University of Kansas Medical Center
RESEARCH PROTOCOL INVOLVING HUMAN SUBJECTS
TEMPLATE WITH GUIDANCE

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Study Title: Impact of e-cigarette training on puff patterns, cigarette smoking, and health outcomes among smokers with COPD

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I. Purpose, Background and Rationale

A. Aim and Hypotheses

Nearly 9 out of 10 chronic obstructive pulmonary disease (COPD) deaths in the United States (US) are attributed to smoking. Most (>90%) smokers with COPD are interested in quitting but success rates are very low; only about 12% are able to quit with FDA-approved medications as part of a clinical trial and far fewer (<5%) quit following brief advice to quit. An alternative approach for smokers who cannot or will not quit with first-line therapies is tobacco harm reduction, or transitioning smokers to potentially less harmful products (e.g., e-cigarettes). E-cigarettes (ECs), when used consistently and exclusively, help smokers quit and reduce tobacco-related harms. This is particularly true for smokers with COPD who report significant reductions in COPD exacerbations, improved lung function, and quality of life after switching to ECs. However, the extent of harm reduction is directly related to the degree of switching (i.e., reduction in CPD). Most smokers who transition to ECs make a partial switch to EC (i.e., dual users) and, while they experience harm reduction benefits relative to continued smoking, the benefit is less than those who completely switch. To reduce harm among high-risk smokers with COPD who are unable to quit with first-line therapies, there is an urgent need to understand how training smokers on the optimal EC puff pattern can be optimized to facilitate a complete or predominant pattern of EC use among smokers with COPD. The alternative for these smokers is continued smoking of, arguably, the most harmful tobacco product on the market and imminent disease progression.

Our long-term goal of our research is to decrease tobacco-related disease burden among high-risk smokers unable to quit using standard methods. The overall objective of this application is to evaluate the impact of EC training on changes in puff patterns, nicotine craving and exposure, cigarette smoking, and improvements in COPD-related health effects among smokers with COPD who have been unable to quit smoking using pharmacotherapy. Our central hypothesis is that training on optimal puff behavior with ECs (compared to brief advice to switch to ECs) will result in a greater proportion of patients predominantly using ECs and a greater reduction in COPD-related health effects. Furthermore, greater dose of intervention will result in amplified effects. Our central hypothesis has been formulated on the basis of our preliminary data, which suggest that 1) smokers with COPD have a particularly difficult time quitting, 2) smokers with COPD have high levels of interest in using ECs, and 3) predominant EC users engage in distinct puff patterns compared to continued smokers; this puff pattern can be 'trained' and results in higher rates of switching to EC.

Smokers with COPD, stratified by EC naïve and current dual users, who are unwilling to make a pharmacotherapy-assisted quit attempt but that are willing to use ECs will be randomly assigned to receive 1) brief advice to switch to ECs at baseline, 2) a single session of training on optimal EC puffing and use at baseline, or 3) enhanced EC training on optimal EC puffing and use at baseline, day 3, and wks 4, 8, and 12. Participants will complete a human laboratory assessment of EC use patterns and a complementary 12-week RCT of real-world smoking and EC use patterns. The human lab trial will be conducted over two visits to assess acute changes in puff patterns and nicotine craving and exposure. The RCT will provide real-world data on changes in cigarette smoking, COPD-related health effects, and EC puff patterns.

1. Our specific aims are:

   Aim 1: Understand differences in acute (i.e., in-lab) changes in puff patterns (i.e., puff duration), cigarette craving, and nicotine exposure from pre- to post-EC training/brief advice between smokers who received brief advice versus EC training (single episode and enhanced EC training arms combined). Smokers who receive EC training will show greater increases in puff duration compared to brief advice (*H1a*), greater reductions in cigarette craving compared to brief advice (*H1b*), and greater increases in nicotine exposure compared to brief advice (*H1c*).

