line to support anyone who calls with questions. Upon return to our office, data are entered into our database, and these individuals comprise the consented sample. However, the sample is reduced

further to those with whom we are able to establish first phone contact (Day 0); i.e., the enrolled sample. This enrolled sample is the intent-to-treat sample. We have used this procedure in 3 other nationwide trials, and, as noted above, consistently get about ~45% which we think is an inefficient use of resources, both financial and personnel. As a second strategy to attempt to increase recruitment efficiency, we will insert $5 cash within the packet of consent/baseline questionnaire for a subset of participants. This is based on findings elsewhere (102-104) that show the effectiveness of pre-payment to increase survey response in large, nationwide mail-based studies. This pre-payment is NOT tied to any behavior, and is independent of whether the individual returns the consent form, or not. The amount is kept low to decrease any coercive impression. We simply wish to know whether such pre-payment increases the rate of returned mailings (above 45%). Toward that end, and merely because we aim to pilot these procedures, we will randomize these mailings 1:4, such that 20% will get this $5 pre-payment, and 80% will not. The outcome is merely the return rate, and will be compared to doxy.me completion rates above, all with the intent to optimize efficiency of recruitment (proportion of **eligible and interested** individuals who complete consent). We do not offer a second consent for these procedures because the single aggregate outcome is % enrolled (i.e., no individual level outcomes). This itself becomes an outcome we can report in the literature.

Finally, though we cannot fully ensure that this will be a representative sample, we make efforts toward that goal. One strategy is to pick cities with large, diverse populations, noted above in Table 3. But within a city, we are unsure how fast or slow recruitment might take, and we run the possibility that several hundred participants could come from one locale. We wish to avoid that and will impose an upper limit of 80 participants per city. As we approach this upper limit, we can limit further enrollment by either removing the ad or temporarily removing the screening link. We had to do this in one prior national survey when 300+ survey respondents joined over a 3-day weekend. Given the demands of phone calls and mailings on our end, we may have to take more explicit measures to titrate our flow if this should happen again. As a last resort, and if more than 80 participants enroll from one city, we may need to turn eligible people away, and will send them a letter to such effect ("thank you for your interest but our study has reached full capacity in your geographic area") and will include cessation referral information specific to that area.

Recruitment & Retention Feasibility Our primary concern with regard to recruitment is the increasing use of e-cigarettes nationally (38, 105), balanced by our focus on minimal users. While e-cigarette use is increasingly common, non-use is still the norm by far (45). We initially considered eligibility to be based on never-users, but decided to follow recent precedent (94) to restrict to allow prior experimenters. We will review this issue prior to study start; our guiding philosophy is a focus on smokers new to e-cigarettes, or at least with minimal history. In our prior local studies of alternative tobacco, with almost no recruitment budget, we recruited 34 participants in 2 months (78), and 65 participants in 11 months (79). In our prior statewide study of mailed NRT, we recruited 165 participants in 6 months (77). Rates of recruitment for our national studies are noted above within Preliminary Studies. For the current study, we anticipate an overall recruitment period of 42 months (60 minus 8 months setup, minus 6 months of final follow-up, minus 4 months of data analyses at study end). We are confident in our ability to recruit 16 participants per month (660/42). Retention: The same table above demonstrates our consistently strong rates of retention, as measured by % of scheduled contacts completed. One subset of the current study will be recruited locally, in which we are also still strong with retention: across 264 scheduled in-person visits in our prior studies of Ariva/Stonewall and Camel Snus (collapsed), we completed >95%. Within our recent R21, we completed 89% of all scheduled follow-up visits.

Local Subset / Biomarkers

One strength of our study is the collection of exposure biomarkers: CO, cotinine, and NNAL (the latter to be tested at Roswell Park). We do this based on the targeted recruitment of smokers local in our area who complete a baseline in-person lab visit (N=120). This subset will be managed via phone and email as are all other participants, with the sole exception that they will be asked/incentivized to provide biospecimen samples 4 times: a) baseline, b) +10 days (first sampling week; CO only), c) +1 month, and d) +6 months. We will accommodate biospecimen collection at local participants' home or work, or visit to our lab, in order to minimize participant burden and research office contact. Furthermore, we will provide transportation via Yellow Cab of Charleston (paying them directly through Addiction Sciences Division account) for participants who are eligible, but do not

have reliable transportation to in-person visits. Power and sample size estimations for this subset are presented below.

Beginning November 2021, we will ask ***all*** participants to complete a carbon monoxide breathalyzer remotely four times (at Weeks 0, 1, 4, and 24 – the same time points we were doing in person) and send us the results. Our rationale for doing so is to ensure that we reach our target sample size within the funding time, especially given COVID constraints, recognizing that biospecimen collection is critically dependent upon CO breath samples (which can now be collected remotely; not available at the outset of the study).

We will mail an iCO Smokerlyzer to all participants after they complete the week 0 call. The device connects to a smartphone (both Android and iOS); thus, we require this as an eligibility criterion. The iCO can detect CO concentrations of 0-100 ppm, and has strong test-retest reliability, as well as concordance with traditional device. We will include instructions to complete the iCO breathalyzer, and all CO readings will be time/date stamped, providing objective recordings. The $70 iCO device can be used repeatedly within a person, but it is not returned at end of study as it is not transferable to another user. A portion of participant compensation is contingent upon iCO compliance (not abstinence). We define abstinence as 7-day point prevalence (no smoking in prior week), with CO ≤4ppm.

Randomization

We considered a host of potential moderators on which to stratify randomization, but ultimately the sample size should be sufficient to equalize groups (if incorrect, analyses will include covariates). However, outcomes might very well be moderated by readiness to quit, and thus randomization will be stratified based on desire to quit in next 30 days (0-6 vs. 7-10 on a VAS scale). We will also stratify on locally recruited vs. not. Participants will be randomized via a stratified, mixed block design, overseen by our statistician.

E-cigarette Group Our general aim within this group is to approximate the real-world scenario in which smokers are exposed to e-cigarette products and decide on their own if and how they will use them. There are numerous products on the market offering a range of nicotine delivery. Recent evidence suggests that any association between e-cigarettes and cessation is restricted to users of tank systems, as opposed ciga-like devices (53). Our guiding intent is to use the most efficient yet non-adulterable product available, optimizing user satisfaction. We previously evaluated a 1st Generation product (BluCig), with generally strong patterns of uptake. We were hesitant to move to a 2nd generation system because we could find none that were **pre-filled, closed, disposable** ("ego style") **tank systems**, a necessary requirement given our methods (we do not want home consumers adulterating the tank [spilling, adding more] in any way, for both safety and scientific reasons). Recently a new product came to market that meets this requirement: NJoy's pre-filled tank & battery. This is a closed tank system, sufficiently powered (1000MAH), and delivering sufficient nicotine (95, 106), even among smokers naïve to e-cigarettes (107). NJoy comes in 10 flavors, including traditional tobacco and menthol. Given the popularity of flavors within these devices, and potential role they may have for helping to reduce smoking, we will offer an assortment of each: top 5 selling flavors only; none of which contain diacetyl which some reports link to "popcorn lung" (108). We believe that a range of flavors more closely mimics the real world scenario of multiple options from which to choose; if e-cigarette uptake within our study is low, we do not want that to be an artifact of unrealistic range of flavors. If menthol or any other flavors are banned by FDA, as has been discussed, we will abide. We will offer participants 3ml pre-filled tanked, 15mg/ml of nicotine. NJoy does come in 25mg dosage but we opt for the 15mg to conform to SREC comparability (see below).

One clear advantage of NJoy system is that is the basis for the newly released NIDA Standardized Research E-Cigarette (SREC), which now provides a naturalistic test of a standardized product that will be used in other lab-based studies (http://www.e-cigarette-summit.us.com/files/2017/05/Kevin-Walton.pdf). In fact the only difference between our product and the SREC will be packaging; ours will be provided in original NJOY packaging. A menu of several e-cigarette products would better reflect our naturalistic intent, but this would introduce too much variability, as we would need to account for switching between products and a range of product characteristics. While this study is based on one product alone, we view it as a test of the concept of e-cigarettes in general, and thus more broadly generalizable. We recognize that products change regularly and what we choose now may not be the best option once this study starts. There are other options that may meet our criteria (e.g., V2, LogicPro) and if a more efficient, closed tank-based system becomes available, we will

consider it. Throughout this decision process, we will work within our investigative team prior to study onset to verify product and will discuss changes with NIH. NJoy availability or design might also change after the study starts, and if so the same guiding principles will apply. We expect product changes during the course of the study, as occurred within our R21. We view this as a strength, not a weakness, in that a) it gives us an opportunity to inventory a small number of each product for lab testing and product comparison, b) allows us to examine product evolution over time, and c) allows for sub-analyses of each product, recognizing limited power to do so. The overall comparison of e-cigarette vs. control group will control for any product changes as a covariate. Finally, to **authenticate key biological variables**, we will verify the nicotine content (through sub-contract with Dr. Goniewicz) on a regular basis (e.g., xx times per year, or every N^{th} product; depending on participant flow).

Samples will be provided in two 2-week shipments, with sufficient number of tanks to last ~4 weeks. We will send 2nd shipment only after request for more product is initiated by participant, either through response to diary question, call to our 1-800 number, or return of a mailback card sent along with 1st shipment. Flavors for 2nd shipment will be participant-driven. No more than 30 tanks will be sent to any one participant, no more than 20 for first shipment (slightly more than half of sampling period, to account for lag time after 2nd mailing) and 10 for second shipment. Each shipment will contain instructions not to allow anyone else to use the product, to store in a location out of reach of minors, and how to safely charge/clean product, per FDA guidelines. Based on a recent experience from Dr. Wagener and also through personal communications with both he and Dr. Goniewicz, we anticipate that ~25% of the sample will use daily; 50% will use for about 2weeks, and 25% will use less than that; these are all conservative estimates, as we do not want to artificially suppress uptake through insufficient sampling. Driven largely by our prior studies on product sampling, we believe this 4-wk period allows for a sufficient period of acclimation, in which smokers determine if they like it, and how to use it to manage cravings. This period also allows sufficient time to observe naturalistic changes in cigarette smoking, dynamic and concurrent in time with uptake of e-cigarette use. Smokers will not be asked to return product, but we will assess sustained and/or intermittent use over extended duration (6 months). Our group has a strong record of this sampling "intervention," in which we give smokers the opportunity to try new products over a short period, testing their impact both during and beyond the sampling period (see above).

We carefully deliberated the instructions we would provide for e-cigarette use. On one hand, providing minimal instruction is most reflective of the real-world scenario in which smokers self-determine amount of use. It is also consistent with our primary aim, in which we examine usage under natural conditions. On the other hand, we are concerned that a total absence of suggested use could result in minimal usage, which would undermine the study's secondary aim to examine prospective changes in smoking behavior. Thus, we will provide minimal suggestion, guided in large part by our previous sampling studies (NRT, snus, e-cigarettes; see preliminary studies above) ~"*studies e-cigarettes are likely much safer than conventional cigarettes, but they are not entirely safe. We encourage you to use them as much as you can, either to cut down or quit smoking, or to help manage smoking restrictions. You are not required to use e-cigarettes and how you use it is completely up to you*. As with all tobacco products, you should keep these out of reach from children." Product will be provided in original packaging, inclusive of instructions and marketing themes (reduced individual harm as compared to smoking). At the end of the 4-week sampling period, we discontinue any further e-cigarette administration but allow participants to keep any existing product, which we believe is most consistent with the real world experience of sampling a new product.

Control Group Smokers in this group will smoke their own brand of cigarettes, as they wish, for the duration of the sampling period, but will engage in all study assessments including diary assessments. We considered a placebo-controlled study, but our interest is not in the pharmacological intake of nicotine (vs. not), but rather the use (inclusive of behavioral substitution) vs. non-use of e-cigarettes. Blinding of active vs. placebo e-cigarettes is easily managed for lab-studies, but less so for nationwide, naturalistic studies. To control for cost differential with e-cigarette group, participants in the control group will receive extra reimbursement; we do not want changes in behavior to be a function of free product. We debated whether to provide same general message of e-cigarettes as above. On one hand, doing so would decrease study-induced demand to try e-cigarettes, making this equivalent across groups. However, this would artificially inflate e-cigarette use within the non-sampling control group, which impinges on internal validity. We opt not to include such messaging, but will acknowledge

this as a potential confound. We do anticipate that some control participants will use e-cigarettes, and this too is an outcome we assess (along with all other uptake variables). Within our R21, 1/21 control participants (4.7%) used an e-cigarette (see Figure above). E-cig use is escalating, but still low and we expect nominal initiation within control group. Primary analyses will be based on ITT principles (i.e., group assignment as the independent variable, not product use).

Smokers in both groups will be assessed at screening for interest in cessation support. All comers will be accepted, but smokers actively using cessation medication at baseline will be excluded. At all contacts, we will assess motivation to quit and, as necessary, offer referral information to state quitlines. Such transitions to cessation support are included as study outcomes.

Diary of E-cigarette Uptake

All smokers will be asked to complete a brief diary to assess smoking behavior, both conventional and e-cigarettes. We make no claim that this purely follows ecological momentary assessment procedures. Rather, ours is more accurately described as regular, periodic diary assessment, which we believe still captures our intent to understand uptake behavior as it happens. Diaries will be electronically collected daily for 28 days. We have established procedures to auto-send an email or SMS text (their choice) on a set schedule for intended diary days (first 28 days of sampling). SMS text messaging is possible via Twilio, embedded within our RedCap system, which allows participants to complete a survey directly from their phone, without having to access a webpage. Note that diaries are not completed via texting, just prompted via text with link to RedCap. Participants can choose to receive their diary invitations via email if they wish, again with a link to an secure RedCap survey. Thus, per eligibility criteria above, we require participants to have either 1) SMS text capacity with internet access OR 2) regular (at least daily) use of email. Diaries consist of a brief (2-5 minutes) survey, directly entered into an online protected database (REDCap) through secure encryption; all PHI is protected. Participants will be compensated for compliance based on % diaries completed (e.g., $100 for 90-100% compliance across all 28 entries, $70 for 75% compliance, etc). Diary data include items on I) conventional smoking behavior (amount, frequency, time to first cigarette), II) e-cigarettes (puffing episodes, puffs per episode and per hour, time to fist puff), and III) general mood & stress. There is some debate as to whether EMA/diary procedures alter behavior, but recent evidence suggests that assessment is unrelated to smoking (109). We considered a non-diary control group, but believe a third group is unwise; our trial is not a test of EMA/diary methods and any diary-specific effect, if it exists, is uniform across both groups. See preliminary studies above for documentation of diary compliance using similar methods.

