Switching to a Vaping Device: Evaluating Risk Reduction among Quitline Treatment Failures

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Abstract

There remains a lack of prospective and controlled research on the behavioral, toxicological, and physiological effects of electronic cigarettes (ECs) to help the public health community come to a clear and accurate consensus on their risk-benefit. Moreover, the studies that have been completed used various commercially available ECs, e-liquid flavors, and nicotine concentrations, many of which are unavailable today and for which we know very little about, making the generalizability and comparisons between past, present, and future studies very difficult. The present funding opportunity (PAR-17-156) is meant to begin to evaluate, with a high degree of fidelity, ECs as a potential means of reducing smoking-related risks and to provide information on the use and effects of JUUL; it is also meant to do so quickly (two-year study). In order to successfully execute the proposed study, we plan to recruit and enroll recent smoking cessation treatment failures from a state quitline (QL), which predominately serves priority populations (e.g., low socioeconomic status, high levels of mental health conditions). QLs provide ready access to a large number of tobacco users, as well as infrastructure for delivering and testing study interventions quickly. With a two-year time window, QLs are potentially the best real-world platform to quickly and with sufficient statistical power, meaningfully examine smokers' ability and willingness to switch to JUUL, and its impact on their tobacco use behaviors, nicotine dependence, and health. The proposed study will randomly assign 420 smokers who were recent QL treatment failures to JUUL or combination nicotine replacement therapy (NRT). All participants will receive three calls from QL coaches. JUUL and NRT will be provided at no cost for 8 weeks, and the final follow-up will occur 12-weeks post baseline. Our specific aims are to evaluate 1) provision of JUUL vs. NRT on product switching/substitution, craving/withdrawal, abuse liability, number of cigarettes smoked, and perceived nicotine dependence; 2) changes in carbon monoxide (iCO), a biomarker of tobacco constituent exposure; and 3) which EC device characteristics and effects (e.g., satisfaction, "throat hit", craving reduction) influence complete (vs. partial or no) switching.

Project Narrative/relevance to public health:
E-cigarettes are proliferating and evolving rapidly. To date, it is not clear how e-cigarette products will impact health, especially among recent smoking cessation treatment failures and among priority populations for tobacco treatment (i.e., smokers with low socioeconomic status and mental health conditions), such as those served by state tobacco quitlines. The proposed work will prospectively examine the effect of switching to the JUUL vs. NRT on changes in smoking patterns, dependence, exposures to harmful toxicants, and downstream health effects.

A. Specific Aims

Since their market emergence, electronic cigarettes (ECs) have garnered both criticism and praise regarding their potential promise to reduce the risks associated with conventional cigarette use. While researchers have attempted to keep pace, ECs and e-liquids have rapidly evolved from products with minimal nicotine delivery, to products capable of matching the nicotine delivery of cigarettes. While the research base is growing, there remains a lack of prospective and controlled research on the behavioral, toxicological, and physiological effects of ECs to help the public health community come to a clear and accurate consensus on their risk-benefit. Moreover, the studies that have been completed used various commercially available ECs, e-liquid flavors, and nicotine concentrations, many of which are unavailable today and for which we know very little in terms of device characteristics, e-liquid/aerosol toxicological or pharmacological profile, making the generalizability and comparisons between past, present, and future studies very difficult.

A prospective randomized trial assessing the impact of switching to JUUL on smoking behaviors, nicotine dependence, exposure to toxicants, and health effects, will greatly accelerate our understanding of ECs.

The purpose of the present funding opportunity (PAR-17-156) is to begin to evaluate, with a high degree of fidelity, ECs as a potential means of reducing smoking-related risks and to provide information on the use and effects of JUUL; it is also meant to be completed quickly (two-year study). In order to successfully execute our research plan, we will conduct the present study with a quitline (QL) population, characterized by high levels of nicotine dependence, low socioeconomic and educational attainment, and high levels of substance use and mental health disorders—priority populations for tobacco control. QLs provide ready access to a large number of tobacco users, as well as infrastructure for delivering and testing study interventions. Our team has successfully carried out large-scale QL recruitment (e.g., 2,000 smokers in 8 months) for past trials. QLs are potentially the best real-world platform to quickly and with sufficient statistical power, meaningfully examine smokers' willingness to switch to JUUL and its downstream effects on smoking and health.

Therefore, the overall aim of the proposed study is to evaluate the provision of JUUL versus NRT on smoking behavior, product use patterns and continued use, and iCO, a biomarker of toxicant exposure, among a sample of recent QL treatment failures. We will randomly assign 420 smokers to JUUL or treatment as usual, combination nicotine replacement therapy control (NRT). All participants will receive three calls from QL coaches and JUUL and NRT will be provided at no cost for 8 weeks. The final follow-up will occur 12-weeks post baseline.

Aim 1: To assess JUUL **vs. NRT on product switching/substitution, craving/withdrawal, abuse liability, number of cigarettes smoked, and perceived nicotine dependence.** *Hyp 1a: Complete product substitution (vs. partial or no substitution) will occur at a significantly higher rate among smokers randomized to the* JUUL *compared to those randomized to NRT at 8 and 12-week follow-ups. Hyp 1b: Compared to those randomized to NRT,* JUUL *participants will report less nicotine craving, fewer nicotine withdrawal symptoms, smoke fewer cigarettes per day, and higher perceived nicotine dependence.*

Aim 2: To evaluate changes iCO, a biomarker of tobacco constituent exposure. *Hyp 2: The degree of change will be directly associated with the degree of substitution with J or NRT—greater levels of substitution will confer a larger decrease in exposure to harmful constituents.*

Aim 3: To evaluate which EC device characteristics and perceived effects influence complete (vs. partial or no substitution). *Hyp 3a: Participants reporting higher product satisfaction, including product durability, battery life, "throat hit", taste, craving reduction, improved mood with use, and ease of use, will achieve higher rates of complete substitution.*

B. Significance

Quitting is Difficult for Many Smokers
Nearly 50% of smokers make a quit attempt each year, but less than 5% remain abstinent for 3-12 months after quitting.[1-3] As a result, the prevalence of cigarette smoking among adults in the U.S. remains disturbingly high.[1] Current cessation products and counseling are effective, doubling a smokers chances of long-term abstinence, but are not universally effective for all smokers, and most smokers fail to quit on their first attempt.[4-7] Moreover, a significant minority of smokers finds it very difficult to quit smoking with current FDA-approved products.[8] To prevent these individuals from returning to smoking following a failed quit-attempt, offering them other less toxic and carcinogenic forms of nicotine would potentially offer a significant health benefit over smoking. This approach is consistent with a tobacco harm reduction model, which asserts that it is preferable to reduce tobacco-related harm by having smokers switch to less toxic products when complete cessation is unobtainable[9]; electronic cigarettes maybe one such product.

The Promise of Electronic Cigarettes: Overview and Limitations of the Available Research
Electronic cigarettes (ECs), which deliver nicotine and mimic many of the behaviors and sensations of smoking a conventional cigarette, may be a product that reduces harm to smokers as they do not require combustion.[10-12] Unfortunately, there is a lack of prospective and controlled research on the behavioral, toxicological, and physiological effects of ECs.[13-15] The studies that have been completed used various commercially available ECs filled with various e-liquid flavors and nicotine concentrations.[13] Many of these devices and e-liquids are unavailable today or have been modified from their original form. Moreover, we know very little about these commercial products in terms of their device characteristics (e.g., wattage), e-liquid or aerosol toxicological profile, or their pharmacological profile (e.g., nicotine delivery), making the generalizability and comparisons between past, present, and future studies very difficult.[13] Below, we detail a brief overview of the available EC research base.

EC Behavioral Profile: While limited, the EC research to date generally suggests that ECs significantly reduce cigarette cravings and withdrawal symptoms, especially for experienced users,[10,16-18] and increase motivation and confidence to quit smoking, even among unmotivated smokers.[10] Moreover, cross-sectional surveys and longitudinal cohort studies,[19-22] and one small randomized, wait-list control trial (n=48)[23] are beginning to indicate that newer e-cigarette models (i.e., higher-wattage tank-style devices), with better nicotine delivery,[24-26] are more helpful for smoking cessation than earlier, low-wattage (<5 watts), cig-a-like devices. To date, only two prospective, long-term, randomized controlled EC trials have been conducted, demonstrating modest smoking abstinence rates with early, low-wattage EC devices (Study 1: 12-month abstinence rate of only

11%[27]; Study 2: 6-month abstinence rate of 7.3% (vs. 5.8% nicotine patch and 3.1% placebo).[28] Unfortunately, the same studies also suggest that the most common outcome of e-cigarette use is continued dual use of cigarettes and e-cigarettes. While dual use of ECs and cigarettes may be characterized as a prolonged period of eventual transition to ECs, it is also possible that these will become long-term dual users.[29,30]

EC Toxicological Profile: Toxicological studies of EC liquid and aerosol suggest that while levels of harmful and potentially harmful constituents (HPHCs) are generally much lower than what is found in conventional cigarettes,[31-34] the quality control of e-liquid manufacturing is lacking and EC aerosols still contain measureable levels of carcinogens and other toxicants (see Table 1).[31-34] Moreover, some laboratory studies have demonstrated that under certain use conditions (e.g., high heating temperatures) ECs may deliver cigarette-like levels of at least one carcinogenic constituent—formaldehyde.[35-38] Recent cross-sectional and short-term (2-week), within-subjects observational studies echo these laboratory findings—overall switching from conventional cigarettes to ECs significantly reduces user's exposure and uptake of some HPHCs (e.g., tobacco-specific carcinogens, such as NNN and NNK), while others remain unchanged (e.g., nicotine, certain polycyclic aromatic hydrocarbons).[18,39,40]

Table 1: Comparison of toxin levels between conventional and electronic cigarettes

Toxic compound	**Cigarette (µg mainstream)**	**E-cig (µg per 15 puffs)**	**Average ratio (conv. cig vs. e-cig)**
Formaldehyde	1.6-52	0.20-5.61	9
Acetaldehyde	52-140	0.11-1.36	450
Acrolein	2.4-62	0.07-4.19	15
Toluene	8.3-70	0.02-0.63	120
NNN[a]	0.005-0.19	0.00008-0.00043	380
NNK[a]	0.012	0.00011-0.00283	40

Source: (33); [a]Tobacco-specific carcinogen

EC Physiological Profile: Other than nicotine delivery, most available research on physiological effects of ECs is limited largely to self-report data. Most users report improved breathing, endurance, and physical capability since switching from cigarettes; however, clinical laboratory trials have produced mixed results suggesting ECs may or may not increase airway resistance[41,42] and may or may not negatively affect blood pressure, heart rate, and myocardial function.[43-46] However, survey studies, as well as cross-over and randomized trials reported mild and tolerable side effects that generally resolved completely over time with continued use; the most common of which were nausea, mouth and throat irritation, cough, and headache[20,47-49].