   Aim 2: Determine the longer-term impact of EC training and training dose on switch patterns (i.e., % predominant EC users), health effects (i.e., changes in cardiovascular health, functional activity, lung function) and puff patterns. In a dose response pattern, enhanced EC training will result in the greatest proportion of predominant EC users at Wk12 (*H2a*), the greatest improvements in health outcomes at Wk12 (*H2b*), and the greatest increases in puff duration from baseline to Wk12 (*H2c*) followed by single session training and brief advice.

B. Background and Significance

Cigarette smoking among patients with chronic obstructive pulmonary disease (COPD): Over one third of smoking-related deaths are a result of COPD and up to 90% of COPD cases are caused by smoking.[1] COPD is associated with profoundly reduced quality of life due to symptoms including wheezing and sleep disturbance.[2] Therefore, the benefits of quitting smoking and symptom reversal are enormous for this population. Despite these potential benefits, about 40% of patients with COPD continue to smoke.[3] The majority of smokers with COPD report interest in quitting smoking[4] but when offered pharmacotherapy, only 12-14% succeed in a sustained quit, indicating that smokers with COPD have a very difficult time quitting.[5]

Electronic cigarettes (ECs) and tobacco harm reduction for smokers with COPD: Evidence indicates that ECs are less harmful compared to combustible cigarettes.[6] In their consensus statement, the National Academies for Science, Engineering, and Medicine concluded that there is "conclusive evidence" that completely switching to ECs reduces smokers' exposure to toxicants carcinogens, or cancer-causing substances.[6] While there are no long-term studies of cancer risk due to EC use, mounting evidence from in vivo and in vitro studies suggests reduced cancer risk from ECs compared to cigarettes.[1,2] For smokers that are unable or unwilling to quit combustible smoking, the question is whether ECs offer a reduction in harm (not elimination of harm) compared to cigarettes. For smokers that are unable or unwilling to quit nicotine and tobacco use, completely switching to ECs likely reduces their cancer-risk.[3] Moreover, smokers with smoking attributable diseases, like COPD, who already experience a heightened risk due to continued smoking, may experience the greatest benefit from making a complete switch from combustible cigarettes to ECs.[4] In randomized trials, ECs have resulted in better quit rates compared to control and NRT.[7,8] In a prospective, non-randomized study of COPD smokers who switched to ECs or continued smoking, EC users showed a significant reduction in COPD exacerbations and

improvements in lung function and measures of quality of life.[9] These data indicate ECs may be a promising harm reduction tool for smokers with COPD that have been unable to quit.

Factors associated with successful switching: One primary factor that predicts successful switching is EC puff behavior. The experience of vaping differ significantly from the experience of smoking cigarettes, resulting in a learning curve to achieve sufficient nicotine delivery. Cross-sectional studies of exclusive EC users indicate that they are able to extract more nicotine from ECs compared to naïve or dual users.[10-12] Existing research shows that smokers who successfully switch to ECs take longer puffs compared to those who only partially switch, suggesting that smokers who are successful in switching naturally learn how to effectively puff on an EC. It remains unknown whether smokers can be trained on optimal puff behavior.

C. Rationale

Studies by our team[13] and others show that smokers who achieve predominant or exclusive EC use have unique puff patterns compared to continued smokers (i.e., greater puff duration).[13-16] Smokers who switch to ECs and become predominant or exclusive EC users adapt their puff patterns within 1 week by taking longer, slower puffs.[14] While no studies have examined methods for training smokers on optimal topography, one study showed that a slight variation in instructions to switch resulted in reduced smoking.[15]

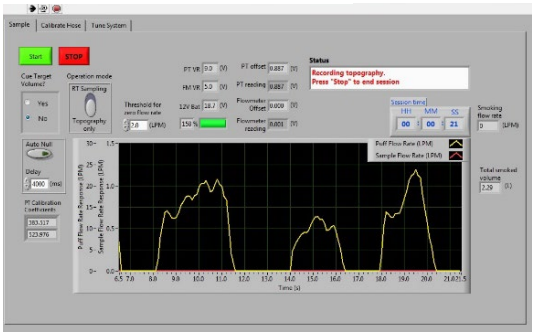
This study is innovative in the following ways. First, the study will enroll a high-risk population of smokers that is not only understudied but stands to experience marked improvements in health and quality of life from quitting smoking. The alternative for these smokers is continued smoking of the most harmful tobacco product on the market and imminent disease progression. Second, the concept of providing training on optimal use of ECs is innovative. Despite evidence that those who successfully switch to ECs show distinct topography patterns compared to EC "failures", no studies have attempted to train on optimal use. This strategy pulls from the NRT literature[17,18] and posits that a similar form of training on "optimal" use will increase EC effectiveness of facilitating switching and reduce smokers' tobacco-related harm.