Other Assessments

Assessments will occur at 7 points: baseline, weekly x4 for first month, and at both 3 and 6 months. Our baseline demographic questionnaire will include common items from NHIS and Adult Tobacco Survey. We will assess prior quit history (#, duration of attempts, medications used), motivation to quit, dependence, using standardized surveys were possible (110-113). We also assess withdrawal (114), and attitudes towards novel products (115-119). Follow-up assessments (~20-25min phone call, based on our prior experience) include:

Uptake Based in part on marketing theory that describes product adoption/diffusion (120), we will report incidence rates for uptake of use, based on participants who engage in: a) first time use, b) repeat use, c) first time buyer, d) repeat buyer, and e) advocacy; i.e., promoting/suggesting to others. We will also be poised to assess the time course for each. We will also track transitions to other e-cigarette systems, e.g., tanks, flavors.

Patterns of E-Cigarette Use Through both diaries and phone-based assessments, we will determine the duration, quantity, and frequency of e-cigarette use, as well ascertain the context in which it is used (e.g., places with smoking restrictions vs. other) using prior methods (121). We will specifically ask if e-cigarettes are used "not to quit, but to reduce the amount you smoke" or "not to quit or reduce smoking, but to get you through times when you cannot smoke." Some research (122) suggests a distinction between purpose-driven use vs. mere experimentation, with different trajectories/consequences of each, and we will assess this as well. We will also assess any use of other tobacco products, and can determine patterns of dual use as well.

Other e-cigarette outcomes We will also assess likeability/preference of e-cigarettes through items derived from the Cigarette Evaluation Scale (123) and related acute effects from smoking (e.g., calming, relaxing, arousing) (124), and select items from the Product Evaluation Scale (125) that is specifically meant for evaluation

of novel products. Lastly, though assessment of e-cigarette dependence is not well understood (126), we will use the recently developed scale from Foulds et al (127).
Motivation and Confidence to Quit will be assessed separately for conventional and e-cigarettes, using our modification of the Contemplation Ladder (128) to measure readiness to quit in the next 1 month and readiness to quit in the next 6 months. Our ladders have adequate test-retest stability and predictive validity (129).
Use of Other Cessation Resources We will assess use of other cessation resources, including use of NRT and non-NRT pharmacotherapy, behavioral counseling, quitlines, and consultation with other health professionals. We will also clarify the intensity (i.e., duration) and timing of use of these cessation resources.
Changes in Smoking We have established procedures to assess: a) smoking reduction, b) self-defined quit attempts, c) CDC-defined 24hr quit attempts (130). Abstinence will be based on established definitions (131) and will include: d) floating abstinence (any 7-day period of non-smoking throughout the course of the study), which may be more appropriate for non-cessation trials (132), e) point prevalence, and f) sustained abstinence.
Adverse Events Prior e-cigarette literature suggests that adverse events are rare and mild: headache, mouth/throat irritation, and nausea (24, 32, 56). Dr. Gray provides medical oversight throughout.
Biomarkers Within the locally recruited subset who complete the baseline in-person lab visit, urine cotinine and NNAL level will serve as a biomarker for nicotine exposure, both to conventional and e-cigarettes. Four samples will be collected per person: a) baseline, b) after 1st wk of sampling, c) 1 month follow-up, and d) 6 month follow-up. Samples will be assayed locally by our Department of Psychiatry's Clinical Neurobiology lab (cotinine) and remotely at Roswell Park Cancer Institute (NNAL). Collection of NNAL (tested beyond week 1, so as to not be confounded with baseline cigarette smoking), as well CO, will allow us to discriminate between use of e- vs. conventional cigarettes. We do not expect cotinine to change as smokers switch from one product to another, but we do expect decreases in CO and NNAL, to the extent that smokers switch from cigarettes to e-cigarettes (issues of compensation notwithstanding).
CAPTURE (Chronic Obstructive Pulmonary Disease Assessment in Primary Care to Identify Undiagnosed Respirator Disease and Exacerbation Risk): To be asked at Baseline only, to ascertain the distribution of capture scores among a general community-based sample of smokers.

Added Assessments: Charleston/Local Sample
For the local study sample who complete the baseline in-person lab visit (N=120), we previously included a number of in-depth mechanistic and outcome measures that are not possible with phone-based assessment of a national sample. These outcomes were considered exploratory and were not vital to the main aims of the project. In the context of COVID-19 and the ongoing need to minimize unnecessary in-person study procedures, we will now send a REDCap link to these questionnaires to local participants via text/email after the corresponding study phone call. The Go/No-Go task (Task-based measure of Inhibitory Control), which is not able to be completed via REDCap survey, will be eliminated. The in-person lab visit will be used ONLY to collect CO and urine samples, for biomarker testing (which are vital to the main aims of the study). These revised procedures will require ~5 minutes of lab time only and will incur minimal interaction between study staff and participants. We will follow all SOPs for appropriate social distancing that are applicable to our lab studies as a whole. Participant remuneration for these lab visits remain unchanged. The only change for them is a shorter visit.

Thus, for this sample alone, we include additional measures to capture the following, all of which will be sent as a REDCap survey after the following phone calls: 1) baseline, 2) week 4 (end of sampling), and 3) 6 month (final follow-up).

a) Task-based measure of Inhibitory Control: This task will be eliminated, as it is not able to be asked via REDCap survey and is not a main outcome of the study.
b) Task-based measure of Inhibitory Control: Delay Discounting. Delay discounting is a behavioral economic construct that helps explain addictive behaviors. It is well established that smokers have higher levels of discounting (impulsivity) than do non-smokers. However, no prospective study has examined discounting as a predictor of vaping uptake or how transitioning to vaping may alter discounting (135). The current study will fill these gaps by testing whether discounting at baseline

predicts vaping uptake/substitution during the sampling period and at follow-up, and how sampling e-cigarettes changes discounting (relative to control). Participants will undergo a 5-trial (136) adjusting delay discounting task, with delay timeframes ranging from 1hr to 18yrs, with magnitudes of either $500 now or $1000 at the specified delay. This task is used to determine the preference for smaller magnitude immediate rewards compared to larger magnitude delayed rewards, or *k value*. To efficiently determine *k* values, the task uses a progressive forced choice sequence over five choice trials. A higher *k* value indicates steeper discounting; i.e., impulsivity.

c) Subjective measure of impulsivity: Barrett Impulsivity Scale (BIS). The BIS is the most widely cited instrument to assess impulsiveness, and complements above objective measures of the same (137). The 30-item BIS captures 6 sub-factors: attention, cognitive instability, motor, perseverance, self-control, and cognitive complexity.

d) Experimental Tobacco Marketplace (ETM): The ETM (138) allows us to address questions of whether e-cigarette sampling changes demand for cigarettes; i.e., substitutability, in ways that complement or our other outcomes. During the ETM (~10 minutes), participants make hypothetical purchases of cigarettes and other tobacco products at various prices. This task can be used to understand how demand for cigarettes changes as price is increased and which products are likely to substitute for cigarettes as higher prices. During each of these sessions, participants will view an online store of tobacco products, and be instructed to make purchases, with access to an account balance consistent with weekly expenditure on cigarettes/e-cigarettes. Participants will be told that purchases are hypothetical, but to complete the task as if purchases are real. A picture, description, and price will be displayed for each tobacco products. Products may include cigarettes, e-liquid, nicotine gum, nicotine lozenges, snus, and dip. Participants will complete five trials, and across trials prices will vary for cigarettes (1/2x, 1x, 2x, 4x, 8x market price). Nicotine replacement therapies (gum/lozenge), smokeless tobacco (snus, dip), and e-cigarettes / e-liquids will be available at a constant price across all purchase decisions.

Statistical Considerations – Sample Size & Power

Our primary focus in this study is the short and long term behavioral impact of e-cigarettes. We considered a trial that was powered on e-cigarette uptake or substitution of conventional cigarettes (Specific Aim 1). These questions alone are important outcomes that would inform the public health debate. However, it would be a missed opportunity to not ask about overall exposure (Specific Aim 2) and quitting (Specific Aim 3). We also believe that, if group differences in quitting do exist, it would be entirely shortsighted if we lacked sensitivity (i.e., power) to demonstrate them. So while we focus on uptake, adoption, and patterns of dual use, we power our study on the most stringent outcome: point prevalence abstinence at 6 months (continuous abstinence is more stringent, but inappropriate here since there is no quit date to commence cessation). Table 4 depicts various sample size scenarios, under the guiding belief that e-cigarettes will facilitate quitting (see Intro). These scenarios are all based on proposed 2:1 randomization, in an effort to be have better precision (i.e., tighter confidence intervals) for our primary outcome, involving only the e-cigarette group. Our base rates for quitting come from our three prior/ongoing nationwide studies, in which 6-month abstinence rates within control group ranged 4-13% (75, 76). We also recognize other population estimates (~5%) of population-based quitting (133), and ultimately take an estimate within this range: 8%. As for quit rates in the e-cigarette group, we note outcomes from most relevant study yet published: an uncontrolled observational cohort (i.e., naturalistic) study of smokers given e-cigarettes for up to 6 months (47), in which 23% (ITT, based on full N) and 33-39% (respondent only analyses) were quit at 6 months. We think that is a bit high. Given that we provide e-cigarettes for only ~1month, we expect somewhat lower rates of quitting. We power on a RR of 2.0: 8% vs. 16%. We would like to detect even smaller increases in quit rates (5% vs. 10%; RR still 2.0), but clearly that is not feasible. We thus decide on 600 participants, but inflate this by 10% to account for attrition: 660 participants to be enrolled

Table 4: Sample Size Needs

		Quit Rate in E-Cigarette Group				
		10%	15%	16%	20%	25%
Quit Rate in Control Group	5%	1015	332	287	179	117
	8%	7324	755	**600**	305	174
	10%		1576	1135	463	233
	15%				2067	2486

2:1 randomization (ecig:control); 80% power

(440 e-cigarette vs. 220 control). With this sample, we have 80% power to detect differences of 10% vs. 18.5%, with a two-sided α=0.05 chi-square test. If provision of e-cigarettes should undermine quitting, we are able to detect a decrement of 4% (8% vs. 4%; OR = .48; 95% CI: 0.23 - 0.98).

Precision of Proportional estimates within Aim 1 With 440 e-cigarette participants, a two-sided 95.0% confidence interval will have a maximum half-width of 0.047 (for any outcome in Aim1) (e.g., 95% CI on an observed rate of 50% would range from 0.453 to 0.547). As the observed proportion deviates from 50% (either higher or lower), the 95% confidence interval will decrease in width, providing more precision on the estimate (e.g., 95% CI on 90% would range from 0.872 to 0.928). A confidence interval as wide as +/- 5% is a relatively small width and one we are willing to accept for our estimates on uptake, adoption, and patterns of dual use.

Sample size estimate for local subset, to capture biomarkers of exposure We searched for prospective e-cigarette studies (controlled or not) that were NOT cessation based but reported on biomarkers, either CO or cotinine. We found only one (47) but acute decreases (within 1 month) in CO were only indirectly reported (in graph, separated by smoking group outcomes). Consistent with those data, we expect an overall decrease in CO within 1month of 35%, compared with no such decreases within the control group. A sample size of 80 in the e-cigarette local subset group (total of n=120 for the local subset who complete the baseline in-person lab visit) will have at least 80% power to detect a 35% decrease in CO (23.5ppm to 15.3ppm in the e-cigarette group vs. no change in the control group, assuming a standard deviation of 15.0 in the control group and 10.0 in the e-cigarette group (standard deviations were estimated from the interquartile ranges reported in the Polosa study (47) using standard procedures (134)). We expect no group differences in cotinine. We recognize that this technically implies a test of equivalence, and we are willing to accept up to +/-3% difference to conclude equivalence. With a local subset sample size of n=120 (40 control and 80 e-cigarette), α=0.05, a two-sided t-test has >90% power to reject the null hypothesis that the two groups are not equivalent (1400ng/ml +/- 45ng/ml) in favor of the alternative hypothesis that the mean cotinine levels of the two groups are equivalent (assuming an expected difference in means of 0ng/ml and a common standard deviation of 70.0ng/ml) (135).

Statistical Considerations – Data Analyses

All analyses are based on an intent-to-treat approach, and are nearly identical to analyses from our prior studies. Exploratory analysis will be performed on all outcomes, and both graphical displays and summary statistics will help determine if transformations will be needed. Any significant baseline differences between groups will be included in regression analyses described below. Missing Data: The most conservative approach for handling missing data (136) is to substitute them with baseline values, assuming outcomes have all returned to baseline, with no quit attempts made. If this assumption is incorrect, it biases the results towards the null by reducing between group differences (136). SRNT recommendations (136) suggest that when there are small amounts of missing data (< 10%) the conservative approach can be used with little bias in outcome. If missing data >10%, we will calculate results not only using this conservative method but also using methods in which missing data are imputed as described in the SRNT guidelines. We will also assess whether dropout is differential by study group. In our current and recent studies of cessation induction, this has not been the case, and we expect similar results here. Finally, though sex/gender is not an explicit focus, we are well poised, given our sample size, to address **potential sex/gender influences** on study outcomes.

Hyp 1a: Within the e-cigarette group, we hypothesize that at least 90% of smokers will try at least once, 45% will use regularly (at least 4/7 days, at any time during follow-up), 25% will use daily for ≥7 days (at any time during follow-up), 25%/10% will be using at least some/daily at final follow-up, and 20% will independently purchase e-cigarettes. Within the e-cigarette group (N=440), we will analyze prevalence of each definition of uptake. We will estimate each of these parameters, and the 95% confidence interval for each proportion.