JUUL

The JUUL ENDS (JUUL Labs, San Francisco, CA) is a closed nicotine-salt pod system (NSPS) which aerosolizes an e-liquid solution through vaporization.[157] A temperature control system integrated into the breath-actuated inhalation pathway is designed to maintain an operating temperature and to minimize the generation of combustion-related byproducts.[157] In an experimental setting where ninety subjects were randomized into one of six cohorts, the usual cigarette cohort consumed a mean of 19.3 cigarettes per day, and the NSPS cohorts consumed a mean of 0.79 grams per day.[157] This suggests that an NSPS pod, if completely consumed, would result in the mean total nicotine equivalents excreted associated with consuming 91% of a pack of cigarettes.[157]

Quitlines as a Unique Method to Quickly Conduct Significant, Large-scale JUUL Research

Telephone-based quitlines (QLs) are an effective means for treating tobacco use and dependence.[52-55] They have the ability to reach large numbers of tobacco users (approximately 350,000 in 2015),[56] and have been shown to be effective even in populations that historically have been hard to reach.[57-60] Both clinical and

community practice guidelines recommend QLs as a best practice based on both efficacy and cost-effectiveness.[52,61] Recently, QLs have integrated new treatment modalities such as web-based services, text messages, and emails in an attempt to boost engagement and quit rates. However, quit rates among smokers using a QL seem to have reached "a glass ceiling" with 25-30% of smokers reporting 30-day abstinence at the 6-month follow-up (available responder quit rates, not intent to treat).[56] As such, most smokers who call a QL do not quit for good, but rather eventually return to smoking. Moreover, the majority of quitline callers have made multiple previous quit attempts, [62] and may have tried and failed on established quitting methods that have remained largely unchanged for the past 30 years. Thus, there is a need to examine novel approaches to achieve greater outcomes and to address relapse and treatment failures.

QLs offer a unique opportunity for research, providing ready access to a large number of tobacco users who made recent quit attempt and infrastructure for delivering and testing study interventions,[70] as well as an avenue for quickly translating important findings into standard practice to minimize the 17-year translation gap evidenced for most research.[71] For example, the Oklahoma Tobacco Helpline (OKHL) has previously participated in a number of research projects including trials that required significant levels of recruitment in a short period of time, such as the proposed study. One randomized controlled trial led by Dr. Beebe (Co-I) and Optum, successfully screened, recruited and enrolled 2000 smokers in eight months.[72,73] Additionally, another study in which Dr. Gillaspy (Co-I) is currently involved, has screened, recruited, and enrolled 881 American Indians and Alaska Natives (AI/AN) in seven months. Overall, with a two-year time window, QLs are potentially the best real-world platform to quickly, and with sufficient statistical power, meaningfully examine smokers' ability and willingness to switch to the JUUL, and evaluate the impact of JUUL on tobacco use behaviors, nicotine dependence, and exposure to harmful tobacco-related constituents.

What We Need to Know

While current EC research is promising, we do not have sufficient data to determine what impact they will have on smoking behaviors, nicotine dependence, and health, nor what will be the most effective regulatory strategies. **The proposed study will address the current knowledge vacuum by directly examining smokers switching to JUULin a randomized controlled trial, assessing not only changes in smoking patterns, product use, and nicotine dependence but also differential exposures to tobacco toxicants. Moreover, comparing switching to JUUL to a positive control condition (quitline cessation counseling and combination NRT) will provide a robust ecologically valid comparator.**

Innovation

While EC research is proliferating rapidly as researchers attempt to keep pace with increasing consumer use, there is very limited long-term prospective research on smokers switching to ECs, especially in a randomized, controlled design (only two published studies). Importantly, both of these previous studies utilized ECs with very limited nicotine delivery, unlike the proposed study. **This will be the first switching trial to be conducted with a QL population**—a population characterized by low education/income, Medicaid-insured or uninsured, and a high proportion of mental health and substance use disorders. We will take this a step further and will only recruit from QL callers who recently failed to quit or stay quit—a priority population for outreach. Conducting research in this real-world sample will result in more generalizable findings that will improve the applicability of results on the JUUL device for policy decision making. We will also be one of the first to utilize

daily ecological momentary assessments (EMAs) to begin to elucidate real-time mechanisms associated with switching vs. not, and the first to use individual, portable exhaled carbon monoxide detectors with facial recognition to confirm daily smoking status (see details below). This method will provide granular data never before utilized in QL investigations. Moreover, as the proposed investigation will utilize a recruiting platform with a significant reach but that still allows for controlled recruitment and standardization, **it is potentially the only study that can successfully conduct, within the 2-year U01 timeline, a fully powered, 2-arm, JUUL switching study** capable of examining not only smoking behaviors but also iCO, a biomarker of exposure, and health effects. Overall, this innovative study in its comprehensive examination of JUUL, will quickly provide important information on the impact of the provision of JUUL on multiple tobacco-related behaviors and health outcomes.

C. Approach and Preliminary Studies

Dr. Theodore Wagener (PI) has seven years of experience conducting clinical, clinical-laboratory, and survey studies examining the behavioral,[10,74-79] physiological,[18,76,77] toxicological,[10,18,76] and pharmacological effects of ECs.[18,77] Dr. Wagener is currently the PI of a NCI R01 examining how low vs high-wattage commercial e-cigarettes differentially impact EC use and cancer risk. He also currently serves as PI, Co-I, or Primary Sponsor on seven other NIH-funded clinical/clinical laboratory trials examining alternative tobacco products, four of which examine ECs.

Dr. Laura Beebe (Co-I) has more than 20 years of experience conducting research and evaluation with tobacco control programs including the OKHL. She has a record of NIH-funded research, and currently serves as a Co-I on Dr. Wagener's R01 examining low and high-wattage e-cigarettes. Drs. Beebe and Wagener have collaborated on a number of other EC-related studies, including a survey of American Indian youth to determine EC prevalence, an examination of the geographic distribution of vape shops, and an analysis of the nicotine metabolite ration among American Indians using ECs. Dr. Beebe has conducted the evaluation of the OKHL since 2003, and collaborated extensively with Dr. Vickerman and other researchers at Optum. She co-led the "Weigh2Quit" study which screened, recruited and enrolled 2000 smokers who called the OKHL in eight months.[72,73] As the evaluator for the OKHL, Dr. Beebe has access to all registration and service utilization data for OKHL registrants.

Dr. Stephen Gillaspy (Co-I) is the Director of the OKHL. In this position he is working to improve the OKHL reach to disparate populations and collaborating on innovative research projects. Dr. Gillaspy has successfully collaborated with Drs. Wagener and Beebe on multiple tobacco projects in the area of both ECs and tobacco helpline reach. He has been actively involved in tobacco cessation research and is currently collaborating on a NIMH P20 with researchers at the University of Washington on the American Indians STOMP Smoking by Mobile Phone (AI Stomp) project.

Dr. Katrina Vickerman (Co-I) has worked with tobacco QLs for 7 years as the lead program evaluator at Optum and now as a research scientist. She has led and collaborated on (Co-I) CDC and NIH-funded quitline studies, including randomized trials and EC research. Dr. Vickerman has led efforts to monitor EC use at the QL and served as a subject matter expert on ECs. She has examined characteristics of QL EC users and smoking cessation outcomes for dual users of cigarettes and ECs,[80-82] including collaborating with Dr. Beebe to conduct

focus group and qualitative research with QL smokers who also use ECs.[80] Finally, she has collaborated with Drs. Wagener, Gillapsy, and Beebe on a pilot trial examining smokers' ability to switch to ECs.

Dr. Michael Businelle (Co-I) is Director of the Stephenson Cancer Center mHealth Shared Resource, which will provide the smartphone programming and data collection components for the proposed study. Over the past 13 years, Dr. Businelle's research has focused on testing novel cancer prevention interventions and reducing health disparities in socioeconomically disadvantaged populations. He has expertise in using EMA and advanced statistical methods (e.g., structural equation modeling) to identify mechanisms through which socioeconomic disadvantage influences smoking cessation. Dr. Businelle and Dr. Wagener are currently co-leading a study that incorporates wearable activity monitors, the Bedfont iCO portable carbon monoxide monitor, and a Bluetooth enabled e-cigarette device to identify antecedents to vaping sessions and gestures that are consistent with vaping.

Dr. Matthew Carpenter (Consultant) is a Professor and licensed clinical psychologist and has led a number of large-scale, nation- or statewide clinical trials for smoking. These include tests of NRT sampling,[83-85], smokeless tobacco,[86-89] and EC.[90] He recently completed a naturalistic study of EC-sampling vs. not (NIDA R21), and has a pending R01 (8th percentile) to examine these same themes within a nationwide trial (Dr. Wagener co-I on both EC studies). He is well-versed in randomized, naturalistic designs that emphasize consumer uptake, patterns, and consequences of alternative nicotine products, including ECs.