D. ECs and E-liquid

The Evolv Reflex EC (Figure 1) will be used for the proposed study. Our team has conducted three validation studies with the device and embedded software. It is both a highly effective EC and a topography device that tracks and stores all facets of information about the participant's use of the product, including puffing topography which we view as a great strength. See Figure 2 for an example of the topography feedback provided by the device. The device has the capacity to store 4 weeks of data between in-person visits. We will use the eScribe topography software available specifically for this device. In addition, we will use a secondary topography device (eTop device) during in-person lab-based visits in order to correlate topography from the two devices. Our team has used the eTop device in numerous past trials. The Reflex device is a pod-based device and is compatible with nicotine salt and freebase nicotine e-liquid. We will use commercially available nicotine salt e-liquid in 5% nicotine concentration. The e-liquid has been tested by Drs. Salathe and Kim at KUMC Department of Internal Medicine to independently confirm the e-liquid concentration is within 1% of the advertised levels. We considered other concentrations but chose 5% because it is the most commonly used concentration among

Figure 1. Reflex EC

Figure 2. Example topography



market leaders like JUUL, has demonstrated high appeal[5] and cigarette-like levels of nicotine delivery among smokers,[5-8] and high rates of switching.[9] For the human lab portion of the study, participants will be provided a pre-filled pod for each visit. For the RCT, we will provide pre-filled pods in 4-week increments. If participants cannot tolerate the Evolv Relfex, we will offer a choice of JUUL or Vuse devices. JUUL and Vuse are pod based systems. We will offer menthol or tobacco flavors in 5% or 3% concentration.

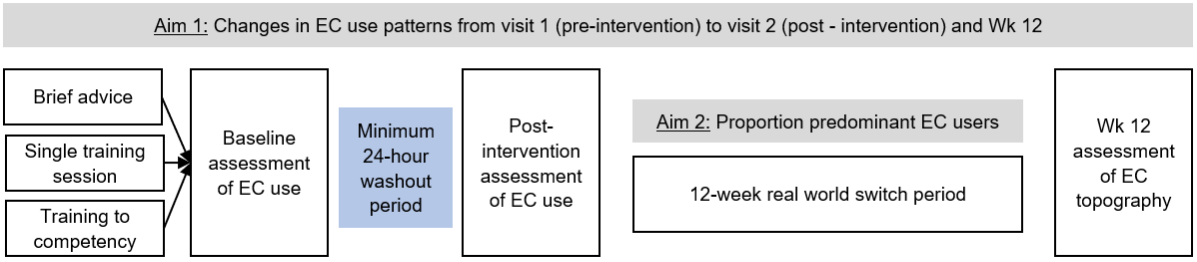
II. Research Plan and Design

A. Study Objectives: The overall objective of this application is to evaluate the impact of EC training on changes in puff patterns, nicotine craving and exposure, cigarette smoking, and improvements in COPD-related health effects among smokers with COPD who are unable to quit smoking using pharmacotherapy.

B. Study Type and Design: The proposed study is an open label randomized clinical trial of EC training and training dose among smokers with COPD. Smokers with COPD (n=45) stratified by EC use history (naïve vs. current use) will be randomized (1:1:1) to receive brief advice to switch to ECs, single session EC training, or enhanced EC training. Participants will complete an in-lab assessment of pre-intervention EC puff patterns followed by intervention and a follow-up assessment of resultant changes in EC puff patterns. Visits will be separated by a standard minimum 24-hour washout period. Participants will complete a final assessment of EC puff patterns at Wk 12. Immediately following completion of the second human lab visit, participants will receive 12 weeks of EC and assistance with switching, based on treatment allocation. Participants will complete in-person follow-up assessments throughout the 12-week switch period and those in the enhanced training arm will receive ongoing training.