Hyp1b: Among smokers in the e-cigarette group, 40% will show a minimum of 50% reduction in cigarettes per day, and as a group, e-cigarette users will show greater decreases in cigs/day as compared to control. Reduction of cigarettes per day will be calculated based on the TLFB at baseline and 6 months for both groups, with "reducers" defined as those that reduce cigarettes per day by ≥50%. We will estimate the mean reduction, 95% confidence interval on the reduction, and the proportion of those that are considered "reducers" in both groups, the latter tested via a chi-square test with α=0.05 two-sided significance level.

Hyp2: Within a subset of locally recruited smokers, we hypothesize that use of e-cigarettes will lead to significant decreases in CO and NNAL, but no net change in overall nicotine exposure. Changes in CO, NNAL and cotinine will be calculated based on the baseline, 1, and 6-month measurements. Mean change in CO/NNAL (thru 1 and 6 months) will be compared via a two-sample t-test with α=0.05 significant level. In order to test equivalence for change in cotinine between the two groups, the TOST procedure (137) will be followed where two one-sided tests will be used to test that the difference in the change between groups (Δ) is within the +/-3% bounds that we are willing to accept (H_{01}: Δ < -3%; H_{02}: Δ < +3%). If Δ is contained completely within the +/-3% bounds, then equivalence will be concluded. We will use an α=0.05 significance level.

Hyp 3: Provision and use of e-cigarettes will lead to increased incidence of (Hyp3a) quit attempts, (Hyp 3b) cessation, and (Hyp 3c) motivation/confidence to quit. Logistic regression analyses will be performed with (1) any quit attempt [QA] within 6 months (1=one or more quit attempts, 0=none), (2) any 24hr QA (same), (3) point prevalence abstinence at 6 months (1=7 day abstinence at 6 months, 0=not abstinent), and (4) floating abstinence (1=any 7 day period of abstinence during study, 0=no abstinence) as the outcomes and group (e-cigarette vs. control) as the covariate. The coefficient on group provides a log odds ratio for measuring the odds of (1) any self-defined QA's, (2) 24hr QA's, (3) point prevalence abstinence, and (4) floating abstinence. Statistical significance of these coefficients will be assessed using a p-value with a two-sided α=0.05, and both the odds ratio and its 95% confidence interval (CI) will be reported. Motivation and confidence to quit are evaluated on a continuous scale (0-10), and linear regression models will be used for both, with group (e-cigarette vs. control) as the covariate (along with any other baseline differences as covariates). To fully capitalize on the longitudinal nature of our data, secondary analyses will include a) regression analyses where number of QA's are compared across groups using poisson or linear regression (depending on the distribution of QA's), b) latency to any quit attempt, and c) stability of e- and conventional cigarette use over time. We will also repeat above analyses: a) based on those who do vs. do not use e-cigarettes, and b) using quit attempts and abstinence of all tobacco products, including e-cigarettes.

Ancillary Analyses:
Moderator analyses We can examine if uptake and/or consequences are moderated by motivation to quit, dependence, concerns of health, and/or any potential changes in e-cigarette product. Mediation of "intervention" effects: For each potential mediator (e.g., changes in harm perception/likeability of e-cigarettes), we will fit logistic models to assess each individually for each outcome. Latent class analyses: Patterns of use may be explored using latent class or other latent variable models to investigate if subjects separate into "classes' of use, which may be defined via reduction in cigarette use, uptake patterns in e-cigarettes and/or patterns of quit attempts. *Adverse Events (AE's):* We will determine the incidence of AEs and the associated 95% CI. A chi-square test will determine if the rate of serious adverse events (i.e., requiring treatment or life threatening) is greater than 5%. Other: 1) We will examine the longest duration of non-smoking between groups via a two-sample t-test. 2) If sufficient data are available, we will also conduct statewide comparisons on outcomes of interest to determine the influence of policy variables like a) level of excise tax, or b) % of state that is smokefree. 3) Urine samples will be frozen, with options for future secondary data analyses of both anabasine/anatabine, two tobacco specific biomarkers, but currently very costly to analyze. 4) Our local lab is developing an assay for 3'OH, which when compared to cotinine, provides an index of nicotine metabolite ratio (138, 139) which could be used as a predictor of e-cigarette uptake, something never before assessed. We are unsure when this assay will be ready, and consider this only ancillary.

Conclusion
We believe this will be the best, **most rigorous test to date of the naturalistic population impact of e-cigarettes**. Methods are strengthened by 1) large sample size (the largest e-cigarette RCT), 2) nationwide recruitment, with 3) locally recruited subset to assess biomarkers, and 4) multiple measures of outcome. The strong investigative team, coupled with our success in prior studies using similar methodology, collectively enhances the probability of success in achieving grant aims. The NIH and FDA have each articulated a clear

Abbreviated Timeline (Full Timeline within Human Subjects Protections)

	Year 1	Year 2	Year 3	Year 4	Year 5
Study Prep. & Refine Protocol	1-6 mnths				
Cumulative N to start	100	285	470	570	609
Data Analysis					57-60 mnths
Manuscript Preparation					57-60 mnths

agenda to understand how smokers use e-cigarettes and what impact such use may have on behavior. The proposed study offers the most methodologically rigorous test of these questions.

Human Subjects Research

1. Risks to Human Subjects

1.1 Human Subjects Involvement and Characteristics

General Inclusion / exclusion criteria are as follows:

a) age 21+,
b) current smoker of ≥5 cigarettes per day for ≥1 year,
c) no recent history of cardiovascular distress (heart attack in past 3 months; arrhythmia, uncontrolled hypertension), or renal disease (e.g., dialysis) that would interfere with urinary biomarker assessment
d) neither pregnant nor breastfeeding,
e) at least some concern for health effects of smoking (>none at all on a Likert scale),
f) no current use of cessation medication,
g) have not purchased in the past 6 months or ever regularly used (daily or weekly) a tank system, mechanical mod, or advanced personal vaporizer e-cigarettes
h) no regular use (daily or weekly) of any e-cigarette (including cig-a-like devices) in the last 6 months,
i) no current use of other tobacco products,
j) capacity to receive SMS text and internet access (for purposes of diary completion and iCO completion),
k) no other household members are enrolled in the study, and
l) no history of seizure disorder.

1.2 Sources of Materials

Research material obtained from the participants include responses to phone-based surveys, collected directly by our research team and entered directly within secure databases. We will also collect urine samples among a subset of participants, locally recruited, to assess biomarkers of smoking (CO and cotinine). Research data will be obtained specifically for research purposes. Every effort will be made to maintain subject confidentiality, in accordance with HIPAA.

1.3 Potential Risks

The research protocol calls for non-treatment seeking smokers to either use e-cigarettes or not. Use of e-cigarettes is entirely self-chosen, since this is one outcome, rather than prescribed. E-cigarettes are no more harmful than conventional cigarettes, and various studies suggest that they may offer reduced harm. Questionnaires and interviews are all non-invasive and involve minimal risk to study participants. Potential risks are as follows:

1) risk of using e-cigarettes
2) concurrent use of e-cigarettes & smoking
3) potential for undermining cessation
4) non-smokers in the home (children) experimenting with e-cigarettes
5) loss of confidentiality

1.3.1 E-Cigarettes E-Cigarettes are not combusted, and therefore levels of carcinogens are markedly reduced, if not eliminated, comparable to trace levels seen in nicotine replacement products (26). Nicotine liquid is based on a solution containing propylene glycol, which some suggest may be harmful. Propylene glycol is an FDA approved food additive, but with uncertain effects upon inhalation. The detailed NIDA-guided DSMP (Section 4 below) presents data on tobacco-specific nitrosamines (TSNAs), within both e-cigarettes and their vapor.

As for adverse events, the majority of e-cigarette studies are based within on-line surveys. We report here on three moderate to large such surveys, 2 recently published (2013) and one from 2011 but is the largest survey to date. In the first (32), three side effects were reported by >20% of respondents: headaches (21%), cough

(27%), and increased phlegm (25%). In the second (33), the most common negative effect of e-cigarette use was throat and mouth irritation, and fewer than 3% "reported a high level of side effects." Finally, the largest online survey to date (56) did not fully assess adverse events, but reported that 26% of e-cigarette users reported burning in throat. In a cross-over study of 40 smokers given e-cigarette for four days (14), the four most common adverse events (within highest dosage group) were mouth/throat irritation (38%), nausea (29%), vertigo (21%) and headache (22%). All other adverse events were rare (<5%). There have also been a small number of reports to the FDA of people using e-cigarettes and experiencing seizures, with most reports involving youth or young adult users. These are rare, but we will inform participants of this risk and monitor.

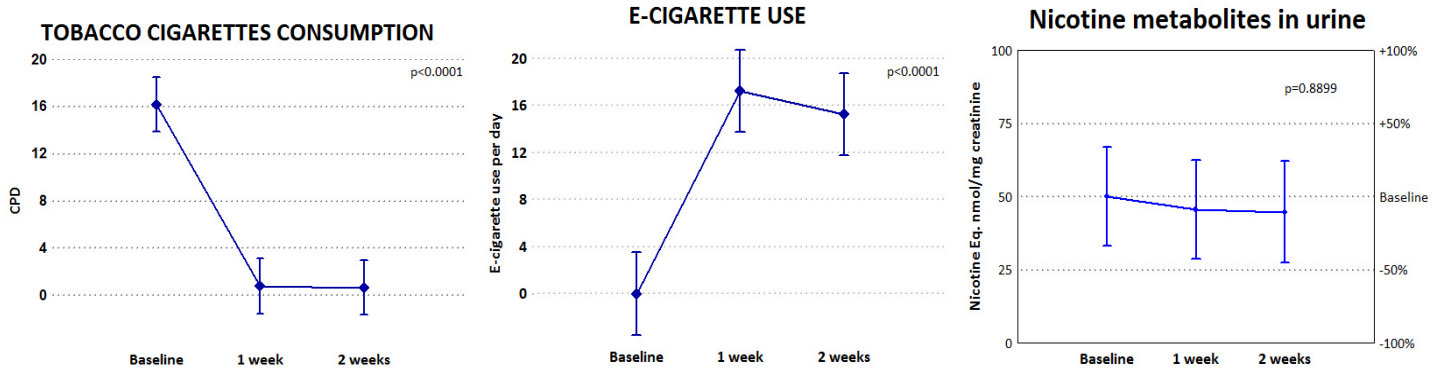
In the recent RCT from New Zealand (67), there was a higher number and proportion of adverse events among active e-cigarette group, but the event rate did not significantly differ as compared to nicotine patches. In the RCT from Italy (66) there was no differential rate of adverse events among high, medium, or placebo e-cigarette groups. The five most common adverse events were dry cough, mouth irritation, shortness of breath, throat irritation, and headache, with no serious adverse events. The study also reported no significant changes in body weight, resting heart rate, or blood pressure.

There have been a number of reports of respiratory illness from individuals using e-devices. No specific substance or product has been linked to these cases. Many of but not all of the cases involved users vaping THC, which is the psychoactive ingredient in marijuana. Some of the instances are specific to nicotine alone. We advise all participants not to add any substances to the devices we give them. We advise against using any e-device or e-liquid that is obtained by questionable or unknown sources (such as off the street or on the black market). While we believe that e-cigarettes are less harmful than combustible cigarettes on a long term basis, there may still be acute (i.e., short term) risks of using e-cigarettes. We will continue to monitor the participant's health in our study.

1.3.2 Concurrent use of e-cigarettes and smoking

If smokers engage in dual use, the major concern will be intake of nicotine, and too much of it. Symptoms of nicotine intoxication include nausea, dizziness, headache, and stomachache (140). In our two prior studies wherein participants who used nicotine gum/lozenge and smoked concurrently, there was no evidence of nicotine intoxication (75, 76), nor have we seen serious adverse events in our current e-cigarette studies. We recently completed a literature review (141) that showed combined NRT, as well as concurrent use of NRT and smoking, were both safe.

Dr. Goniewicz (co-I) recently completed a short term observational study, in which 20 smokers were provided e-cigarettes for ad libitum use over a 2 week period; i.e., a study very similar to current proposal. Data below demonstrate that changes (increases) in e-cigarette use increased in direct proportion with changes (decreases) in cigarette smoked (1st and 2nd panel), resulting in no net change in nicotine (3rd panel). Thus, smokers who engage in dual use are likely to NOT increase total nicotine intake, a finding replicated elsewhere (17). These findings are very much consistent with our own prior work on smokeless tobacco, wherein we provided smokers snus to use ad libitum over two weeks, finding no net increase in nicotine intake.



1.3.3 Undermining Cessation Another potential risk is that the sampling intervention will decrease rather than increase future cessation. We are aware of one recent longitudinal study (61) that showed numerically lower but still statistically similar rates of non-smoking among e-cigarette users vs. non-users, but this study did not assess for timing of e-cigarette use. This is the only study to show this that we are aware of. However, most of the available data available suggest that e-cigarettes either do not affect cessation or increase it (32, 44-46, 56, 66, 67).

1.3.4 Use of E-cigarettes among non-participants and non-smokers, including children
Whenever a product is given to a smoker to take home and use, there is potential that the product will be used by someone else, inclusive of non-smokers and even children. In our ongoing snus trial in which we mail tins of smokeless tobacco to smokers all over the country, such "diversion" (tracked by our team) was not a problem. We will advise participants who receive e-cigarettes to keep them out of reach of children. The fact that we are using pre-loaded cartridges of e-cigarettes (NJoy), rather than refillable tank systems, minimizes the potential for adulterating the system by adding additional substances.