Dr. Irina Stepanov (Consultant) has an 18-year history of conducting research in the field of tobacco carcinogenesis. She has conducted numerous studies analyzing TSNA and other toxicants in cigarette and non-cigarette tobacco products. Dr. Stepanov brings analytical biochemistry expertise to the proposed study and will oversee the statistical analysis and interpretation of study results as they relate to biomarkers of exposure. Dr. Stepanov is a collaborator on three of Dr. Wagener's current studies, including Co-I on his EC R01.

Overall, our team is currently conducting, or has conducted/collaborated on 16 clinical, clinical-laboratory, and survey studies examining the behavioral, pharmacological, toxicological, and physiological aspects of EC use;[10,18,74-82,90-93] more than 12 studies examining QLs generally and 6 examining the OKHL, specifically;[62,67,68,72,73,80-82,94-98] 4 large nationwide switching trials where smokers were mailed non-cigarette tobacco products, including ECs, or NRT; [83-90] and 4 studies examining ecological momentary assessments to measure real-time tobacco use behaviors (including EC use) and their antecedents to explore potential mechanisms associated with their use. [99,100]

D. Research Design and Methods

1. Design Overview

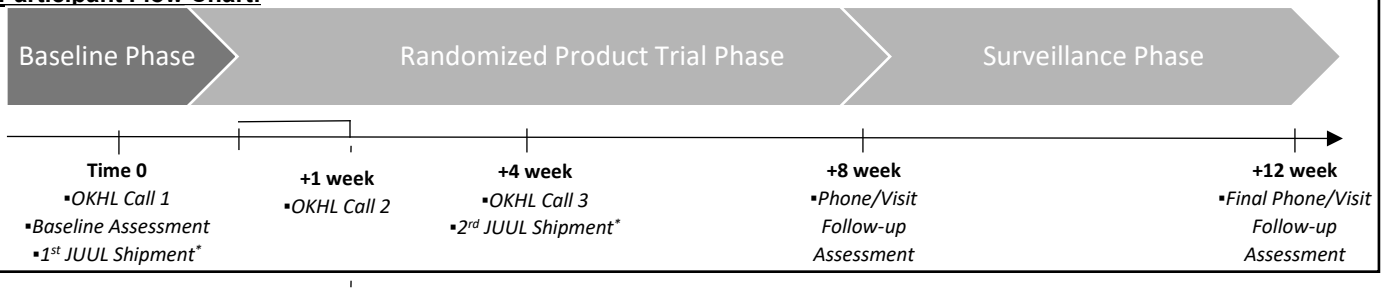
Optum is responsible for executing multiple state QLs including, but not limited to, Oklahoma and South Carolina. With a sample of state QL participants who had enrolled in quitline treatment 4-6 months prior, we propose to conduct a two-arm, randomized, placebo-controlled trial that will proceed in three phases over 12 weeks (see Participant Flow Chart below). During the Baseline Phase (Time: 0), state QL callers who had

enrolled in quitline treatment 4-6 months prior will be offered participation in the present study by Optum or OSU research staff. Those eligible and who agree to participate will be randomized by Optum research staff and mailed JUUL (tobacco or menthol-flavor, 5% nicotine pods) or NRT (nicotine patch plus lozenge) by OSU study staff. Both arms will also be provided three calls from Optum coaches. The Randomized Product Trial Phase (Time: 0-8 weeks) will last 8 weeks and smokers will be asked to attempt to completely switch to JUUL for the 8 week time period. All JUULs will be mailed to the participants in two shipments (Time 0, +4 weeks) by OSU study staff and provided at no cost. Those participating in the JUUL arm will also be provided three calls (~10-15 min each) from an Optum coach (Time 0, +1, +4 weeks) who will provide behavioral counseling including education on ECs, how to use and troubleshoot the EC if issues arise, and help address potential barriers to switching and develop strategies to switch. Those randomized to NRT will be provided nicotine patch plus nicotine lozenge and will also receive three behavioral counseling calls from an Optum coach. Each call will last 10-15 minutes each. The Surveillance Phase (Time: 9-12 weeks) will last 4 weeks, during which time no study product will be provided, only assessment of continued product use (or not) and other outcomes of interest (see Table 3), as well as iCO, a biomarker of toxicant exposure and effects will be measured. Over the course of the study, participants will complete a larger assessment battery at three time points: 0, +8, +12 weeks over the phone with OSU study staff. Time points for study visits are based on matching other switching studies in the literature and to fit within the short time-window of the U01. All participants will also be provided a study smartphone and a portable carbon monoxide monitor (iCO) which will be sent by OSU study staff. Participants will be asked to complete two brief (<3 minute each) daily smoking/JUUL diary assessments and iCO readings (to verify smoking status) for the 12-week duration of the study using the provided smartphone and portable iCO.

Study Weaknesses and Design Considerations

A potential weakness is the level of participant burden, by asking participants to complete two daily EMAs. We have attempted to attenuate this by keeping EMAs for this study very brief (<5 minutes) and automatically prompted by the smartphone. We are also compensating participants for their completion and providing them with a study smartphone and service at no cost. Overall, we decided on this method because it has been successfully used by our team in previous studies (each achieving >80% EMA completion rates) and provides near real-time data over the entire course of the study, helps us maintain contact with participants to reduce attrition, and will give us daily smoking status (using daily iCO readings) over the 12-week study period; something never before achieved with a QL study. Lastly,, we will be gathering daily CO readings from the entire sample, which will provide some biomarker of exposure data.

Participant Flow Chart:



2. Study Procedures

Participant Screening and Randomization

State QL registrants who have recently failed quitting smoking using the standard quitline program will be screened for potential eligibility in the present study (n=420) by Optum or OSU research staff. Potential participants, who enrolled in quitline treatment 4-6 months prior, will be recruited during proactive calls by Optum or OSU research staff or online screener via REDCap. Optum or OSU staff will screen, consent and complete baseline measures over the telephone or online via REDCap. Randomization will be stratified by sex, location, educational attainment, and ever use of ECs. Participants who meet the following eligibility criteria will be invited to participate in the study. Inclusion criteria: 1) Smoke, even a puff, within the past 24 hours; 2) currently smoke ≥5 cigarettes per day; 3) read, write, and speak in English; 4) report at least minimal interest in switching to an alternative nicotine delivery product (> "not at all" on a Likert-type scale); 5) enrolled in the state tobacco quitline within the last 4-7months; and 6) valid mailing address. Exclusion Criteria: 1) Currently enrolled in a contradictory study (Project ENDSmoking Study, the American Indian/Alaskan Native program, or the Pregnancy Quitline program); 2) cohabitates with a currently enrolled participant in the REACH study; 3) <21 years old; 4) current daily use of an e-cigarette over the last month; 5) change in activities or taking medication to treat a rapid or irregular heartbeat or serious or worsening angina or heart pain in the past 6 months;6) had a heart attack or stroke/TIA within the last six months; 7) current diagnosis of bipolar disorder, or schizophrenia or hospitalization in the past year for psychiatric condition (past and current stable conditions will be allowed); 8) reaction to using patch medication or adhesive tape that resulted in a rash or hives, swelling of face or throat, wheezing or shortness of breath, or high fever or skin irritation that continued despite moving patch medication or adhesive tape to a difference site and/or using hydrocortisone cream; 9) known allergy to propylene glycol or vegetable glycerin; and 10) currently pregnant, planning to become pregnant within the next 3 months, or breastfeeding.

Recruitment Feasibility and Retention

Recruitment: We intend to enroll 420 participants over an 12-month period (out of 24 months: 6 months for planning and Optum technology application changes, 12 months for recruitment, 3 months for final follow-up, and 4 months for data cleaning/analysis). Estimating based on FY16, the total number of QL registrants over the study period will include ~74,000 smokers (~3,000 registrants per month). Assuming a 30% abstinence rate, our pool of potential participants is 51,800 (74,000 x .70). Because we are trying to recruit 420 participants (0.7% of our potential pool) over a 12-month period, we are confident that our recruitment approaches will yield sufficient numbers and in our ability to recruit ~31 smokers per month (420/12 months). Moreover, Dr. Beebe (Co-I) and research scientists from Optum conducted a randomized controlled trial with the OKHL and successfully screened, recruited and enrolled 2000 smokers in eight months (Bush 2008, Bush 2012, Beebe 2015), lending further credibility to our methods, team, and ability to recruit sufficient numbers for the present study.

Retention: All participants who complete baseline and follow-up self-report assessments by phone will receive $25 per assessment (up to $75), and up to $255 for completing daily EMAs over the 12-week study period for a total of $330. For daily surveys (2 per day) and breath tests completed, participants can earn based on a percentage of completion. Completion of 50-79% will earn $45, 80-89%% will earn $$70, and ≥90% will earn $85 at the Week 4, Week 8, and Week 12 study periods, up to $255 during the 12-week active study period for

a total of $330. Participants will be compensated up to $25 at Baseline, $85 at Week 4, $110 at Week 8 and $110 at Week 12 study periods. Payments will be made using the Greenphire ClinCard to increase accountability and facilitate ease of payment. Participants will also be provided a study smartphone for the duration of their participation with paid service for 3 months so that they can immediately contact study staff for questions, receive reminders of upcoming appointments and study protocol, and complete EMAs and iCO tests. We will also facilitate study calls/visits by offering evening and weekend call times/appointments as well as additional retention strategies (e.g., multiple sources of contact, reminder calls/texts/emails). These methods are consistent with our team's previous studies and have resulted in excellent retention rates (>80%).[75,87,88,90,99,100,104,105]

Detailed Study Procedures

Coach Calls: All study participants will receive three calls (~10-15 minutes) from trained tobacco cessation coaches at Time 0, +14 days, and +4 weeks. Prior to randomization, participants will complete the baseline assessment over the phone or online via REDCap. For participants randomized to JUUL, coaches will provide behavioral counseling and education on ECs, how to use and troubleshoot the JUUL device, and aid in helping the participant develop strategies to help them switch to JUUL. Coaches will also asses for JUUL usage at the +14 days and +4 week calls to help determine if the quantity of the study product that was mailed to the participant should be increased or decreased. For those randomized to NRT control, coaches will provide smoking cessation counseling grounded in social cognitive theory and the US PHS clinical guidelines. Specifically, cessation counseling will emphasize five keys to quitting tobacco: setting a quit date, using cessation medications, tobacco-proofing one's environment, coping with urges to smoke, and enlisting social support.[106]
Baseline and Follow-up Assessments: All participants will have the baseline assessment battery (0) completed over the phone or online via REDCap with an Optum coach or OSU study team member before they are randomized to a study group; , follow-up assessments calls and mailing of JUUL pods and NRT will be conducted by Dr. Wagener's staff at the Ohio State University. Follow-up assessments will be conducted at +8 and +12 weeks.