1.3.5 Confidentiality A final risk is breach of confidentiality.

2. Adequacy of Protection Against Risks

2.1 Recruitment and Informed Consent

All research personnel have up to date CITI Certification for Protection of Human Subjects, and will keep this training current throughout the course of the study. Study participants will be recruited through local media outlets. Those who call expressing interest in study participation will be screened for all inclusion criteria. We will provide participants with the option to complete consent 1) via MUSC's doxy.me system (teleconsent), 2) via REDCap electronic consent (e-consent),combined with a discussion over the phone, or 3) by mail.

For those who have the required hardware and software for doxy.me, we will describe the basic mechanics of the teleconsent process and ask for preference for mode of consent. Participants who do not have access to the required technology to complete consent remotely via doxy.me or REDCap will be mailed a consent form. Signatures on the consent form may be obtained electronically via REDCap/doxy.me.

For those who elect teleconsent, we will follow procedures as per precedent (101) and through consultation with MUSC researchers (Dr. Brandon Welch). All doxy.me signed consent forms will be saved as pdf files within our study records. Research staff will then have the participant complete the baseline questionnaire (that would otherwise be sent with mailed questionnaire; see below). We anticipate that 10-20% of study participants might enroll through this method.

For those opting to receive consent packet through the mail, we will follow our prior procedures, sending a packet inclusive of two copies of the consent, a baseline questionnaire, and a pre-addressed, pre-stamped return envelope. Participants will sign and return one consent and their completed baseline questionnaire. We have

a toll-free phone line to support anyone who calls with questions. Upon return to our office, data are entered into our database, and these individuals comprise the consented sample.

In the past, about 45-50% of individuals who are mailed a consent return it; we do not badger those who decline. However, not all consenting individuals are able to be reached (~10% from previous studies) and those that are (~90%) will comprise the intent-to-treat enrolled sample. We will abide by all HIPAA regulations as set forth by our institution. The PI will supervise all aspects of the recruiting process.

2.2 Protection Against Risk

2.2.1 Use of E-cigarettes Participants will be screened for general medical precautions (pregnancy, cardiovascular disease), and all participants will be monitored for adverse events during the study period. We will clearly advise against use of e-cigarettes during pregnancy and breast-feeding and will verify non-pregnancy at study onset. Two study physicians (Drs. Gray and Warren) are available for consult for all adverse events. Participants will be educated about potential risks of e-cigarette use, including concurrent use with cigarettes. Any adverse events will be reported to the IRB. The most likely adverse event (potential for nicotine overdose) is anticipated to be rare (~5%) and mild (mouth/throat irritation, headache, nausea, headache), and will be handled quickly (i.e., advice to participant to reduce or stop e-cigarettes). Lab studies of toxin exposure (above) suggest that e-cigarettes confer no greater risk to health than do conventional cigarettes. It is unlikely that e-cigarette users will become addicted to the product in the 3-week sampling period, though that is one outcome we will track. All participants will be provided with cessation information (referrals to Quitline) as part of this study.

2.2.2 Concurrent Use of E-cigarettes & Smoking Per above, the most common effects from too much nicotine are nausea, headache, and disturbed sleep. The sampling period is up to a month in duration, and thus we do not expect sustained patterns of dual use. We will track adverse events at every study contact, and will have a toll-free number available for participants to call if they experience an adverse event (AE). All study contacts will remind participants of this number. A physician will be on call throughout the study for questions about AEs, etc. Participants will be encouraged to contact the Study PI as soon as possible for serious events. If they wish, they may contact their local MD or give the study physician permission to do so. We will withdraw participants who have a serious AE, become pregnant or begin breast-feeding. For other AEs, if the study physician, the participant's physician or the participant wishes it, the participant will be withdrawn from the study. If interim checks show the percent of serious or severe AEs to be greater than 5%, our Data Safety and Monitoring Board will be notified to make a decision on early termination of the study.

2.2.3 Undermining Cessation We emphasize that this is not a cessation trial, though we will collect various cessation outcomes. Nonetheless, it is possible that use of e-cigarettes will undermine quitting (though this would be contrary to existing literature). To protect against this outcome, we will form a Data Safety and Monitoring Board (DSMB; see below) and have them conduct an interim analysis after 33%, 50% of the sample has completed 6 month follow-up. If the rate of quit attempts or abstinence within the e-cigarette group is >10% below that within the control group, the DSMB will independently decide on whether to stop the study.

2.24 Diversion of e-cigarettes We now plan to send e-cigarette samples in multiple shipments instead of one. We will ask at each visit if the product has been diverted to anyone in the house. Any affirmed response to this question, or suspicion of it by our team, will result in discontinuation of product for that individual. We cannot directly assess any diversion/uptake from the perspective of adolescents, since that would require separate consent, and is a separate research question. We are aware e-cigarette flavoring might hold appeal to youth, but believe this risk is mitigated by: a) childproof packaging from manufacturer, b) providing no more than 30 tanks (no more than 20/10 for first/second shipment), and c) repeated instruction (oral and written) to study participants to keep this and all tobacco products out of reach of children. Our protocol follows our prior study of mailed sampling of snus (also offered with multiple flavors), and also the sampling experience of our co-investigators, all without such problems of diversion. The fact that we are using pre-loaded cartridges of e-

cigarettes (NJoy), rather than refillable tank systems, minimizes the potential for adulterating the system by adding additional substances.

2.25 Confidentiality We will use the participant's name only on the screening and informed consent documents and these will be kept in a locked file, to be kept centrally at our study office. Copies of informed consent will be kept by research personnel under lock and key. The research materials will become part of the modern record keeping facility of the Institute of Psychiatry, which will minimize risks to the privacy of participants. All interviews, records, charts, rating scales, and other patient information will be kept in locked files at the Cancer Control Program, with limited access to the study personnel. All database files will include password protection to further ensure confidentiality.

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

In an ever-changing marketplace of tobacco-produces and nicotine-delivery devices, e-cigarettes are arguably the most popular new products available to smokers. The two most important questions about e-cigarettes are 1) uptake among non-smokers, and 2) impact among smokers. This study is poised to answer the latter, and is a strength upon existing research that is predominated by cross-sectional surveys and short term lab studies. There is a universal call for randomized trials of e-cigarettes, but these trials do not exist, at least in the U.S. It is important to test e-cigarettes in advance of potential FDA role in regulation of them. E-cigarettes are classified as a tobacco product and in all likelihood will eventually be regulated by the FDA. The FDA will need high-level science to assess overall population impact.

This study is not without benefit to individual participants. However, this is not a treatment trial, and will not be advertised as such. We assess at screening for interest in cessation support. All comers will be accepted, but smokers actively seeking cessation support, or currently using cessation medication at baseline will be excluded. At all contacts, we will assess motivation to quit and uniformly offer referral information to state quitlines. Such transitions to cessation support are included as study outcomes. Two-thirds of the participants in the trial will receive samples of e-cigarettes, which most evidence to date suggests is a) safer than conventional cigarettes, and b) possibly related to quitting.

Data and Safety Monitoring Plan

This fully detailed section is based on the recommendations in NCI's "Guidelines for Developing a Data and Safety Monitoring Plan" as well as NIDA's "Guidelines for Developing a Data and Safety Monitoring Plan."

1. Summary of the Protocol

Eligible smokers, once consented (process described below), will be randomized to receive a onetime sample of e-cigarettes (NJoy; n=440) or not (n=220). E-cigarette samples are inclusive of a battery and self-contained tanks of assorted flavors to last up to 4 weeks. Participants will be recruited nationally, but a subset (N=120) will be recruited locally to allow for biomarker collection (locally recruited participants will be managed via phone/mail as are all other participants; details below). All smokers will be asked to provide smoking diary data, captured electronically, daily for 4 weeks. More substantive phone assessment will track smoking and related behaviors at baseline (Day 0) and +10, +17, and +24 days (weekly during initial 3 weeks, following brief lag for delays in product mailing), and at +1, +3, and +6 months (7 phone assessments total). Major outcomes during both the sampling and follow-up periods are noted below.

2. Primary and secondary outcomes

During the sampling period and beyond, uptake of e-cigarettes is the primary outcome. Uptake is defined in several ways, including a) first time use, b) repeat use, c) first time buyer, d) repeat buyer, and e) advocacy; i.e., promoting/suggesting to others. Following a brief sampling period, smokers are then followed for six months, in which outcomes include subsequent e-cigarette use, biomarkers of exposure, quit attempts, and cessation.

3. Inclusion/exclusion criteria

General Inclusion / exclusion criteria are as follows:

a) age 21+,
b) current smoker of ≥5 cigarettes per day for ≥1 year,
c) no recent history of cardiovascular distress (heart attack in past 3 months; arrhythmia, uncontrolled hypertension), or renal disease (e.g., dialysis) that would interfere with urinary biomarker assessment
d) neither pregnant nor breastfeeding,
e) at least some concern for health effects of smoking (>none at all on a Likert scale),
f) no current use of cessation medication,
g) have not purchased in the past 6 months or ever regularly used (daily or weekly) a tank system, mechanical mod, or advanced personal vaporizer e-cigarettes
h) no regular use (daily or weekly) of any e-cigarette (including cig-a-like devices) in the last 6 months,
i) no current use of other tobacco products,
j) capacity to receive SMS text and internet access (for purposes of diary completion and iCO completion)
k) no other household members are enrolled in the study, and
l) no history of seizure disorder.

4. Sample Size

The sample size is 660 participants. (For this IRB application, we are increasing the total number of study participants by ~10% from 540 to 600 for the national sample and from 120 to 150 for the local sample, for a total of 750 study participants, to account for the ~10% of participants who mail us a consent back but who we never reach for the first study phone call – see section 2.1 Recruitment and Informed Consent on page 18 of this protocol.)

5. List of participating / enrolling sites

The study will recruit nationally, in pre-determined cities with high percentages of minorities and/or latinos. A subset of smokers will be recruited locally in the Charleston SC area, to collect biomarkers of smoking behavior. Locally-recruited participants will count toward the local/Charleston sample of n=120 only after they complete the baseline in-person lab visit. If a participant is recruited in the Charleston area but does not complete the baseline lab visit, they will be counted toward the national sample enrollment total and not eligible for any further lab visits.

6. Projected Timetable

The timetable is as follows:

	Year 1 (months)	**Year 2** (months)	**Year 3** (months)	**Year 4** (months)	**Year 5** (months)
Refine all procedures / IRB	1-6				
Procure supplies	5-6				
Hire and Train Personnel	5-6				
Study Enrollment					
Cumulative N to start**	(105)	(305)	(505)	(615)	(660)
First Participant Starts	7				
First Participant Completes		13			
Last Participant Starts					50
Last Participant Completes					56
Data Analysis					57-60
Manuscript Preparation					57-60

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

7. Target Population

Women will be included in this protocol. Currently, women are about 50% of smokers (slightly less among African American women) and thus it is estimated that 50% of the study sample will be women. If there are discrepancies in terms of gender, efforts will be made to improve recruitment of women into the study through oversampling via online recruitment.

Minorities are also included in this study, at proportions (aggregate 22%) generalizable to US Census data, wherein 78% of US residents are White, 13% Black, 5% Asian, 1% Native American, and <1% native Hawaiian or Pacific Islander. These same census data indicate that 17% of the US residents are of Hispanic origin. The Targeted Enrollment Table reflects these proportions accordingly. We have chosen recruitment cities that meet or exceed national estimates proportions of minorities and/or Hispanics, which should facilitate recruitment goals.

8. Data Acquisition and Transmission

Participants are recruited nationally, and contacted via mail and phone. The study will be managed centrally from the Division of Clinical Neuroscience within the Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina (MUSC), but physically based within the Cancer Control Program of the Hollings Cancer Center, where the PI is based. A subset of study visits will occur in lab space within our study group. Urine assays will be managed locally within our departmental lab.

9. Data Analysis Plan

Data will be entered centrally by research assistants directly in real time, into a computer-assisted telephone REDCap (Research Electronic Data Capture) database. RedCAP is a secure, web-based application designed exclusively to support data capture for research studies. Our group has been using REDCap for all studies since 2009, reducing errors with data entry. All databases are password protected. Cotinine and carbon monoxide data will be managed through the Department of Psychiatry's Clinical Neurobiology Lab. Samples will be stored in deidentified fashion, with unique SID numbers alone.

Hyp 1a: Within the e-cigarette group, we hypothesize that at least 90% of smokers will try at least once, 45% will use regularly (at least 4/7 days, at any time during follow-up), 25% will use daily for ≥7 days (at any time during follow-up), 25%/10% will be using at least some/daily at final follow-up, and 20% will independently purchase e-cigarettes. Within the e-cigarette group (N=440), we will analyze prevalence of each definition of uptake. Each of these outcomes will be estimated, and 95% confidence intervals will be calculated for each.

Hyp1b: Among smokers in the e-cigarette group, 40% will show a minimum of 50% reduction in cigarettes per day, and as a group, e-cigarette users will show greater decreases in cigs/day as compared to control. Reduction of cigarettes per day will be calculated based on the TLFB at baseline and 6 months for both groups, with "reducers" defined as those that reduce cigarettes per day by ≥50%. We will estimate the reduction, 95% confidence interval on the reduction, and the percent of those that are considered "reducers" in both groups, the latter tested via a chi-square test with an α=0.05 two-sided significance level.

Hyp2: Within a subset of locally recruited smokers, we hypothesize that use of e-cigarettes will lead to significant decreases in CO, but no net change in overall nicotine exposure. Changes in CO and cotinine will be calculated based on the baseline, 1, and 6-month measurements. Change in CO (thru 1 and 6 months) will be compared via a two-sample t-test with α=0.05 significant level. In order to test equivalence for change in cotinine between the two groups, the TOST procedure (137) will be followed where two one-sided tests will be used to test that the difference in the change between groups (Δ) is within the +/-3% bounds that we are willing to accept (H_{01}: Δ < -3%; H_{02}: Δ < +3%). If Δ is contained completely within the +/-3% bounds, then equivalence will be concluded. We will use an α=0.05 significance level.