Baseline Phase (Randomization)

Immediately following the baseline assessment, participants will be randomized to one of two arms for a period of 8 weeks: JUUL or NRT. Randomization will occur using a stratified block-randomization procedure with small, random sized-blocks. Randomization will be stratified by sex, education level (high school or less, GED, or greater than GED/High School), location and EC regular use history (ever at least once weekly for a month). Consistent with our previous and ongoing switching studies[10,75,107], participants will be instructed on how to use the JUUL, provided a starter kit (device and a charger) as well as pods initially at a 1:1 level based on established baseline smoking rate. Given JUUL pods, if completely consumed, have been found to excrete mean total nicotine equivalents associated with consuming 91% of a pack of cigarettes. We will assume that most pack a day smokers will require no more than one pod per day. The amount provided to participants will be documented and tracked throughout the study. Provision of additional pods will be titrated up or down based on use. All products will be given to participants in their original packaging and at no cost. Consistent with previous QL studies, participants in the NRT arm will be provided patch and lozenge (2 or 4 mg); for the nicotine patch, dosing will be determined by reported cigarettes per day. Specifically, for participants smoking 5-10 cigarettes per day they will be provided with 4 weeks of the 14 mg and 4 weeks of the 7 mg nicotine

patches; participants smoking 11+ cigarettes per day will be provided 4 weeks of 21mg, 2 weeks of 14mg, and 2 weeks of 7mg nicotine patches. All NRT will be provided for up to 8 weeks.

Randomized Product Trail Phase

The purpose of this 8-week phase will be to assess the effect of JUUL on product uptake and use, smoking behavior, and nicotine dependence, as well as level of toxicant exposure.. During this phase, participants will receive three OKHL coaching calls (0, +14 days, +4 weeks), complete EMAs twice a day (~120 EMAs over the phase), and complete two follow-up full assessment battery calls (0 and +8 weeks). Participants randomized to JUUL will be provided EC education, behavioral counseling, and asked to attempt to completely switch to the product for the next 8 weeks. Those randomized to NRT will be provided OKHL smoking cessation counseling and provided 8 weeks of NRT. All products to which participants will be randomized, will be provided at no cost and will be mailed to them. New cartridges will be provided based on estimated use given cigarettes per day. (see Table 2 for measures collection schedule).

Surveillance Phase

The purpose of this 4-week period is to assess how EC use evolves over time; specifically, continued use as measured by reported purchase of commercial EC product, transitions to other types or styles of ECs, smoking and other tobacco use behavior and patterns, as well as continued monitoring of iCO, a biomarker of toxicant exposure, and health effects over the 4-week period. During this phase, participants will continue to complete daily EMAs (~60) and a follow-up full assessment battery call at +12 weeks. Participants will be sent saliva collection kits if iCO is unable to be completed. Participants will not be provided ECs or NRT during this phase, but use of ECs, NRT, and other tobacco products will continue to be tracked. Also, this phase will help us to continue to track any adverse events that may occur following use of the JUUL and NRT. Those continuing to use any tobacco or EC product at the end of the surveillance phase will be advised that they can contact their state quitline and/or other local smoking cessation resources.

JUUL Education and Counseling

At the first visit, JUUL participants will be provide instructions on how to use the product and asked to attempt to completely switch to the product for the next 8 weeks so that we can accurately assess the use of the products on their health. Consistent with our previous EC switching studies,[75,107] participants will be asked how they intend to completely switch to the product and asked about concerns they have about switching. Optum coaches will help participants address any reported barriers to switching to assist them in remaining switched over the 8-week period. Study staff will provide participants trouble-shooting tips for the mechanics of their product, provide replacement parts as needed, and also address adverse events as they arise (though <2% and mild in our team's previous EC studies).

<u>Protocol Adherence and Quality Control</u>

Data Management

All data collection will follow HIPAA guidelines. Data will be collected directly from the participant by a research assistant or RIU coach. Data will include participant responses to computer-based, smartphone/EMA-based, and phone based survey questionnaires. All participants will be asked for an iCO sample daily for 12 weeks. A total of approximately 84 iCO samples will be collected from a single participant not to exceed 90 samples for any individual within the 12 week period.

Access to Identifiable Information and Data Storage: Only research assistants who have completed training in the ethical conduct of research and the study PI (Dr. Wagener) will have access to individually identifiable private information about human subjects. All data will be treated as confidential and will never be stored or reported in association with identifying information. Participants will be consented verbally or electronically and mailed a hard copy of the consent. A common identification number will link identifiable forms (consent forms and contact information) and study-related data. Computer entered data will be de-identified and password protected.

Quality Assurance

All research staff will have completed Human Subjects and HIPAA training. Standard operating procedures (SOP) will be developed and all staff will be trained to ensure adherence to the SOP. Optum coaches will be trained in the delivery of the JUUL behavioral counseling and are already trained in provision of NRT and smoking cessation counseling. Training will include JUUL product safety, device features, how to use the device and troubleshooting, assessing barriers and developing switching strategies. Coach calls will be monitored and recorded to assess for fidelity (20% of calls assessed). Optum coaches all have more than 200 hours of tobacco cessation training, and thus a high degree of comfort engaging with the target population by phone. As is standard practice for our team's current studies, each assessment call/visit will have its own checklist of specific measures to be completed and the order in which they are to be administered. To reduce data entry errors, we will use secured computer-based questionnaires for research assistants to complete while completing phone-based assessments. All key on-site personnel will meet face-to-face weekly throughout the entire study. Off-site investigators will participate in these weekly meetings during the first year for project start-up; however, this will be reduced to every other week as the study progresses. During these meetings, recruitment, enrollment, data collection, data monitoring results, and any concerns or issues that may arise will be discussed.

Regulatory Issues

Reporting mechanisms: Reports to the sponsor and IRB will be made accurately and on a timely basis. These include:

- Any *unanticipated adverse device effect* occurring during an investigation will be submitted no later than 72 hours after the investigator first learns of the effect.
- *Progress reports* on the investigation will be provided at regular intervals and a copy of the report will also be sent to the study monitor. These reports include annual, interim and final NIH Research Performance Progress Report (RPPR), IRB Continuing Reviews, and any other progress reports required by NIDA.
- Any *deviation from the investigational plan* made to protect the life or physical well-being of a subject in an emergency will be reported to the sponsor and IRB as soon as possible but no later than 5 working

days after the emergency occurs. Except in emergency situations, prior approval will be obtained from the sponsor and IRB for any protocol change necessary to reduce risk for subjects or data quality and if the change may affect the scientific soundness of the plan or the rights, safety, or welfare of subjects, prior FDA, NIDA, and IRB approvals will be obtained as required by 21 CFR 812.150.

- Any use of the device *without obtaining informed consent* will be submitted within 5 working days after such use.
- A *final report* will be submitted within 3 months following termination or completion of the investigation or the investigator's part of the investigation. These will include Annual Progress Reports and Final Reports.
- *Any further information* requested by FDA or the IRB about any aspect of the investigation.
- *Withdrawal of IRB approval* of the investigator's part of the investigation will be reported to only the Sponsor within 5 working days of such action.
- *All changes to the protocol or DSMP (other than staffing changes)* will require approval by the NIDA Program Officer prior to implementation.
- *Serious Adverse Events* must be reported to NIDA within 72 hours.
- A *DSM report* will be sent to NIDA annually with contents to include:
    - Brief description of the trial
    - Baseline sociodemographic characteristics
    - Retention and disposition of study participants
    - Quality assurance Issues
    - Regulatory issues
    - Adverse event listing
    - Severe adverse event descriptions

Conflicts of Interest: There are no conflicts of interest to report.

3. Measures

All measures, including EMAs and iCO, have been used previously by Dr. Wagener and his team. iCO, a biomarker of health and exposure, was chosen because it has shown reasonable laboratory reproducibility, has clear differences in levels between smokers and nonsmokers, demonstrate a dose-response relationship, and/or decrease upon tobacco cessation[108,109].

Questionnaire data will be collected over the phone or in-person by a trained research assistant and data will be entered into a secured and encrypted database using REDCap. See Table 2 for timing of measures. Sociodemographic data will assess participant age, sex, marital status, ethnicity, employment status, occupation, years of education, and socioeconomic status. Tobacco use history will assess years of smoking, age of smoking onset, average number of cigarettes per day, number and recency of previous 24-hour quit attempts, number of smokers in the household, prior use of nicotine replacement therapy and other stop smoking medications, and history of receiving smoking cessation counseling, and cigarette and EC expectance effects. It will also assess tobacco type, brand, frequency, quantity, and duration of use all of nicotine/tobacco products including cigars, cigarillos, little cigars, pipe tobacco, chewing tobacco, snuff, snus, EC, combustible tobacco hookah, and dissolvable tobacco. Complete Substitution will be defined as ≥7 days with no more than 1 conventional cigarette smoked (assessed via EMAs), daily exhaled carbon monoxide of ≤6 ppm as measured by iCO (see biomarker measures below), and reported use of ECs over the same 7-day period.

Cigarette Dependence will be measured with the 12-item *Cigarette Dependence Scale* [110]. EC Dependence will be assessed using an EC-adapted version of the *Cigarette Dependence Scale* [110] Abuse Liability of usual-brand cigarette and JUUL will be measured across several domains: 1) experiences of positive/negative drug effects, 2) behavioral-economic choice tasks, and 3) craving for and suppression of craving and withdrawal. An adapted version of the *Drug Effects/Liking Questionnaire*[112] will assess the desire and liking of products, positive and negative effects (i.e., side effects), and perceived strength and effectiveness. The *Cigarette Purchase Task* [113,114] and *modified Cigarette Purchase Task*[113,114] will ask participants how much they would be willing to pay (ranging from 0¢ to $1,120) for a puff of their own brand cigarette or JUUL. Specifically they will be asked, "How much would you be willing to pay for…a puff of your usual cigarette brand [a puff of the study e-cigarette]". Willingness to spend more money will indicate greater abuse liability. Smoking and vaping urges/craving will be measured using the *Tiffany-Drobes Questionnaire of Smoking Urges: Brief Form*.[115] A modified version (replacing the word "cigarette" with "e-cigarette") for EC users. This is a 10-item measure where participants rate smoking-related items ("All I want right now is a cigarette [e-cigarette].") on a 7-point Likert scale ranging from 'strongly agree' to 'strongly disagree'. Similar to previous studies, we will collapse the items into two previously identified factors (Factor 1: strong desire and intention to smoke [vape]; Factor 2: anticipation of relief from nicotine withdrawal symptoms). Nicotine withdrawal will be assessed using the empirically validated 15-item version of the *Minnesota Nicotine Withdrawal Scale*.[116] This measure assesses smoking craving, anger/irritability, anxiety, depressed mood, restlessness/difficulty concentrating, increased appetite, sleep problems, and somatic symptoms (nausea, constipation, sore throat, dizziness, coughing). Motivation Rulers including importance, confidence, and readiness to quit smoking (3-items total, with a scale ranging from 0 "not at all important/confident/ready" to 10 "extremely important/confident/ready") will be collected to assess for changes in motivation over time for those who continue to smoke [118].

Ecological Momentary Assessment (EMA) & iCO

All participants will be mailed a study smartphone and iCO device, and provided 3 months of unlimited call and data service at no charge and will complete EMAs twice a day for all 12 weeks. Participants will receive one EMA delivered randomly during the day and an evening daily diary (~30 minutes before bedtime). Given the half-life of CO (4-12 hours), we will only request that participants complete iCO measurement for the evening daily diary. Consistent with our team's previous studies, random EMAs will assess: mood, affect, nicotine craving and withdrawal symptoms, stress, recency of vaping/smoking, alcohol use, current setting, and switching self-efficacy; daily diary EMAs will assess conventional cigarettes smoked per day, number of JUUL pods used (if applicable), cigarette/EC satisfaction and pleasure, and measurement of exhaled carbon monoxide with the iCO (see Table 2 for specific EMA measures). All EMAs will be prompted and initiated by the phone. The phone will audibly and visually cue these EMAs for 30 seconds. If the participant has not responded after 3 prompts, the assessment will be recorded as missed. Typically, random sampling assessments take ~1-2 minutes to complete and daily diary assessments take approximately ~3-4 minutes to complete. Participants will be compensated for EMA completion at the 8 and 12 week follow-ups. All assessments will be date and time stamped for future analyses. Participants have the ability to call (e.g., if they have problems completing EMA's) and receive calls from research staff through the smartphone free of charge. The EMA methodology used in this study has been successfully followed by our team as well as other researchers in multiple studies.[119-128] All participants will be sent prepaid mailing boxes and asked to return

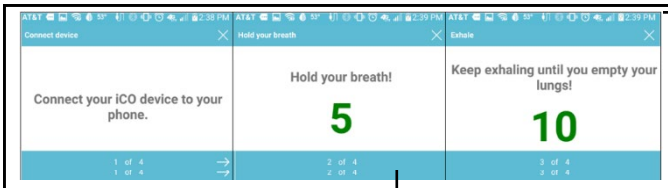


Figure 4. Bedfont iCO monitor completion steps.

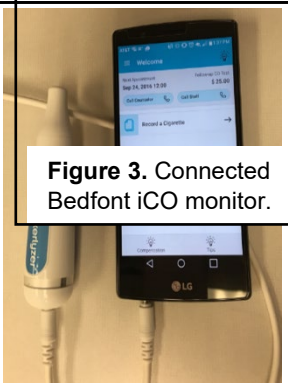


Figure 3. Connected Bedfont iCO monitor.

study phones at the end of the EMA period of the study. Participants will receive the final payment for completing EMAs when the study phone is received by research staff.***Bedfont iCO smokerlyzer monitor*** will measure daily CO levels and biochemically confirm smoking abstinence over the course of the 3-month study. Participants will be prompted to connect the iCO device to the study smartphone each day following completion of the EMA and follow step-by-step directions to complete the CO test (see Figures 3 and 4). Results of these tests will be date and time stamped and saved. Participants will not receive feedback on test results. Our CO criteria for abstinence is consistent with numerous other studies using cutoffs of ≤ 6 ppm.[129-134] As ECs do not produce CO, expired CO is a valid indicator of smoking status (i.e., switching completely to ECs) and compares favorably with cotinine and other biochemical measures that have longer detection windows.[135-138] Self-reports of abstinence combined with facial recognition and CO levels suggestive of recent abstinence provide an accurate, immediate, and practical measure of abstinence. We have validated the iCO against the Vitalograph CO monitor, and our mHealth core has already integrated the iCO device into our platform. The manufacturer indicates that the iCO is valid for approximately 200 CO tests and has a sensor sensitivity of 1 ppm.[139] Our protocol will require no more than 90 CO testing sessions; well within the defined valid use range.

Table 2. Measures

Measure	**Baseline (0)**	**Product Trial (+8 weeks)**	**Surveillance (+12 weeks)**	**EMA ASSESSMENTS**
Sociodemographic & Socioenviroment	x			Daily 90 days
Cig Dependence Scale	x			Daily Diary EMAs*
Product Use Status	x			# Cigarettes Smoked
Product Use - NRT	x			# Vaping Sessions
JUUL Use Evaluation		x	x	Other tobacco use
NRT Use Evaluation		x	x	EC product info
JUUL Expectancies – Cig		x	x	MNWS
JUUL Expectancies – Ecig		x	x	E-liquid Used
NRT Expectancies		x	x*	iCO Assessment
MNWS		x	x	Random EMAs
QSU cig		x	x	Affect/Mood/Stress
QSU ecig		x	x	Urge to Smoke
QSU NRT		x	x	Urge to Vape

Adverse Events		x	x	Recency of Smoking
Ecig Dependence Scale		x	x	Recency of Vaping
NRT Dependence Scale		x	x	Social setting/Location
SRNT		x	x	Abstinence Self-Efficacy
TLFB		x	x	Cigarette/Vape Availability
Motivation Rulers – 8 to 12		x	x	Cessation Motivation
Cigarette Purchase Task		x	x	Smoking Restriction
iCO		x	x	Vaping Restriction
				Cigarette Reward Value
				Alcohol Use
* Daily Diary EMAs also include Random EMA items				

E. Statistical Methods

1. Power Analysis

Complete substitution of combustible cigarettes for EC products is the primary outcome of the study, as the rate of product substitution will likely drive the outcomes for all of the other aims. We will compare the proportion of participants with complete substitution in the JUUL vs. NRT at the end of the product trial phase (8-week follow-up) using the Fisher's exact test. There are no direct data available on which we can base sample size estimates for the proposed study. The closest estimate for the JUUL arm was based on the 6 week, 35% switch rate for JUUL in a pilot study of a community sample of African American/Black smokers (N. Nollen, personal communication). Likewise, we estimate that the percent of complete substitution will be 35%. For the NRT, the closest estimate was the 4 week, 30% abstinence rate for preferred NRT product among a sample of smokers motivated to quit smoking[156]; however, we will conservatively assume a NRT substitution rate of 20% since participants will have tried NRT previously and were not successful. We will assume an attrition rate of 20%. Assuming 20% attrition among a total of 420 participants (186/group), will allow 300 participants to be analyzed in the final sample. A sample size of 300 will provide >80% power to detect a difference in complete substitution between JUUL and NRT groups for a two-sided .05 level chi-squared test. It is important to note that this sample size is deliberately conservative, as it does not assume the availability of repeated outcome measures that will be taken throughout the study. By choosing models that utilize longitudinal data, we will further increase the power to detect differences between arms

2. Data Analytic Plan

Statistical analyses will be performed using SAS 9.4. P-values less than .05 will be considered statistically significant. Baseline demographics and smoker characteristics will be summarized by groups (JUUL and NRT), as appropriate. Continuous variables will be presented as mean±SD and compared among the 2 groups using ANOVA test. Categorical variables will be presented as counts and proportions and compared among the 2 groups using the chi-squared test.

Aim 1: The focus of aim 1 is the examination of differential levels of (Hyp 1a) substitution between JUUL and NRT, and (Hyp 1b) reported nicotine craving, withdrawal symptoms, number of cigarettes smoked per day, product abuse liability, and nicotine dependence, between JUUL and NRT. *Hypothesis 1a:* Complete substitution rates, at the 8 and 12 week follow-ups, will be compared between JUUL and NRT arms using logistic regression analysis, adjusting for baseline variables such as age, gender, number of cigarettes per day and/or randomization stratification factors. The GEE model will be performed for the repeated measure analysis of complete substitution rate across multiple visits. *Hypothesis 1b:* If needed, we will apply a normalizing transformation to the response measure (e.g., taking the logarithm of cigarettes per day) before proceeding with the analysis, as a means of removing the effects of potential outliers. We will examine changes in each outcome over time across the two groups using linear mixed model (LMM) regression analysis. We will employ a random intercept or slope parameter, as appropriate, and model the covariance structure for the repeated outcome measures, while accounting for baseline value of the outcome and potential confounders (including any variables not equally distributed between groups). Modeling is done using a likelihood-based approach and thus makes use of all available data (on the intention-to-treat (ITT) sample) to produce consistent estimates of the regression parameters. Contrast estimates comparing group effects over time will be used as measure of effect. A similar approach will be used to explore the EMA data collected.