Hyp 3: Provision and use of e-cigarettes will lead to increased incidence of (Hyp3a) quit attempts, (Hyp 3b) cessation, and (Hyp 3c) motivation/confidence to quit. Logistic regression analyses will be performed with (1)any quit attempt within 6 months (1=one or more quit attempts, 0=none), (2) any 24hr quit attempt (1=one or more 24 hour quit attempt, 0=none), (3) point prevalence abstinence at 6 months (1=7 day abstinence at 6 month call, 0=not abstinent), and (4) floating abstinence (1=any 7 day period of abstinence during study, 0=no abstinence) as the outcomes and group (e-cigarette vs. control) as the covariate. The coefficient on group provides a log odds ratio for measuring the increased odds of (1) any self-defined quit attempts, (2) 24hr quit attempts, (3) point prevalence abstinence, and (4) floating abstinence in the e-cigarette group compared to the control group. Statistical significance of these coefficients will be assessed using a p-value with a two-sided alpha of 0.05, and both the odds ratio and its 95% confidence interval (CI) will be reported. Motivation and confidence to quit are evaluated on a continuous scale (0-10), and linear regression models will be used with motivation/confidence to quit at 6 months as the outcomes with group (e-cigarette vs. control) as the covariate (along with baseline motivation/confidence and any other variables that are different between groups at baseline treated as covariates). Secondary analyses will include regression analyses where number of quit attempts are compared across groups using poisson or linear regression (depending on the distribution of number of quit attempts). We will also repeat this analysis: a) based on those who do vs. do not use e-cigarettes, and b) using quit attempts and abstinence of all tobacco products, including e-cigarettes.

10. Quality Assurance Plan

The REDCap system has validation options to not accept outliers, illogical response patterns, etc. The PI will have weekly meetings with the research assistants to discuss qualitative comments received during data collection and any problems in data collection. The statistician will periodically examine the database to look for irregularities. Initial data analyses will examine distributions of variable scores, comparability of baseline characteristics, follow-up rates and use of extra-study cessation treatment across conditions in case analyses need to be adjusted for these.

11. Reporting mechanisms of AEs/SAEs to IRB, FDA, NIH

Prior to the start of the study, the protocol will be registered on the clinicaltrials.gov registry. This study closely resembles three of our prior trials on alternative products, but the regulatory paths for these 3 studies varied. Two studies were small pilot studies (N=34, 57), much like herein (proposed N=60). One was of a test of Ariva/Stonewall, and the other was based on Camel Snus (both smokeless tobacco products). Both were prospective (2 weeks each). In neither case did we ask for, nor were we required by our IRB, to seek an IND from the FDA. The third study, ongoing (N=1236; year long RCT of Camel Snus) had a very different regulatory process, mired in months of debate. In seeking an IND exemption from the FDA, we were initially denied exemption, much to our surprise. We challenged that ruling, with months of back and forth emails and even a trip to the FDA. In the end, the FDA recognized the study for what it was: a naturalistic study of uptake of snus and its consequences. Though we assess quit attempts and cessation, and even *a priori* hypothesized increased

quitting among snus users, this hypothesis was based entirely on the literature at the time. Like the snus trial, we are NOT seeking any new claims for e-cigarettes within the current trial. Ultimately, we were granted an IND exemption for the snus study, and, after charting those murky waters for almost one year, have every reason to believe that the current trial will also be exempt from needing an IND.

Serious Adverse Events (SAEs) are defined as any even that is fatal or life threatening, is permanently or significantly disabling (physically or psychologically), requires inpatient hospitalization or prolongation of hospitalization, contributes to a congenital anomaly/birth defect or is any medical event that requires treatment to prevent one of the medical outcomes listed above.

For a study of this size and duration, we do expect some deaths to naturally occur, all of which will be reported to IRB, but given that we are providing a mere few weeks of e-cigarettes, we do not anticipate any study-related SAEs. In our ongoing trial of now 1200 smokers followed for 1 year, there have been <5 deaths total.

All serious AEs, study related or not, will be reported to the MUSC Committee on Human Research within 48 hrs. A summary of these SAE will be submitted annually to NIH via progress report. Follow-up of all unexpected and serious AEs will also be reported. All AEs are reviewed weekly by the PI and yearly by the IRB. Any significant actions taken by the local IRB, protocol changes will be relayed to the funding agency. We estimate the significant AE rate to be 5% or less. If the monthly monitoring indicates the rate is above this, we will convene a special meeting of the DSMB.

12. Reporting mechanisms of IRB actions to NIH & Report of changes or amendments to the protocol

We will a) discuss with NIH in advance any need for major protocol changes (e.g., change in aims, significant (+/-10%) change in sample size), and b) provide IRB approval to NIH once these major protocol changes have been local approved. We will report any IRB-actions within 5 business days. Notice of annual continuing approval will be included within each annual progress report to NIH.

13. Trial stopping rules

There are two potential reasons to stop the trial prematurely: a) undermining of cessation, and b) significant rate of adverse events. Each is addressed below.

a) To protect against undermining of cessation, we will form a Data Safety and Monitoring Board (DSMB) and have them conduct an interim analysis after 50% of the sample has completed 6 month follow-up. We chose this number as this is the minimum necessary given our base rate is projected to be 10% and one has to see clear trend toward an even lower rate. To do this, the statistician will provide a copy of the dataset to the board. If this occurs, this board will independently decide on whether to stop the study.

b) The research staff will report any unexpected AEs or any scores of “severe” on the side-effect symptom rating form or any FDA-defined serious AEs to the PI within 24 hrs so that the PI can decide on the appropriate action. All unexpected AEs will be monitored while they are active to determine if treatment is needed. Since a maximum three week supply of e-cigarettes, adverse events will be rare. Nonetheless, they will be coded on a weekly basis using the FDA’s COSTART rules (142) and entered into a database. For each weekly study meeting, the research assistants will prepare a summary of all AEs, including their severity, whether they occurred during smoking or abstinence, caused a dropout, required treatment and presumed relation to drug intake. The PI will review this at the weekly study meeting (or before if more urgent). At the weekly meeting (or before if urgent), research assistants will report any premonitory symptoms of emergence of a mental disorder such as depression or alcohol dependence. Dr. Gray, a board-certified psychiatrist, Dr. Warren, a radiation oncologist (both with expertise in nicotine dependence and treatment) will be available for medical supervision. Any study-related SAE will be reported to the DSMB immediately, which may convene a special meeting. Aggregate summary of all AEs will be provided quarterly to the DMSB and at each regularly scheduled DSMB meeting.

14. Conflicts of Interest

The Medical University of South Carolina is fully compliant with federal laws in reporting of conflicts of interest. All key personnel listed within this application have complied with this policy. Any conflicts of interest will be acknowledged in any publications or conference proceedings.

15. Potential risks and benefits to participants

The research protocol calls for non-treatment seeking smokers to either use e-cigarettes or not. Use of e-cigarettes is entirely self-chosen, since this is one outcome, rather than prescribed. E-cigarettes are no more harmful than conventional cigarettes, and various studies suggest that they may offer reduced harm. Questionnaires and interviews are all non-invasive and involve minimal risk to study participants. Potential risks are as follows:

1) risk of using e-cigarettes
2) concurrent use of e-cigarettes & smoking
3) potential for undermining cessation
4) non-smokers in the home (children) experimenting with e-cigarettes
5) loss of confidentiality

15.1 E-Cigarettes Tables **I** and **II** below provide, respectively, levels of tobacco-specific nitrosamines across a number of nicotine delivery devices, and levels of toxicants within cigarette smoke and e-cigarette vapor. Table **I** data show that TSNAs within e-cigarettes are much lower than tobacco products, including low-nitrosamine smokeless tobacco. Table **II** shows that e-cigarette vapor includes significantly lower levels of a number of toxicants as compared to cigarette smoke.

Table **I**: Tobacco-Specific Nitrosamines within Nicotine-Delivery Products

Tobacco-Specific Nitrosamines					
Product	**NNN**	**NNK**	**NAT**	**NAB**	**Total**
Nicorette gum	2.00	ND	ND	ND	2.00
Nicoderm CQ patch	ND	8.00	ND	ND	8.00
E-cigarettes	3.87	1.46	2.16	0.69	8.18
Swedish Snus	980	180	790	60	2010
Marlboro (Ultra-light)	2900	750	1100	58	4808
Marlboro (full)	2900	960	2300	100	6260
Source: Cahn 2010					

Among human studies, the majority of e-cigarette studies are based within on-line surveys. We report here on three moderate to large such surveys, 2 recently published (2013) and one from 2011 but is the largest survey to date. In the first (32), three side effects were reported by >20% of respondents: headaches (21%), cough (27%), and increased phlegm (25%). In the second (33), the most common negative effect of e-cigarette use was throat and mouth irritation, and fewer than 3% "reported a high level of side effects." Finally, the largest online survey to date (56) did not fully assess adverse events, but reported that 26% of e-cigarette users reported burning in throat. In a cross-over study of 40 smokers given e-cigarette for four days (14), the four most common adverse events (within highest dosage group) were mouth/throat irritation (38%), nausea (29%), vertigo (21%) and headache (22%). All other adverse events were rare (<5%).

Table **II**: Toxicant Levels within E-cigarette Vapor vs. Cigarette Smoke

Toxic compound	*Conventional cigarette [µg in mainstream smoke]*	*Electronic cigarette [µg per 15 puffs]*	*Average ratio (conventional vs. electronic cigarette)*
Formaldehyde	*0.85-10*	*0.20-5.61*	*2*
Acetaldehyde	*52-140*	*0.11-1.36*	*130*

Acrolein	*4.6-14*	*0.07-4.19*	*4*
Toluene	*6.4-9.0*	*0.02-0.63*	*23*
NNN	*0.012-0.37*	*0.00008-0.00043*	*145*
NNK	*0.009-0.08*	*0.00011-0.00283*	*30*
Cd	*0.03-0.35*	*0.001-0.022*	*16*
Ni	*0.003-0.60*	*0.011-0.029*	*15*
Source: Goniewicz 2014			

15.2 Concurrent use of e-cigarettes and smoking

If smokers engage in dual use, the major concern will be intake of nicotine, and too much of it. Symptoms of nicotine intoxication include nausea, dizziness, headache, and stomachache (140). In our two prior studies wherein participants who used nicotine gum/lozenge and smoked concurrently, there was no evidence of nicotine intoxication (75, 76), nor have we seen serious adverse events in our current e-cigarette studies. We recently completed a literature review (141) that showed combined NRT, as well as concurrent use of NRT and smoking, were both safe.

15.3 Undermining Cessation Another potential risk is that the sampling intervention will decrease rather than increase future cessation. However, the limited data available suggest this is unlikely (32, 44, 45, 56).

15.4 Use of E-cigarettes among non-participants and non-smokers, including children

Whenever a product is given to a smoker to take home and use, there is potential that the product will be used by someone else, inclusive of non-smokers and even children. In our ongoing snus trial in which we mail tins of smokeless tobacco to smokers all over the country, such “diversion” (tracked by our team) has not been a problem. In the rare possibility that someone in the household takes an e-cigarette, either knowingly or unknowingly from study participants, this risk would be no greater than if that same individual took the participant’s cigarettes. The fact that we are using self-contained cartridges of e-cigarettes (NJoy), rather than refillable tank systems, minimizes the potential for adulterating the system by adding additional substances.

15.5 Confidentiality A final risk is breach of confidentiality.

Benefits: In an ever-changing marketplace of tobacco-produces and nicotine-delivery devices, e-cigarettes are arguably the most popular new products available to smokers. The two most important questions about e-cigarettes are 1) uptake among non-smokers, and 2) impact among smokers. This study is poised to answer the latter, and is a strength upon existing research that is predominated by cross-sectional surveys and short term lab studies. There is a universal call for randomized trials of e-cigarettes, but these trials do not exist. It is important to test e-cigarettes before they become more popular, in advance of potential FDA role in regulation of them. E-cigarettes are classified as a tobacco product but in all likelihood will be subject to FDA regulation. The FDA will need high-level science to assess overall population impact. While this small pilot study alone will surely not address that need, it will certainly guide forthcoming research in this area.

This study is not without benefit to individual participants. However, this is not a treatment trial, and will not be advertised as such. We assess at screening for interest in cessation support. All comers will be accepted, but smokers actively seeking cessation support, or currently using cessation medication at baseline will be excluded. At all contacts, we will assess motivation to quit and uniformly offer referral information to state quitlines. Such transitions to cessation support are included as study outcomes. Two-thirds of the participants in the trial will receive samples of e-cigarettes, which most evidence to date suggests is a) safer than conventional cigarettes, and b) possibly related to quitting.

16. Collection, reporting and management of AEs and SAEs

Adverse events will be tracked and rated as mild, moderate or severe by the patient and rated as related to e-cigarettes by the research assistant using guidelines. We will determine if any adverse events result in dropouts or are serious according to FDA guidelines. A DSMB will assist in determining if the rate or severity of adverse events exceeds expectations.

The research staff will report any unexpected AEs or any scores of "severe" on the side-effect symptom rating form or any FDA-defined serious AEs to the PI within 24 hrs so that the PI can decide on the appropriate action. All unexpected AEs will be monitored while they are active to determine if treatment is needed. Since the e-cigarette sampling period is for a few weeks only, adverse events will be rare. Nonetheless, they will be coded on a weekly basis using the FDA's COSTART rules and entered into a database. For each weekly study meeting, the research assistants will prepare a summary of all AEs, including their severity, whether they occurred during smoking or abstinence, caused a dropout, required treatment and presumed relation to drug intake. The PI will review this at the weekly study meeting (or before if more urgent). At the weekly meeting (or before if urgent), research assistants will report any premonitory symptoms of emergence of a mental disorder such as depression or alcohol dependence. Dr. Gray, a board-certified psychiatrist, and Dr. Warren, a radiation oncologist, will be available for on-site medical supervision.

17. Plans for Interim Analyses of efficacy data

We plan to examine the data halfway through enrollment to determine if observed differences in quit rates are so large that the trial should be stopped early. Using the method of O'Brien and Fleming (143) the significance level for this interim analysis is $\alpha = 0.005$. According to this same reference, conducting this analysis decreases our power for detecting our projected differences only from 0.80 to 0.79.