Aim 2: The focus of aim 2 is the examination of changes in a biomarker of toxicant exposure. *Hypothesis 2:* We will examine changes in iCO, a biomarker of toxicant exposure, and EMA data using the methods outlined in Hypothesis.

Aim 3: The focus of aim 3 is (Hyp 3a) to determine which EC device characteristics and perceived effects are associated with complete (vs. partial or no) substitution. Hypothesis 3a: We will examine whether changes in EC device characteristics and perceived effects obtained by EMA over time differ between those who achieve complete (vs. partial or no) substitution using linear mixed model (LMM) regression analysis. We will employ a random intercept or slope parameter, as appropriate, and model the covariance structure for the repeated outcome measures, while accounting for potential confounders. We will use similar methods to explore return to smoking in those who report complete substitution at any time during the study.

3. Missing Data

In the event of missing data, we will contact participants immediately. If a participant drops out, we will attempt to gather follow-up information by calling the study phone and trying to reach the participant through other provided contact information. However, if a participant refuses to be contacted or loses contact with the investigators, we will censor data at point of loss. Two statistical approaches will be used to handle missing data. First, we will use inverse probability weighting with propensity scores. This is a two-step procedure in which we first model the probability of missingness as a function of baseline covariates and previous outcomes. Next, the inverse of the resulting predicted probabilities (from the logistic regression model) will serve as weights in our proposed model of the response. We will compare these results to a more conservative ITT approach as a final step.

F. Gender/Minority/Pediatric Inclusion for Research

1. Inclusion of Women and Minorities

No restrictions will be placed on enrollment by race, ethnicity, or gender. Based upon the FY16 OKHL Annual Report, 57.7% of OKHL enrollees were female and 74.7% White, 11.6% American Indian/Alaska Native, 8.9% Black or African American, 1.0 % Asian, Native Hawaiian/Other Pacific Islander, and 3.1% two or more races. The ethnic composition of the OKHL was 8.9% Hispanic/Latino and 91.1% Non-Hispanic/Latino. Based upon the 2018-2019 contract dates for the South Caroline Quitline (SCQL), 60.6% were female and 62% White, 1.7% American Indian/Alaska Native, 24% Black or African American, 0.25 % Asian, Native Hawaiian/Other Pacific Islander, and 12.05% other or unknown races. The ethnic composition of the SCQL was 2.2% Hispanic/Latino, 90.6% Non-Hispanic/Latino and 7.2% unknown. We expect that our enrollment distribution, including gender specific data, will be similar for this study.

4. Inclusion of Children

Participation in the proposed study will be restricted to individuals 21 years of age and older. This exclusion is for two primary reasons: 1) the use of tobacco products by minors is illegal, and 2) the concern of introducing and potentially addicting children and adolescents to another tobacco product.

G. Human Participants

5. Recruitment and Informed Consent

At first contact, all participants will be screened by Optum or OSU research staff, according to the studies inclusion/exclusion criteria. Those who are eligible will be contacted, given a verbal overview of the study and invited to participate. Once a potential participant fully understands each element of the consent (including the nature, purpose, risks, and benefits of the study), the individual will be asked to provide informed consent (verbal or electronic). The voluntary nature of the study and the participant's right to withdraw at any time will be stressed during the consent process. The date and time verbal consent is obtained, the Optum or OSU research staff whom is providing the oral explanation of the study and any questions a participant has regarding the verbal consent will be documented and captured in the Optum system or REDCap. When verbal consent is completed by Optum research staff, this data will be sent to OSU study staff and uploaded into REDCap for documentation. When verbal consent is completed by OSU research staff, data will be entered into REDCap for documentation. If electronic consent is obtained, the eligible potential participant will receive an email with the electronic consent form using REDCap. Participants will be required to enter a personal data reference (i.e. date of birth) in order to authenticate their identity and access the consent form in REDCap. ESignature will be documented in REDCap with a timestamp. A written copy of the informed consent will be mailed to the participant after the time of consent for them to keep. We will not require participants to send

back written informed consent prior to initiation of intervention services, however, as doing so would impose an artificial delay in the delivery of services. All participants will provide consent before any study data is collected.

6. Potential Risks

The research protocol calls for current smokers who recently failed to quit smoking using the standard QL program, to attempt to completely substitute JUUL or NRT. E-cigarettes are no more harmful than conventional cigarettes, and there is some evidence that that may offer reduced harm. Questionnaires and the exhaled breath collection procedure is non-invasive and involves minimal risk to study participants. Potential risks are as follows: a) risk of using NRT, b) risk of using e-cigarettes, c) dual use of cigarettes and e-cigarettes, d) loss of confidentiality or privacy, e) potential for undermining smoking cessation, and f) lack of appropriate storage of nicotine-containing products in a house with children and pets.

7. Protections Against Risk

Efforts to reduce risk are as follows:

a) Risk of using the NRT: The risk of side effects and adverse events is very low. These product are FDA-approved for smoking cessation, and sold at convenience stores nationwide, without a prescription. Nevertheless, participants will be screened for general medical precautions (pregnancy, cardiovascular disease), and all participants will be monitored for adverse events during the study period. Study personnel will assess for adverse events via self-report at all follow-up visits. Smokers will also be provided a study smartphone with a direct line to report an adverse event between follow-up visits. Any Serious Adverse Events will be reported to the study's medical monitor and then to the OSU IRB and to NIDA. We will withdraw participants who have a Serious Adverse Event, or become pregnant or begin to breastfeed. The most likely adverse event (potential for nicotine overdose) is anticipated to be rare (<5% in our team's previous studies) and mild (nausea, headache, disrupted sleep), and will be handled quickly (i.e., advice to participant to reduce or stop NRT use).

b) Risk of using e-cigarettes: The risk of side effects and adverse events are very low. These products are sold online, and at e-cigarette specialty stores and convenience stores nationwide, without a prescription. Nevertheless, all participants will be screened for general medical precautions (pregnancy, cardiovascular disease) and monitored for adverse events during the study period. Study personnel will assess for adverse events via self-report at all follow-up visits. Smokers will also be provided a study smartphone with a direct line to report an adverse event between follow-up visits. Any Serious Adverse Events will be reported to the study's medical monitor and then to the OSU IRB and to NIDA. We will withdraw participants who have a Serious Adverse Event, or become pregnant or begin to breastfeed. The most likely adverse (potential for nicotine overdose) event is anticipated to be rare (<5% in our team's previous studies) and mild (nausea, headache, disrupted sleep), and will be handled quickly (i.e., advice to participant to reduce or stop EC use). Lab studies of toxin exposure suggest that ECs incur no greater risk to health than do conventional cigarettes. Indeed, e-cigarettes generally show lower levels of harmful and potentially harmful constituents. To date, five e-cigarette studies discuss adverse events (3 survey and 2 randomized clinical trials), reporting mild and tolerable side effects that generally resolved completely over time with continued use (90% of cases); the most predominant of which were mouth/throat irritation, cough, and headache. In both randomized clinical trials, no Serious

Adverse Events were reported and the e-cigarette group and the nicotine patch group had comparable levels of adverse events. The most common were mouth irritation, throat irritation, dry cough and headache.

c) Risk of dual use of cigarettes and e-cigarettes: The concern of smokers engaging in dual use is that they will substantially increase their uptake of nicotine, leading to nicotine overdose. The symptoms of nicotine overdose include nausea, vomiting, dizziness, headache, and rapid heart rate. In our previous trials with e-cigarettes, none of the participants reported any indication of nicotine overdose in their dual use of e-cigarettes and conventional cigarettes. In fact, most reduced their level of conventional cigarette use in proportion with their uptake of e-cigarettes. Preliminary analyses (n=20) from another one of our current randomized trials investigating the use of ECs by caregiver's as a means of reducing their children's SHSe (i.e., parents asked to use EC anytime they are in the home, car, or around their child), indicate that caregivers *decreased* in their level of salivary cotinine ($M_{baseline}$=447.9 to $M_{3\text{-}mo}$=314.8). Caregivers' also reported reduction in number of tobacco cigarette per day from baseline to 3-month follow-up ($M_{baselin}$e=19.6 to $M_{3\text{-}mo}$=9.5). Consistent with these findings, parents reported no adverse events, no Serious Adverse Events and specifically no nicotine overdose event.

d) Loss of Confidentiality and Privacy: Confidentiality will be maintained by numerically coding all data, disguising identifying information, and keeping data locked in file drawers or in a secure, password protected database. Names of participants will be kept in separate from participant data. Only study research assistants and the PI will have the information that connects participant's name and ID number. All electronic data will be numerically coded and stored in a password protected database, on a password protected computer in a secure research space. EMA Confidentiality Procedures. The following features are designed to address smartphone/EMA data security issues: 1) the data stored on the smartphone device is in a SQLite database in a sandbox environment where read/write operations are only available through the programming application. No file or output is readable to end users, 2) a password (only known to researchers) is required to authenticate the current user before data can be downloaded from the smartphone device to the server, 3) the web browser application linking the principal investigator's computer to the database is on HTTPS protocol (SSL certificate with encryption) which will guarantee the data transfer from web browser to the backend database is well protected, and 4) the backend database is hosted by the University of Oklahoma Data Center in a secure setup. Participant information will be accessible only to research staff, who are pledged to confidentiality and complete training in the ethical conduct of research (i.e., both HIPAA and CITI trainings). Identifying information will not be reported in any publication.