18. Responsibility for data and safety monitoring

The PI will be responsible for monitoring the trial. The statistician will monthly examine the outcomes database for missing data, unexpected distributions or responses, and outliers. The PI will weekly check the AE database prepared by the research assistants immediately prior to the lab meeting a) to see if any particular COSTART categories are being endorsed more frequently than normal and b) to determine if any side-effect symptom checklist scores are higher than expected. A DSM report will be filed with the IRB and funding agency on a yearly basis, unless greater than expected problems occur. The report will include participant characteristics, retention and disposition of study participants, quality assurance issues and reports of AEs, significant/unexpected AEs and serious AEs. We will report efficacy at the end of the trial.

19. Frequency of DSM reviews

The DSMP will be reviewed annually.

20. Content of DSM report

The DSM report, which will be provided to all DSMB members, will include: a) enrollment data, in aggregate and split by gender and race, b) retention (% of all scheduled contacts that are completed), and c) adverse event data. Adverse event data will be presented in aggregate but will also include a detailed listing of all serious adverse events (SAEs).

21. DSMB

We will create a Data Safety and Monitoring Board to monitor both the rate and severity of adverse events, and any decremented rate of quitting in the e-cigarette-group. This panel will include 3 clinicians with expertise in smoking cessation trials, and a statistician. Potential conflicts of interest will be discussed jointly by the PI and the Chair of the DSMB; at least 1 member of the DSMB will be from outside the PI's home department. The DSMB will meet yearly upon anniversary of starting of recruitment (i.e. 1 year following first participant) to review any adverse events related to the study, as well as review any data management related errors. The board may be called at any point if needed for unexpected AEs, etc. Modification will be made in the procedures and/or the protocol if necessary based on the findings of the board. We will update the DSMB quarterly with a listing of all

Adverse Events, and we will update them in real-time with any substantive information we may learn about the new reports of vaping illness, be it from CDC, FDA, NCI, or any other credible scientific/regulatory source.

Inclusion of Women

Women will be included in this protocol, expected to be approximately 50% of study sample.

Inclusion of Minorities

Minorities are included in this study, at proportions (aggregate 22%) generalizable to US Census data, wherein 78% of US residents are White, 13% Black, 5% Asian, 1% Native American, and <1% native Hawaiian or Pacific Islander. These same census data indicate that 17% of the US residents are of Hispanic origin. The Targeted Enrollment Table reflects these proportions accordingly. We have chosen recruitment cities that meet or exceed national estimates proportions of minorities and/or Hispanics, which should facilitate recruitment goals.

For the locally recruited subset, we will target recruitment proportional to US Census data for our state: 68% white, 28% black or African American, <1% Asian, Native American, or Hawaiian, and 5% Latino.

Inclusion of Children

Children under 21 will be excluded. Though e-cigarettes are not regulated by the FDA, it seems reasonable to believe that, if they ever were, they would approved for adults.

REFERENCES

1. Azer V, Small G. E-cigarettes: Early adopters and the per capita conundrum. In: Equities CR, editor.: Citigroup Global Markets; 2013.

2. Herzog B, Gerberi J. E-cigs revolutionizing the tobacco industry. In: Securities WF, editor. 2013.

3. Stimson GV, Thom B, Costall P. Disruptive innovations: The rise of the electronic cigarette. International Journal of Drug Policy. 2014;25:653-5. doi: 10.1016/j.drugpo.2014.05.003.

4. Chen IL, Husten CG. Introduction to tobacco control supplement. Tobacco Control. 2014;23:ii1-ii3. doi: 10.1136/tobaccocontrol-2013-051504; PMCID: 3995278.

5. Benowitz NL. Emerging nicotine delivery products: Implications for public health. Annals of the American Thoracic Society. 2014;11:231-5. doi: doi: 10.1513/AnnalsATS.201312-433PS.

6. Etter JF, Bullen C, Flouris AD, Laugesen M, Eissenberg T. Electronic nicotine delivery systems: A research agenda. Tobacco Control. 2011;20(3):243-8. Epub 2011/03/19. doi: tc.2010.042168 [pii] 10.1136/tc.2010.042168. PubMed PMID: 21415064; PMCID: 3215262.

7. Henningfield JE, Zaatari GS. Electronic nicotine delivery systems: Emerging science foundation for policy. Tobacco Control. 2010;19:89-90.

8. Etter JF. Commentary on Wagener et al. (2012): Electronic cigarettes – the Holy Grail of nicotine replacement? Addiction. 2012;107:1550-2. doi: 10.1111/j.1360-0443.2012.03909.x.

9. Wagener TL, Siegel M, Borrelli B. Electronic cigarettes: Achieving a balanced perspective. Addiction. 2012;107:1545-8. doi: 10.1111/j.1360-0443.2012.03826.x.

10. Bell K, Keane H. Nicotine control: E-cigarettes, smoking and addiction. International Journal of Drug Policy. 2012;23:242-7. doi: 10.1016/j.drugpo.2012.01.006.

11. Cobb NK, Abrams DB. E-cigarette or drug-delivery device? Regulating novel nicotine products. New England Journal of Medicine. 2011;365:193-5. doi: 10.1056/NEJMp1105249.

12. Grana R, Benowitz N, Glantz SA. E-Cigarettes: A scientific review. Circulation. 2014; 129:1972-86. doi: 10.1161/CIRCULATIONAHA.114.007667; PMCID: 4018182.

13. Eissenberg T. Electronic nicotine delivery devices: Ineffective nicotine delivery and craving suppression after acute administration. Tobacco Control. 2010;19:87-8. doi: 10.1136/tc.2009.033498; PMCID: 3208854.

14. Bullen C, McRobbie H, Thornley S, Glover M, Lin R, Laugesen M. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: Randomised cross-over trial. Tobacco Control. 2010;19:98-103. doi: 10.1136/tc.2009.031567.

15. Nides MA, Leischow SJ, Bhatter M, Simmons M. Nicotine blood levels and short-term smoking reduction with an electronic nicotine delivery system. American Journal of Health Behavior. 2014;38:265-74. doi: 10.5993/AJHB.38.2.12.

16. Goniewicz ML, Kuma T, Gawron M, Knysak J, Kosmider L. Nicotine levels in electronic cigarettes. Nicotine & Tobacco Research. 2013;15:158-66. doi: 10.1093/ntr/nts103.

17. Etter JF, Bullen C. Saliva cotinine levels in users of electronic cigarettes. Eur Respir J. 2011;38(5):1219-20. Epub 2011/11/03. doi: 10.1183/09031936.00066011. PubMed PMID: 22045788.

18. Vansickel AR, Eissenberg T. Electronic cigarettes: Effective nicotine delivery after acute administration. Nicotine & Tobacco Research. 2013;15:267-70. doi: 10.1093/ntr/ntr316; PMCID: 3524053.

19. Dawkins L, Corcoran O. Acute electronic cigarette use: nicotine delivery and subjective effects in regular users. Psychopharmacology. 2014;231:401-7. doi: 10.1007/s00213-013-3249-8.

20. Polosa R, Rodu B, Caponnetto P, Maglia M, Raciti C. A fresh look at tobacco harm reduction: The case for the electronic cigarette. Harm Reduction Journal. 2013;10:19. doi: 10.1186/1477-7517-10-19; PMCID: 3850892.

21. Westenberger BJ. Evaluation of e-cigarettes. FDA Center for Drug Evaluation and Research 2009.

22. Trehy ML, Ye W, Hadwiger ME, Moore TW, Allgire JF, Woodruff JT, Ahadi SS, Black JC, Westenberger BJ. Analysis of electronic cigarette cartridges, refill solutions, and smoke for nicotine and nicotine related impurities. Journal of Liquid Chromatography & Related Technologies. 2011;34:1442-58. doi: 10.1080/10826076.2011.572213.

23. Goniewicz ML, Knysak J, Gawron M, Kosmider L, Sobczak A, Kurek J, Prokopowicz A, Jablonska-Czapla M, Rosik-Dulewska C, Havel C, Jacob P, Benowitz N. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. Tobacco Control. 2014;23:133-9. doi: 10.1136/tobaccocontrol-2012-050859; PMCID: 4154473.

24. Hua M, Alfi M, Talbot P. Health-related effects reported by electronic cigarette users in online forums. Journal of Medical Internet Research. 2013;15:e59. doi: 10.2196/jmir.2324; PMCID: 3636314.

25. Vansickel AR, Weaver MF, Eissenberg T. Clinical laboratory assessment of the abuse of liability of an electronic cigarette. Addiction. 2012;107:1493-500. doi: 10.1111/j.1360-0443.2012.03791.x; PMCID: 3330136.

26. Cahn Z, Siegel M. Electronic cigarettes as a harm reduction strategy for tobacco control: A step forward or a repeat of past mistakes? Journal of Public Health Policy. 2011;32:16-31. doi: 10.1057/jphp.2010.41.

27. Regan AK, Promoff G, Dube SR, Arrazola R. Electronic nicotine delivery systems: adult use and awareness of the 'e-cigarette' in the USA. Tobacco Control. 2013;22:19-23. doi: 10.1136/tobaccocontrol-2011-050044.

28. Goniewicz ML, Hajek P, McRobbie H. Nicotine content of electronic cigarettes, its release in vapour and its consistency across batches: Regulatory implications. Addiction. 2014;109:500-7. doi: 10.1111/add.12410.

29. Weaver M, Breland A, Spindle T, Eissenberg T. Electronic cigarettes: A review of safety and clinical issues. Journal of Addiction Medicine. 2014;8:234-40. doi: 10.1097/ADM.0000000000000043; PMCID: 4123220.

30. Hecht SS, Carmella SG, Kotandeniya D, Pillsbury ME, Chen M, Ransom BW, Isaksson Vogel R, Thompson E, Murphy SE, Hatsukami DK. Evaluation of toxicant and carcinogen metabolites in the urine of e-cigarette users verses cigarette smokers. Nicotine and Tobacco Research. 2015;17:704-9. doi: 10.1093/ntr/ntu218; PMCID: 4481723.

31. Goniewicz ML, Gawron M, Smith DM, Peng M, Jacob P, Benowitz NL. Exposure to nicotine and selected toxicants in cigarette smokers who switched to electronic cigarettes: A longitudinal within-subjects observational study. Nicotine & Tobacco Research. in press. doi: 10.1093/ntr/ntw160.

32. Goniewicz ML, Lingas EO, Hajek P. Patterns of electronic cigarette use and user beliefs about their safety and benefits: An internet survey. Drug and Alcohol Review. 2013;32:133-40. doi: 10.1111/j.1465-3362.2012.00512.x; PMCID: 3530631.

33. Dawkins L, Turner J, Roberts A, Soar K. 'Vaping' profiles and preferences: An online survey of electronic cigarette users. Addiction. 2013;108:1115-25. doi: doi: 10.1111/add.12150.

34. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Characteristics, perceived side effects and benefits of electronic cigarette use: A worldwide survey of more than 19,000 consumers. International Journal of Environmental Research and Public Health. 2014;14:4356-73. doi: 10.3390/ijerph110404356; PMCID: 4025024.

35. Ayers JW, Ribisl KM, Brownstein JS. Tracking the rise in popularity of electronic nicotine delivery systems (electronic cigarettes) using search query surveillance. American Journal of Preventive Medicine. 2011;40:448-53. doi: 10.1016/j.amepre.2010.12.007.

36. Dockrell M, Morrison R, Bauld L, McNeill A. E-cigarettes: Prevalence and attitudes in Great Britain. Nicotine & Tobacco Research. 2013;15:1737-44. doi: 10.1093/ntr/ntt057; PMCID: 3768337.

37. Grana RA, Ling PM. “Smoking Revolution”: A content analysis of electronic cigarette retail websites. American Journal of Preventive Medicine. 2014;46:395-403. doi: 10.1016/j.amepre.2013.12.010; PMCID: 3989286.

38. Pearson JL, Richardson A, Niaura RS, Vallone DM, Abrams DB. e-Cigarette awareness, use, and harm perceptions in US adults. American Journal of Public Health. 2012;9:1758-66. doi: 10.2105/AJPH.2011.300526; PMCID: 3474361.

39. Pokhrel P, Fagan P, Little MA, Kawamoto CT, Herzog TA. Smokers who try e-cigarettes to quit smoking: Findings from a multiethnic study in Hawaii. American Journal of Public Health. 2013;103:e57-e62. doi: 10.2105/AJPH.2013.301453; PMCID: 3780693.

40. Kralikova E, Novak J, West O, Kmetova A, Hajek P. Do e-cigarettes have the potential to compete with conventional cigarettes?: A survey of conventional cigarette smokers' experiences with e-cigarettes. Chest. 2013;144:1609-14. doi: 10.1378/chest.12-2842.

41. McMillen RC, Gottlieb MA, Shaefer RM, Winickoff JP, Klein JD. Trends in electronic cigarette use among U.S. Adults: Use is increasing in both smokers and nonsmokers. Nicotine & Tobacco Research. 2015;17(10):1195-202. Epub 2014/11/09. doi: 10.1093/ntr/ntu213. PubMed PMID: 25381306.

42. Tan AS, Bigman CA. E-cigarette awareness and perceived harmfulness: Prevalence and associations with smoking-cessation outcomes. American Journal of Preventive Medicine. 2014;47:141-9. doi: 10.1016/j.amepre.2014.02.011; PMCID: 4107147.

43. Delnevo CD, Giovenco DP, Steinberg MB, Villanti AC, Pearson JL, Niaura RS, Abrams DB. Patterns of electronic cigarette use among adults in the United States. Nicotine & Tobacco Research. 2016;18:715-9. doi: 10.1093/ntr/ntv237.

44. Siegel MB, Tanwar KL, Wood KS. Electronic cigarettes as a smoking-cessation tool: results from an online survey. American Journal of Preventive Medicine. 2011;40:472-5. doi: 10.1016/j.amepre.2010.12.006.

45. Adkison SE, O'Connor RJ, Bansal-Travers M, Hyland A, Borland R, Yong H-H, Cummings KM, McNeill A, Thrasher JF, Hammond D, Fong GT. Electronic nicotine delivery systems: International tobacco control four-

country survey. American Journal of Preventive Medicine. 2013;44:207-15. doi: 10.1016/j.amepre.2012.10.018; PMCID: 3627474.

46. Polosa R, Caponnetto P, Morjaria JB, Papale G, Campagna D, Russo C. Effect of an electronic nicotine delivery device (e-Cigarette) on smoking reduction and cessation: A prospective 6-month pilot study. BMC Public Health. 2011;11. doi: 10.1186/1471-2458-11-786; PMCID: 3203079.

47. Polosa R, Morjaria JB, Caponnetto P, Campagna D, Russo C, Alamo A, Amaradio M, Fisichella A. Effectiveness and tolerability of electronic cigarette in real-life: A 24-month prospective observational study. Internal and Emergency Medicine. 2014;9:537-46. doi: 10.1007/s11739-013-0977-z.

48. Caponnetto P, Auditore R, Russo C, Cappello GC, Polosa R. Impact of an electronic cigarette on smoking reduction and cessation in schizophrenic smokers: A prospective 12-month pilot study. International Journal of Environmental Research and Public Health. 2013;10:446-61. doi: 10.3390/ijerph10020446; PMCID: 3635154.

49. Etter JF, Bullen C. A longitudinal study of electronic cigarette users. Addictive Behaviors. 2014;39:491-4. doi: 10.1016/j.addbeh.2013.10.028.

50. Zhuang Y-L, Cummins SE, Sun JY, Zhu S-H. Long-term e-cigarette use and smoking cessation: A longitudinal study with US population. Tobacco Control. 2016;25:i90-i5. doi: 10.1136/tobaccocontrol-2016-053096.

51. Biener L, Hargraves JL. A longitudinal study of electronic cigarette use in a population-based sample of adult smokers: Association with smoking cessation and motivation to quit. Nicotine & Tobacco Research. 2015;17:127-33. doi: 10.1093/ntr/ntu200 PMCID: 4375383.

52. Brose LS, Hitchman SC, Brown J, West R, McNeill A. Is the use of electronic cigarettes while smoking associated with smoking cessation attempts, cessation and reduced cigarette consumption? A survey with a 1-year follow-up. Addiction. 2015;110:1160-8. doi: 10.1111/add.12917; PMCID: 4862028

53. Hitchman SC, Brose LS, Brown J, Robson D, McNeill A. Associations between e-cigarette type, frequency of use, and quitting smoking: Findings from a longitudinal online panel survey in great britain. Nicotine & Tobacco Research. 2015;17:1187-94. doi: 10.1093/ntr/ntv078; PMCID: 4580313.

54. Popova L, Ling PM. Alternative tobacco product use and smoking cessation: A national study. American Journal of Public Health. 2013;103:923-30. doi: 10.2105/AJPH.2012.301070; PMCID: 3661190.

55. Etter JF. Electronic cigarettes: A survey of users. BMC Public Health. 2010;10. doi: 10.1186/1471-2458-10-231; PMCID: 2877672.

56. Etter JF, Bullen C. Electronic cigarette: Users profile, utilization, satisfaction and perceived efficacy. Addiction. 2011;106:2017-28. doi: 10.1111/j.1360-0443.2011.03505.x.

57. Barbeau AM, Burda J, Siegel M. Perceived efficacy of e-cigarettes versus nicotine replacement therapy among successful e-cigarette users: A qualitative approach Addiction Science and Clinical Practice. 2013;8. doi: 10.1186/1940-0640-8-5; PMCID: 3599549.

58. Brown J, Beard E, Kotz D, Michie S, West R. Real-world effectiveness of e-cigarettes when used to aid smoking cessation: A cross-sectional population study. Addiction. 2014;109:1531-40. doi: 10.1111/add.12623; PMCID: 4171752.

59. Lechner WV, Tackett AP, Grant DM, Tahirkheli NN, Driskill LM, Wagener TL. Effects of duration of electronic cigarette use. Nicotine & Tobacco Research 2015;17:180-5. doi: 10.1093/ntr/ntu061.

60. Vickerman KA, Carpenter KM, Altman T, Nash CM, Zbikowski SM. Use of electronic cigarettes among state tobacco cessation quitline callers. Nicotine & Tobacco Research. 2013;15:1787-91. doi: 10.1093/ntr/ntt061.

61. Grana RA, Popova L, Ling PM. A longitudinal analysis of electronic cigarette use and smoking cessation. JAMA Internal Medicine. 2014;174:812-3. doi: 10.1001/jamainternmed.2014.187; PMCID: 4122246.

62. Al-Delaimy WK, Myers MG, Leas EC, Strong DR, Hofstetter CR. E-Cigarette use in the past and quitting behavior in the future: a population-based study. American Journal of Public Health. 2015;105:1213-9. doi: 10.2105/AJPH.2014.302482.

63. Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: A systematic review and meta-analysis. Lancet. 2016;4:116-28. doi: 10.1016/S2213-2600(15)00521-4.

64. Malas M, van der Tempel J, Schwartz R, Minichiello A, Lightfoot C, Noormohamed A, Andrews J, Zawertailo L, Ferrence R. Electronic cigarettes for smoking cessation: A systematic review. Nicotine & Tobacco Research. 2016;18:1926-36. doi: 10.1093/ntr/ntw119.

65. Adriaens K, Van Gucht D, Declerk P, Baeyens F. Effectiveness of the electronic cigarette: An eight-week Flemish study with six-month follow-up on smoking reduction, craving, and experienced benefits and complaints. International Journal of Environmental Research and Public Health. 2014;11:11220-48. doi: 10.3390/ijerph111111220; PMCID: 4245610.

66. Caponnetto P, Campagna D, Cibella F, Morjaria JB, Caruso M, Russo C, Polosa R. Efficiency and safety of an electronic cigarette (ECLAT) as tobacco cigarettes substitute: A prospective 12-month randomized control design study. PLoS ONE. 2013;8:e66317. doi: 10.1371/journal.pone.0066317; PMCID: 3691171.

67. Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, Walker N. Electronic cigarettes for smoking cessation: A randomised controlled trial. Lancet. 2013;382:1629-37. doi: 10.1016/S0140-6736(13)61842-5.

68. Fraser D, Borland R, Gartner C. Protocol for a randomised pragmatic policy trial of nicotine products for quitting or long-term substitution in smokers. BMC Public Health. 2015;15:1-9. doi: 10.1186/s12889-015-2366-1; PMCID: 4596390.

69. Bullen C, Williman J, Howe C, Laugesen M, McRobbie H, Parag V, Walker N. Study protocol for a randomised controlled trial of electronic cigarettes versus nicotine patch for smoking cessation. BMC Public Health. 2013;13. doi: 10.1186/1471-2458-13-210; PMCID: 3602285.

70. McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. Cochrane Database of Systematice Reviews. Oxford: John Wiley & Sons; 2014.

71. Lopez AA, Cobb CO, Yingst JM, Veldheer S, Hrabovsky S, Yen MS, Foulds J, Eissenberg T. A transdisciplinary model to inform randomized clinical trial methods for electronic cigarette evaluation. BMC Public Health. 2016;16:217. doi: 10.1186/s12889-016-2792-8; PMCID: 4778292.

72. Pearson JL, Stanton CA, Cha S, Niaura RS, Luta G, Graham AL. E-cigarettes and smoking cessation: Insights and cautions from a secondary analysis of data from a study of online treatment-seeking smokers. Nicotine & Tobacco Research. 2015;17:1219-27. doi: 10.1093/ntr/ntu269; PMCID: 4592337.

73. Hyland A, Ambrose BK, Conway KP, Borek N, Lambert E, Carusi C, Taylor K, Crosse S, Fong GT, Cummings KM, Abrams D, Pierce JP, Sargent J, Messer K, Bansal-Travers M, Niaura R, Vallone D, Hammond D, Hilmi N, Kwan J, Piesse A, Kalton G, Lohr S, Pharris-Ciurej N, Castleman V, Green VR, Tessman G, Kaufman A, Lawrence C, van Bemmel DM, Kimmel HL, Blount B, Yang L, O'Brien B, Tworek C, Alberding D, Hull LC,

Cheng YC, Maklan D, Backinger CL, Compton WM. Design and methods of the population assessment of tobacco and health (PATH) study. Tobacco Control. In Press. doi: 10.1136/tobaccocontrol-2016-052934.

74. Walton KM, Abrams DB, Bailey WC, Clark D, Connelly GN, Djordjevic MV, Eissenberg TE, Fiore MC, Goniewicz ML, Haverkos L, Hecht SS, Henningfield JE, Hughes JR, Oncken CA, Postow L, Rose JE, Wanke KL, Yang L, Hatsukami DK. NIH electronic cigarette workshop: Developing a research agenda. Nicotine & Tobacco Research. 2015;17:259-69. doi: 10.1093/ntr/ntu214; PMCID: 4311173.

75. Carpenter MJ, Hughes JR, Solomon LJ, Callas PW. Both smoking reduction with nicotine replacement therapy and motivational advice increase future cessation among smokers unmotivated to quit. Journal of Consulting and Clinical Psychology. 2004;72:371-81. doi: 10.1037/0022-006X.72.3.371. PubMed PMID: 15279521.

76. Carpenter MJ, Hughes JR, Gray KM, Wahlquist AE, Saladin ME, Alberg AJ. Nicotine therapy sampling to induce quit attempts among smokers unmotivated to quit: A randomized clinical trial. Archives of Internal Medicine. 2011;171:1901-7. doi: 10.1001/archinternmed.2011.492; PMCID: 3372898.

77. Jardin BF, Cropsey KL, Wahlquist AE, Gray KM, Silvestri GA, Cummings KM, Carpenter MJ. Evaluating the effect of access to free medication to quit smoking: A clinical trial testing the role of motivation. Nicotine & Tobacco Research. 2014;16:992-9. Epub 2014/03/13. doi: 10.1093/ntr/ntu025. PubMed PMID: 24610399; PMCID: 4133568.

78. Carpenter MJ, Gray KM. A pilot randomized study of smokeless tobacco use among smokers not interested in quitting: changes in smoking behavior and readiness to quit. Nicotine & Tobacco Research. 2010;12(2):136-43. Epub 2010/01/08. doi: 10.1093/ntr/ntp186. PubMed PMID: 20053788; PMCID: 2816197.

79. Burris JL, Carpenter MJ, Wahlquist AE, Cummings KM, Gray KM. Brief, instructional smokeless tobacco use among cigarette smokers who do not intend to quit: a pilot randomized clinical trial. Nicotine & Tobacco Research. 2014;16(4):397-405. Epub 2013/10/17. doi: 10.1093/ntr/ntt161. PubMed PMID: 24130144; PMCID: 3954419.

80. Carpenter MJ, Wahlquist AE, Burris JL, Gray KM, Garrett-Mayer E, Cummings KM, Alberg AJ. Snus undermines quit attempts but not abstinence: A randomized clinical trial among U.S. smokers. Tobacco Control. in press. doi: 10.1136/tobaccocontrol-2015-052783; PMCID: 5061602.

81. Burris JL, Wahlquist AE, Alberg AJ, Cummings KM, Gray KM, Garrett-Mayer E, Carpenter MJ. A longitudinal, naturalistic study of U.S. smokers' trial and adoption of snus. Addictive Behaviors. 2016;63:82-8. doi: 10.1016/j.addbeh.2016.07.008; PMCID: 4993634

82. Meier E, Wahlquist AE, Heckman BW, Cummings KM, Froeliger B, Carpenter MJ. A pilot randomized crossover trial of e-cigarette sampling among smokers. Nicotine & Tobacco Research. in press.

83. Czogala J, Goniewicz ML, Fidelus B, Zielinska-Danchm W, Travers MJ, Sobczak A. Secondhand exposure to vapors from electronic cigarettes. Nicotine & Tobacco Research. 2014;16:655-62. doi: 10.1093/ntr/ntt203.

84. Goniewicz ML, Gawron M, Peng M, Jacob P, Benowitz N. Electronic cigarettes deliver similar levels of nicotine and reduce exposure to combustion toxicants after switching from tobacco cigarettes. 18th Annual Meeting for the Society for Research on Nicotine and Tobacco; Houston, TX2012.

85. Jacob P, Goniewicz ML, Havel CM, Schick SF, Benowitz NL. Nicotelline: A proposed biomarker and environmental tracer for particulate matter derived from tobacco smoke. Chemical Research in Toxicology. 2013;26:1615-31. doi: 10.1021/tx400094y; PMCID: 3929594.

86. Shahab L, Goniewicz M. Electronic cigarettes are at least as effective as nicotine patches for smoking cessation. Evidence-Based Medicine. 2014;19:133. doi: 10.1136/eb-2013-101690.

87. Brandon TH, Goniewicz ML, Hanna NH, Hatsukami DK, Herbst RS, Hobin JA, Ostroff JS, Shields PG, Toll BA, Tyne CA, Viswanath K, Warren GW. Electronic nicotine delivery systems: A policy statement from the American Association for Cancer Research and the American Society of Clinical Oncology. Clinical Cancer Research. 2015;21:514-25. doi: 10.1158/1078-0432.CCR-14-2544.

88. Hajek P, Goniewicz ML, Phillips A, Myers Smith K, West O, McRobbie H. Nicotine intake from electronic cigarettes on initial use and after 4 weeks of regular use. Nicotine & Tobacco Research. 2015;17:175-9. doi: 10.1093/ntr/ntu153.

89. Lee YH, Gawron M, Goniewicz ML. Changes in puffing behavior among smokers who switched from tobacco to electronic cigarettes. Addictive Behaviors. 2015;48:1-4. doi: 10.1016/j.addbeh.2015.04.003; PMCID: 4457608.

90. Nelson VA, Goniewicz ML, Beard E, Brown J, Sheals K, West R, Shahab L. Comparison of the characteristics of long-term users of electronic cigarettes versus nicotine replacement therapy: A cross-sectional survey of English ex-smokers and current smokers. Drug and Alcohol Dependence. 2015;153:300-5. doi: 10.1016/j.drugalcdep.2015.05.005; PMCID: 4528068.