e) Potential for Undermining Cessation: The study sample is comprised of current smokers who recently failed to quit smoking with the quitline and have not used NRT within the last week. Therefore, we are not asking smokers who are in the process of quitting to stop. Moreover, our previous study of e-cigarette sampling and use among smokers unmotivated to quit smoking suggested that e-cigarette use increased smokers' readiness and confidence to quit smoking. At the end of the study, all participants will be debriefed and educated about ECs and conventional cigarettes. This education will include the information that: a) there is no safe cigarette, b) the best thing a smoker can do to improve health is to quit, c) some ECs are manufactured by the tobacco industry, d) ECs, though able to be regulated by the FDA as a tobacco product, are largely unregulated by the FDA until they are able to develop appropriate guidelines, and e) it is unclear whether ECs reduce the risks associated with smoking. The PI will be available for any questions that participants may have about ECs, smoking, or smoking cessation. It is important to note that the use of ECs incurs no greater harm than if the participant decided on his/her own to use the product. ECs are available online and over-the-counter at various

convenience stores, e-cigarette specialty stores and places where tobacco products are sold. Among those screened and ineligible/uninterested, referral resources for smoking cessation will be provided for those who inquire. Among study participants, information on cessation resources will be provided at the final visit and participants will be told that if at any time during the study they are interested in smoking cessation services, a list of smoking cessation resources will be provided, including reenrollment into the state quitline.

f) Lack of Appropriate Storage of EC/NRT Products: Consistent with Dr. Wagener's previous studies, participants will be instructed to keep their EC/NRT up and away from their children and pets to protect against unintentional poisoning. Only childproof e-liquid cartridges will be provided to participants. Although overdose or accidental ingestion is very unlikely and has not occurred in Dr. Wagener's previous studies, all participants will be provided the state and national poison control telephone line as well as a "tip sheet" on recognizing signs of nicotine overdose. All packets of refill cartridges will also have a sticker placed on them with numbers to the state and national poison control line. It is important to note that in the unlikely event that someone other than the participant uses the EC, this risk would be no greater than if that same individual took the participant's cigarettes.

8. Potential Benefits of the Proposed Research

Whereas no assurance can be made to an individual participant that he/she will personally benefit from this research, the experience should be beneficial. All participants will be encouraged to quit smoking at the completion of the study and will be provided referrals to local cessation resources. Adequate protections are in place in the event of unlikely and mild risks for study participation. Overall, it is expected that the potential benefits to participants in the proposed study outweigh the potential risks.

H. Data and Safety Monitoring Plan

Data will be analyzed initially after 20 participants are accrued, to ensure electronic data capture systems employed (i.e., REDCap, Smartphone/EMA system, and Apollo) are accurately capturing data and to ensure the format and completeness of all data collected.

1. Roles and Responsibilities (Trial Management)

<u>Data Collection Centers:</u>

Center for Tobacco Research at the James Cancer Center at The Ohio State University (CTR-OSU): The CTR-OSU will be responsible for shipping study products, smartphones, and iCO monitors directly to the patient. Additionally, they will be responsible for maintaining data from iCO and Ecological Momentary Assessment (EMA) self-report measures as well as compiling data from other sources of collection. EMAs will be sent to the participants twice daily for 12 weeks and will be prompted and initiated by the phone. EMAs will include self-report measures including recency and frequency of use data for nicotine products, product information, affect, mood, stress, and urge to use, availability of products, motivations, restrictions and alcohol

use. Participants will be requested to use their iCO monitor once daily in the evening which will be prompted through the phone as well. At 12 weeks, if iCO data is unable to be collected, then research staff will mail out saliva collection kit along with instructions. Participants will then mail back to research staff.

Optum/Alere Wellbeing, Inc.: For the purpose of this study Optum will conduct verbal consent and HIPPA procedures as well as self-report measures over the phone with participants during coaching/counseling calls at 0, +14 days, and +4 weeks. Optum is a highly specialized, health risk treatment provider for employers, health plans, and government agencies. With 30 years of developing and delivering scientifically based and proven treatment programs, Optum provides services that support health behavior change and has become a national leader in delivery of evidence-based behavior change programs including tobacco cessation quitlines and weight management treatment.

Optum Service Delivery (SD) Staff: Members of the coaching staff are trained in behavior change strategies based on Social Cognitive Theory. Training includes motivational interviewing, cognitive behavioral techniques, and the evidence-base for tobacco dependence treatment interventions. The comprehensive training curriculum requires each Quit Coach to complete over 240 hours of rigorous training and evaluation before they are qualified to speak independently with participants. Training includes classroom-based training and didactics, experiential exercises, and supervised calls, plus ongoing supervision, call monitoring, and feedback. After completion of the training program, coaches are required to meet ongoing quality and productivity measures. Coaches also receive specialized trainings for working with specific populations (e.g., various ethnic groups, participants with mental illness, youth, and pregnant participants). Quit Coaches are required to have a Bachelor's degree. The Research Implementation Unit (RIU) is a select group of Quit Coaches that have shown exceptional skill. This sub-group of coaches is used for research studies that require non-standard interventions and for conducting research procedures such as conducting informed consent discussions and collecting baseline assessment data and they receive additional human subjects training and training in study specific procedures. The Research Implementation Unit (RIU) coaches will administer all by-phone support to participants enrolled in the study and will be assisted in administering assessments by an electronic data capture system (Apollo) which will provide prompts for the RIU coaches to ensure all items are administered appropriately and consistently to all participants. RIU coaches will also be responsible for obtaining verbal consent and HIPAA for participants at enrollment which will be recorded for surety and protection of the participant.

Human Subjects Training via CITI Program (https://www.citiprogram.org/): All research scientist, project managers, research staff, Service Delivery registration staff, and Quit Coaches are required to complete the CITI Human Subjects Research Training as well as Good Clinical Practices Training. Also, we have Federal wide Assurance (FWA) with DHHS OHRP and the Western Internal Review Board (WIRB) is our IRB of record.

HIPAA Compliance: Optum is a "Covered Entity" as defined by the Health Insurance Portability and Accountability Act (HIPAA). As a Covered Entity, we meet the highest standards for maintaining caller confidentiality. We protect our participants' privacy by implementing and training employees in privacy policies and procedures, securing patient records (electronic and paper), and limiting the use and disclosure of information as required under the rule.

2. Adverse events

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to study product will be recorded on the adverse event page(s) of the Adverse Event Form. For the purpose of this study, hereafter Study Product will be used to refer to e-cigarettes. Events involving adverse Study Product reactions or illnesses with onset during the study should be recorded. Exacerbation of pre-existing illness is defined as a manifestation (sign or symptom) of the illness that indicates a significant increase in the severity of the illness as compared to the severity noted at the start of the trial. It may include worsening or increase in severity of signs or symptoms of the illness, increase in frequency of signs and symptoms of an intermittent illness, or the appearance of a new manifestation/complication. Exacerbation of a pre-existing illness should be considered when a patient/subject requires new or additional concomitant medication or non-medication therapy for the treatment of that illness during the trial. Lack of or insufficient clinical response, benefit, efficacy, therapeutic effect, or pharmacologic action should not be recorded as an adverse event. The medical monitor will be responsible for distinguishing between exacerbation of pre-existing illness and lack of therapeutic efficacy. For all adverse events, the PI will pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a Serious Adverse Event requiring immediate notification to the medical monitor. For all adverse events, sufficient information should be obtained by the PI to determine the causality of the adverse event (i.e., Study Product or other illness). The PI is required to assess causality and indicate that assessment on the Case Report Form. Follow-up of the adverse event, after the date of therapy discontinuation, is required if the adverse event or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator or his/her designated representative.

Serious Adverse Events

All Serious Adverse Events regardless of study product group or suspected relationship to Study Medication must be reported immediately to the medical monitor then to IRB and then to NIDA. A Serious Adverse Event is any adverse study product experience occurring at any dose that: (1) results in death; (2) is life-threatening; (3) results in inpatient hospitalization or prolongation of existing hospitalization; (4) results in a persistent or significant disability/incapacity; or (5) results in congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered Serious Adverse Events when, based upon appropriate medical judgment, they may jeopardize the patient/subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Any Serious Adverse Event or death must be reported immediately independent of the circumstances or suspected cause if it occurs or comes to the attention of the principal investigator at any time during the study through the last follow-up visit required by the protocol or 30 days after the last administration of Study Product, whichever comes later. Any Serious Adverse Event occurring at any other time after completion of the study must be promptly reported if a causal relationship to Study Product is suspected. The only exception to these reporting requirements is Serious Adverse Events that occur during a period in which no study product is administered. For all Serious Adverse Events, the investigator is obligated to pursue and provide information as requested by the OSU IRB in addition to that on the Adverse Event Form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, including concomitant medications and illnesses, must be provided. The PI will ensure that information is reported immediately and

information entered in the Adverse Event Form are accurate and consistent. Event will be reported by online portal for NIDA (https://saetrs.nida.nih.gov/saetrs/view/index.cfm) and FDA (https://www.safetyreporting.hhs.gov/srp2/default.aspx?sid=316ef188-4fb7-4100-968f-c6a6c72058d0), by telephone, or other means.

Preventing and Limiting Adverse Events

We will monitor for risk of using e-cigarettes and NRT by screening participants for general medical precautions. The most likely adverse event (potential for nicotine overdose) is anticipated to be rare and mild based on the PI's previous studies, and will be handled quickly (i.e., advice to participant to reduce or eliminate nicotine use). Lab studies of toxin exposure suggest that e-cigarettes incur no greater risk to health than do combustible cigarettes. The PI and study personnel will be available for any questions that participants may have about e-cigarettes, NRT, smoking, or smoking cessation. Participants will be provided a study phone and data plan at no cost, to contact study personnel at any time. Any adverse events, breaks of confidentiality, or any other data or safety issues that arise will be discussed immediately between study personnel and the PI.

Collection of Adverse Events

The collection of adverse events will be on a self-report basis and logged within an electronic data capture system (REDCap) or collected using standardized paper forms and will only be identified with the study's ID of the participant.

Adverse Event Reporting Timelines

- All intervention staff are required to notify the PI of any Serious Adverse Events immediately.
- All Serious Adverse Events will be reported immediately to the medical monitor who will determine their severity and appropriate action or response.
- In accordance with current standard procedure, the PI will notify the OSU IRB of all Serious Adverse Events within 24 hours.
- In accordance with new policy and procedure, the PI will notify the National Institutes of Drug Abuse of all Serious Adverse Events within 72 hours.
- All Non-serious AEs will be reviewed weekly by the medical monitor or PI, for categorization and possible action.

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Verbal Consent to Participate in Research

I, (Quit coach's/OSU Study Team Member'sname), am reading a verbal consent script that explains the REACH Study and Data Repository. The consent will take about 15 minutes. You will be sent a paper version of this information if you decide to participate. Feel free to ask questions before making your decision whether or not to participate.

This research study has been approved by an Institutional Review Board at The Ohio State University.

You are being asked to take part in this study because you are a smoker who has not yet stopped smoking using the current [Oklahoma/South Carolina] treatment. The purpose of this study is to see how effective other methods may be in helping you stop smoking. Your participation is your choice and you can stop being in the study at any time. There will be no penalty to you if you decide not to take part in the study. Your decision will not affect your future relationship with the [Oklahoma/South Carolina] or The Ohio State University (OSU).

The study investigator may end your participation in this study without your consent. Up to 420 participants will take part in this study.

If you decide to participate, you will be enrolled in the study for 16 weeks, instead of receiving usual [Oklahoma/South Carolina] services. If you agree to participate in the study, you will not be able to access the [Oklahoma/South Carolina] services you were previously receiving until 16 weeks after starting the study. In the study, you will receive 3 counseling calls from research study coaches. Counseling sessions will last 10-15 minutes. If you do not complete the first study coaching call, then you will be removed from the study, and you will not receive study benefits or services. If that occurs, you will still be eligible for standard [Oklahoma/South Carolina] services.

You will be randomly assigned to receive an 8 week supply of a study e-cigarette or nicotine patch and lozenge, split over 2 shipments. You will receive your first shipment after your first coaching call and your second shipment only after completing your second study coaching call.

You will be asked to complete an initial survey today, and two follow-up surveys over the phone. The follow up surveys will take about 30 minutes each.

You will be sent a study smartphone with free phone service for the duration of the study. You will complete short, 2 minute, daily surveys about your tobacco use, and daily breath tests with the phone. The phone should be used for study use only and you will be responsible for any personal information you add or exchange on your phone. If breath tests are unable to be competed at 12 week assessment, then a saliva kit will be mailed to you along with instructions.

You will be paid for your time and effort in this study. The amount you will be paid will depend on which surveys you complete. You can earn up to $75 for completed surveys and up to an additional $255 for the daily surveys and breath tests on the smartphone, for a total of $330. For daily assessments (2 per day), you will be paid based on the percentage you complete. Completion of 50-79% will earn $45, 80-89% will earn $70, and ≥90% will earn $85 at the Week 4, Week 8, and Week 12 study periods, up to $255 during the 12-week active study period. You will be compensated up to $25 at Baseline, $85 at Week 4, $110 at Week 8 and $110 at Week 12 study periods.

You may benefit from taking part in the study by having another opportunity to reduce or stop your smoking.

The risks of the study include discomfort in answering questions about your smoking or health, potential loss of privacy and risks associated with using the study products. You do not have to answer any questions that you do not want to and can stop a survey at any time.

Everything you say will be kept private. All information will be kept in locked file cabinets and on secured computers. Only study staff will be able to look at your study information. Reports on findings from this study will not use your name and will only report results as a group. We are required to protect the privacy of your health information.

E-cigarettes, including the study e-cigarette, contain nicotine. E-cigarettes are known to produce substances that can be toxic to humans. However, using an e-cigarette has not been shown to cause any increased harms to your health beyond cigarette smoke to smokers, and e-cigarettes are likely much less harmful than cigarettes. E-cigarette potential side effects include nausea, headache, disrupted sleep, cough, diarrhea, heartburn, and hiccups. Pods for the e-cigarette are sealed and contain liquid nicotine. Liquid nicotine could pose a poison risk, especially to children and pets if ingested. If stored improperly, overheating, fire, and/or explosion of the device may occur, leading to burns and possibly death. Risks related to long-term e-cigarette use are unknown.

The risk of side effects and harms to your health from the nicotine patch and lozenge is very low. These products are FDA-approved for smoking cessation. Possible side effects for the nicotine patch include irritation or redness on your skin, dizziness, headache, nausea, racing heartbeat, muscle pain or stiffness, or problems sleeping. Possible side effects for nicotine lozenges include coughing, gas, heartburn, trouble sleeping, nausea, hiccups, or racing heartbeat.

While rare, nicotine overdose is a possible risk of using any nicotine-containing products. Participants should stop using the study products and seek medical attention if any of these symptoms occur: you develop persistent indigestion; severe sore throat; irregular heartbeat or palpitations occur; severe allergic reaction (rash, hives, itching, difficulty breathing, tightness in the chest, swelling of the mouth, face, lips, or tongue); fast or irregular heartbeat; pounding in the chest; severe diarrhea, dizziness, nausea, vomiting, or weakness.

If you are a female, you must not be pregnant and should not become pregnant nor breast-feed an infant while in this study. Using nicotine and/or tobacco products while you are pregnant or breastfeeding may involve risks to an embryo, fetus, or infant, including birth defects that are currently unforeseeable. If you become pregnant or suspect that you are pregnant while in this study, tell the study staff immediately. The study staff will mail you a pregnancy test. If pregnancy is confirmed, you may be withdrawn from the study.

The Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA) and several states, and federal health departments investigated a multi-state outbreak of severe lung disease associated with vaping. Tetrahydrocannabinol (THC)-containing vaping products, particularly from the black market and other informal sources, were linked to most cases and played a major role in the outbreak, while nicotine containing e-cigarette vaping did not appear to play a major role. The investigation is ongoing but has identified vitamin E acetate added to THC liquid cartridges and pods as the likely cause. We recommend that you use only the products that we provide you during your time in this study and do not add any substances to the e-liquids or alter the device in anyway.

If you suffer an injury from taking part in this study, you should notify the study team after you have contacted a medical professional. The cost for this treatment will be billed to you or your medical or hospital insurance. OSU has no funds set aside for the payment of health care expenses for this study.

If we find information that significantly impacts your health, we will share it with you. If new information found during the study may affect your decision to take part in the study, we will provide it to you.

Every effort will be made to keep your study information confidential. However, there may be times when this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law. Your records may be reviewed by the following groups: Office for Human Research Protections, U.S. Food and Drug Administration, The Ohio State University Institutional Review Board or Office of Responsible Research Practices, and the National Institute on Drug Abuse.

Study staff at OSU, Optum/Consumer Wellness Solutions Inc. and the University of Oklahoma Health Sciences Center may have access to your contact and study information.

Your de-identified study information may be used or shared with other researchers without your additional informed consent. This means we would not share your name or any information that could identify you.

Unless you withdraw your permission to use your health information, there is no date your permission ends. Study information may be analyzed for many years and will be stored indefinitely. It is not possible to know when this will be complete. You may withdraw from the study or take away your permission to use and disclose your health information at any time. If you withdraw your permission, you will not be able to stay in this study. Agreeing to this authorization also means that you may not be able to see or copy your study-related

information until the study is completed. If you decide not to give permission to use and give out your health information, then you will not be able to be in this research study.

If you have any questions about the research, please contact the Reach Study staff at 844-744-2447. If you have questions about the study results, contact Theodore Wagener, PhD, theodore.wagener@osumc.edu, 614-366-4625. If you have any complaints about participation in this project, you may contact the Office of Responsible Research Practices at 1-800-678-6251. If you have any questions relating to your privacy rights, please contact a privacy officer at 614-293-4477.

If you change your mind about taking part in this study after you complete the initial study survey, you can contact Reach staff by email at reach-study@osumc.edu or by phone at 614-314-6531 or 1-844-744-2447. Staff may ask if you want to withdraw from the entire study or parts of it.

Do you have any questions? **(Give individual time for questions)**

We will now ask for your verbal consent for the Reach Study.

Do you agree to participate in the Reach Study? **(Wait for agree or disagree; Response will be documented)**

- Yes

- No

(*If NO, state the following):* Ok. Thank you for taking the time to learn about the study. You will not be enrolled in the study. If you still have time now we can complete a standard coaching call to see how your quit is going. ***(Close out consent and complete standard coaching call with participant.)***

(***If YES, proceed to Repository consent)***:

We would also like to ask if you would allow your study information to be stored and used for future research. There are no direct benefits to you. Allowing us to store and use your data in other studies could help other smokers in the future. You can still participate in the Reach Study, even if you choose to not have your study information stored.

No additional cost or time is required to participate in the Repository. No additional payment is provided. We cannot predict how many times, if any, you might be contacted about future studies. Future studies may benefit you. You may request to stop being contacted at any time.

If you decide you do not want to have your study information stored, you may contact Reach Study staff by email at reach-study@osumc.edu or by phone at 614-314-6531 or 1-844-744-2447.Your data will not be used for future research.

Do you have any questions? **(*Give individual time for questions*)**

Do you agree to have your study information stored? **(*Wait for agree or disagree; Response will be documented*)**

- Yes
- No

(If YES to study consent and YES to Repository): Thank you for agreeing to participate in the study and the Repository. You will be mailed a copy of this consent document.

(If YES to study consent and NO to Repository): Thank you for agreeing to participate in the study. Since you did not agree to take part in the Repository, your information will not be stored in the repository, though as I stated before, you are still enrolled into the study even if you choose not to participate in the Repository. You will be mailed a copy of this consent document.