91. Czoli CD, Goniewicz M, Islam T, Kotnowski K, Hammond D. Consumer preferences for electronic cigarettes: results from a discrete choice experiment Tobacco Control. 2016;25:e30-e6. doi: 10.1136/tobaccocontrol-2015-052422.

92. Saddleson ML, Kozlowski LT, Giovino GA, Goniewicz ML, Mahoney MC, Homish GG, Arora A. Enjoyment and other reasons for electronic cigarette use: Results from college students in New York. Addictive Behaviors. 2016;54:33-9. doi: 10.1016/j.addbeh.2015.11.012.

93. Meier E, Tackett AP, Wagener TL. Effectiveness of electronic aids for smoking cessation. Current Cardiovascular Risk Reports. 2013;7:464-72. doi: 10.1007/s12170-013-0343-8; PMCID: 3851041.

94. Wagener TL, Meier E, Hale JJ, Oliver ER, Warner ML, Driskill LM, Gillaspy SR, Siegel MB, Foster S. Pilot investigation of changes in readiness and confidence to quit smoking after e-cigarette experimentation and 1 week of use. Nicotine & Tobacco Research. 2014;16:108-14. doi: 10.1093/ntr/ntt138.

95. Wagener TL, Floyd EL, Stepanov I, Driskill LM, Frank SG, Meier E, Leavens EL, Tackett AP, Molina N, Queimado L. Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third-generation electronic cigarette users. Tobacco Control. In Press. doi: 10.1136/tobaccocontrol-2016-053041.

96. Busch AM, Leavens EL, Wagener TL, Buckley ML, Tooley EM. Prevalence, reasons for use, and risk perception of electronic cigarettes among post-acute coronary syndrome smokers. Journal of Cardiopulmonary Rehabilitation and Prevention. 2016;36:352-7. doi: 10.1097/HCR.0000000000000179; PMCID: 5001913.

97. Meier EM, Tackett AP, Miller MB, Grant DM, Wagener TL. Which nicotine products are gateways to regular use?: First-tried tobacco and current use in college students. American Journal of Preventive Medicine. 2015;48:S86-S93. doi: 10.1016/j.amepre.2014.09.018.

98. Lechner WV, Meier E, Wiener JL, Grant, D.M., Gilmore J, Judah MR, Mills AC, Wagener TL. The comparative efficacy of first- versus second-generation electronic cigarettes in reducing symptoms of nicotine withdrawal. Addiction. 2015;110:862-7. doi: 10.1111/add.12870.

99. Cummings KM, Dresler CM, Field JK, Fox J, Gritz ER, Hanna NH, Ikeda N, Jassem J, Mulshine JL, Peters MJ, Yamaguchi NH, Warren G, Zhou C. E-cigarettes and cancer patients. Journal of Thoracic Oncology. 2014;9:438-41. doi: 10.1097/JTO.0000000000000129; PMCID: 4040965.

100. Etter JF, Perneger TV. A comparison of cigarette smokers recruited through the internet or by mail. International Journal of Epidemiology. 2001;30:521-5. doi: 10.1093/ije/30.3.521. PubMed PMID: 11416075.

101. Welch BM, Marshall E, Qanungo S, Aziz A, Laken M, Lenert L, Obeid J. Teleconsent: A novel approach to obtain informed consent for research. Contemporary Clinical Trials Communications. 2016;3:74-9. doi: 10.1016/j.conctc.2016.03.002; PMCID: 5096381

102. Newby R, Watson J, Woodliff D. SME survey methodology: Response rates, data quality, and cost effectiveness. Entrepreneurship Theory and Practice. 2003;28:163-72. doi: 10.1046/j.1540-6520.2003.00037.x.

103. Edwards PJ, Roberts I, Clarke MJ, DiGuiseppi C, Wentz R, Kwan I, Cooper R, Felix LM, Pratap S. Methods to increase response to postal and electronic questionnaires (review). Cochrane Database of Systematic Reviews. 2009;3. doi: 10.1002/14651858.MR000008.pub4.

104. White E, Carney PA, Kolar AS. Increasing response to mailed questionnaires by including a pencil/pen. American Journal of Epidemiology. 2005;162:261-6. doi: 1093/aje/kwi194.

105. King BA, Alam S, Promoff G, Arrazola R, Dube SR. Awareness and ever-use of electronic cigarettes among U.S. adults, 2010-2011. Nicotine & Tobacco Research. 2013;15:1623-7. doi: 10.1093/ntr/ntt013; PMCID: 4570561.

106. Farsalinos KE, Spyrou A, Tsimopoulou K, Stefopoulos C, Romagna G, Voudris V. Nicotine absorption from electronic cigarette use: Comparison between first and new-generation devices. Scientific Reports. 2014;5:11269. doi: 10.1038/srep04133; PMCID: 4469966.

107. Lopez AA, Hiler MM, Soule EK, Ramoa CP, Karaoghlanian NV, Lipato T, Breland AB, Shihadeh A, Eissenberg T. Effects of electronic cigarette liquid nicotine concentration on plasma nicotine and puff topography in tobacco cigarette smokers: A preliminary report. Nicotine & Tobacco Research. 2016;18:720-3. doi: 10.1093/ntr/ntv182.

108. Farsalinos KE, Kistler KA, Gillman G, Voudris V. Evaluation of electronic Cigarette liquids and aerosol for the presence of selected inhalation toxins. Nicotine & Tobacco Research. 2015;17:168-74. doi: 10.1093/ntr/ntu176; PMCID: 4892705

109. McCarthy DE, Minami H, Yeh VM, Bold KW. An experimental investigation of reactivity to ecological momentary assessment frequency among adults trying to quit smoking. Addiction. 2015;110(10):1549-60. Epub 2015/05/27. doi: 10.1111/add.12996. PubMed PMID: 26011583; PMCID: 4565778.

110. Shiffman S, Waters AJ, Hickcox M. The Nicotine Dependence Syndrome Scale: A multidimensional measure of nicotine dependence. Nicotine & Tobacco Research. 2004;6:327-47.

111. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström K-O. The Fagerström test for nicotine dependence: A revision of the Fagerstrom Tolerance Questionnaire. British Journal of Addiction. 1991;86:1119-27. doi: 10.1111/j.1360-0443.1991.tb01879.x.

112. Piper ME, McCarthy DE, Bolt DM, Smith SS, Lerman C, Benowitz N, Fiore MC, Baker TB. Assessing dimensions of nicotine dependence : An evaluation of the Nicotine Dependence Syndrome Scale (NDSS) and the Wisconsin Inventory of Smoking Dependence Motives (WISDM). Nicotine & Tobacco Research. 2008;10:1009-20; PMCID: 2614360.

113. Shiffman S, Sayette MA. Validation of the nicotine dependence syndrome scale (NDSS): A criterion-group design contrasting chippers and regular smokers. Drug and Alcohol Dependence. 2005;79:45-52; PMCID: 2659852.

114. Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. Archives of General Psychiatry. 1986;43:289-94.

115. Biener L, Bogen K, Connolly G. Impact of corrective health information on consumers' perceptions of "reduced exposure" tobacco products. Tobacco Control. 2007;16:306-11; PMCID: 2598559.

116. O'Connor RJ, Ashare RL, Fix BV, Hawk LW, Cummings KM, Schmidt WC. College students' expectancies for light cigarettes and potential reduced exposure products. American Journal of Health Behavior. 2007;31:402-10.

117. O'Connor RJ, Hyland A, Giovino GA, Fong GT, Cummings KM. Smoker awareness of and beliefs about supposedly less harmful tobacco products. American Journal of Preventive Medicine. 2005;29:85-90.

118. Parascandola M, Hurd AL, Augustson E. Consumer awareness and attitudes related to new potential reduced-exposure tobacco products. American Journal of Health Behavior. 2008;32(4):431-7. Epub 2007/12/21. doi: 10.5555/ajhb.2008.32.4.431 [doi].

119. Parascandola M, Augustson E, O'Connell ME, Marcus S. Consumer awareness and attitudes related to new potential reduced-exposure tobacco product brands. Nicotine & Tobacco Research. 2009;11:886-95. doi: 10.1093/ntr/ntp082; PMCID: 2722238.

120. Rogers EM. New product adoption and diffusion. Journal of Consumer Research. 1976;2:290-301.

121. Hughes JR, Adams EH, Franzon MA, Maguire MK, Guary J. A prospective study of off-label use of, abuse of and dependence on nicotine inhaler. Tobacco Control. 2005;14:49-54; PMCID: 1747971.

122. Pepper JK, Ribisl KM, Emery SL, Brewer NT. Reasons for starting and stopping electronic cigarette use. International Journal of Environmental Research and Public Health. 2014;11(10):10345-61. Epub 2014/10/07. doi: 10.3390/ijerph111010345. PubMed PMID: 25286168; PMCID: 4210982.

123. Cappelleri JC, Bushmakin AG, Baker CL, Merikle E, Olufade AO, Gilbert DG. Confirmatory factor analyses and reliability of the modified cigarette evaluation questionnaire. Addictive Behaviors. 2007;32:912*23. doi: 10.1016/j.addbeh.2006.06.028.

124. Westman EC, Behm FM, Rose JE. Dissociating the nicotine and airway sensory effects of smoking. Pharmacology Biochemistry and Behavior. 1996;53:309-15. doi: 10.1016/0091-3057(95)02027-6.

125. Hatsukami DK, Zhang Y, O'Connor RJ, Severson HH. Subjective responses to oral tobacco products: Scale validation. Nicotine & Tobacco Research. 2013;15:1259-64. doi: 10.1093/ntr/nts265; PMCID: 3682844.

126. Etter JF. A comparison of the content-, construct- and predictive validity of the cigarette dependence scale and the Fagerstrom test for nicotine dependence. Drug and Alcohol Dependence. 2005;77:259-68. doi: 10.1016/j.drugalcdep.2004.08.015.

127. Foulds J, Veldheer S, Yingst J, Hrabovsky S, WIlson SJ, Nichols TT, Eissenberg T. Development of a questionnaire for assessing dependence on electronic cigarettes in a large sample of ex-smoking E-cigarette users. Nicotine & Tobacco Research. 2015;17:186-92. doi: 10.1093/ntr/ntu204.

128. Biener L, Abrams DB. The contemplation ladder: Validation of a measure of readiness to consider smoking cessation. Health Psychology. 1991;10:360-5.

129. Hughes JR, Keely JP, Fagerstrom K-O, Callas PW. Intentions to quit smoking change over short periods of time. Addictive Behaviors. 2005;30:353-662.

130. USDHS. Current cigarette smoking among adults — United States, 2011. MMWR. 2012;61:889-94.

131. Hughes JR, Keely JP, Niaura RS, Ossip-Klein DJ, Richmond RL, Swan GE. Measures of abstinence in clinical trials: Issues and recommendations. Nicotine & Tobacco Research. 2003;5:13-25. doi: 10.1093/ntr/5.1.13.

132. Aveyard P, Wang D, Connock M, Fry-Smith A, Barton P, Moore D. Assessing the outcomes of prolonged cessation-induction and aid-to-cessation trials: Floating prolonged abstinence. Nicotine & Tobacco Research. 2009;11:475-80. doi: 10.1093/ntr/ntp035; PMCID: 2671463.

133. Hughes JR, Keely JP, Naud S. Shape of relapse curve and long-term abstinence among untreated smokers. Addiction. 2004;99:29-38.

134. Dixon WJ, Massey FJ. Introduction to Statistical Analysis: McGraw-Hill; 1983. p. 142.

135. Shiffman S, Dunbar MS, Benowitz NL. A comparison of nicotine biomarkers and smoking patterns in daily and non-daily smokers. Cancer Epidemiology, Biomarkers and Prevention. 2014;23:1264-72. doi: 10.1158/1055-9965.EPI-13-1014.

136. Hall SM, Delucchi KL, Velicer WF, Kahler CW, Ranger-Moore J, Hedeker D, Tsoh JY, Niaura R. Statistical analysis of randomized trials in tobacco treatment: longitudinal designs with dichotomous outcome. Nicotine & Tobacco Research. 2001;3(3):193-202. Epub 2001/08/17. doi: 10.1080/14622200110050411. PubMed PMID: 11506764.

137. Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. Journal of Pharmacokinetics and Biopharmaceutics. 1987;15:657-80.

138. Lerman C, Schnoll RA, Hawk LWJ, Cinciripini P, George TP, Wileyto EP, Swan GE, Benowitz NL, Heitjan DF, Tyndale RF, Group P-PR. Use of the nicotine metabolite ratio as a genetically informed biomarker of response to nicotine patch or varenicline for smoking cessation: a randomised, double-blind placebo-controlled trial. The Lancet Respiratory Medicine. 2015;3:131-8. doi: 10.1016/S2213-2600(14)70294-2; PMCID: 4480925.

139. Schnoll RA, Patterson F, Wileyto EP, Tyndale RF, Benowitz N, Lerman C. Nicotine metabolic rate predicts successful smoking cessation with transdermal nicotine: A validation study. Pharmacology, Biochemistry and Behavior. 2009(92):6-11. doi: 10.1016/j.pbb.2008.10.016; PMCID: 2657225.

140. Benowitz NL. Nicotine Safety and Toxicity. New York: Oxford University Press; 1998.

141. Carpenter MJ, Jardin BF, Burris JL, Mathew AR, Schnoll RA, Rigotti NA, Cummings KM. Clinical strategies to enhance the efficacy of nicotine replacement therapy for smoking cessation: A review of the literature. Drugs. 2013;73(5):407-26. Epub 2013/04/11. doi: 10.1007/s40265-013-0038-y. PubMed PMID: 23572407; PMCID: 3662024.

142. Center for Drug Evaluation and Research. COSTART Coding Symbols for Thesaurus of Adverse Reaction Terms, Fourth Edition. Rockville, MD: Public Health Services; 1993.

143. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics. 1979;35:549-56.