Participants will remain abstinent from nicotine/tobacco for 12 hours prior to each study visit. Abstinence will be verified by eCO (>12 ppm.[24] Self-report will be used for EC abstinence, as there is currently no objective, reliable measure to verify non-use of these products within the time the participants will be in the lab. Participants will be provided the device of their choice with either tobacco or menthol flavored e-liquid or pods. Participants will puff ad libitum for 30 minutes to establish baseline levels. Throughout the session, puff topography will be measured. Blood sampling for changes in nicotine levels will occur at -5 minutes (pre-vaping session) and +30 minutes (immediately post-session). At the end of Human Lab Visit 1, participants will receive training on the EC based on intervention allocation. Human Lab Visit 2 will be identical to Visit 1 but will not include additional EC training. Human Lab Visit 3 (~Wk 12) will be identical to Visit 2 and will measure longer-term changes in EC puff patterns. The Evolv Reflex EC has the capacity to track and store 4 weeks of data about a participant's use of the product and puffing topography between in-person visits. eScribe topography software will be used for the device. The JUUL and Vuse devices do not collect data. Because daily use of EC is consistently one of the best predictors of exclusive EC use,[10] we will reinforce this pattern across sessions within the enhanced EC training arm and problem-solve barriers related to daily use.

Figure 1: Overall study flow



C. Sample size, statistical methods, and power calculation

1. 45 eligible smokers with COPD will be stratified by EC use history (naïve vs. current use) and randomized (1:1:1) to receive brief advice to switch to ECs, single session EC training, or enhanced EC training. Randomization will be determined by computer-generated random numbers. After baseline data collection has been completed, the research assistant will select the sequential study ID number to determine the randomization assignment.

2. This is an open-label trial. There is no blinding involved.

3. Based upon preliminary data, the standard of change in puff duration over two weeks was 1.5 seconds per puff. Assuming a common standard deviation across groups, 15 participants will allow us to obtain a 95% CI with a margin of error of 0.76 for the mean change for brief advice. In the acute phase (i.e., human lab visits 1 and 2), the single episode and enhanced EC training arms will have the same amount of intervention and will be combined. Thus, 30 participants will allow us to obtain a 95% CI with a margin of error of 0.54 for the mean change in puff duration in the combined intervention groups. We also wish to estimate the proportion of subjects who are predominant or complete switchers at Week 12. Fifteen participants in each group will allow us to estimate the 95% CI for the proportion of switchers in each group with a margin of error no greater than 0.25. This data will allow us to determine the sample size needed for a fully powered randomized trial. For the purposes of the current study, we will need 15 complete cases for each group. Due to potential attrition, we will recruit up to 22 participants per group. We will discontinue recruitment when we have 15 complete cases per group.

D. Subject Criteria (See Vulnerable Populations appendix, if applicable): Participants will be adult smokers ≥21 years old and diagnosed with COPD. The study will be open to both men and women. We have chosen to focus on participants with COPD who are unable to quit smoking using pharmacotherapy because their unique smoking profile places them at a high-risk population of smokers that is understudied and stands to experience marked improvements in health and quality of life from quitting smoking. Women who are pregnant, plan to become pregnant, or are breastfeeding will be excluded from the study because tobacco products will be provided, and smoking is associated with low birth weight and premature labor. Children and those <21 years old will be excluded because the minimum age for purchasing tobacco products is 21 years old.

1. Inclusion criteria:

Smokers:

COPD, ≥21 years old, speak and understand English, smoke on >25 of the last 30 days for the past 3 months, willing to switch from cigarettes to the study e-cigarette for the duration of the study. Have tried but failed to quit smoking in the last year, unwilling to make a pharmacotherapy-assisted quit attempt in the next 30 days,

willing to complete six in-person study visits, willing to have blood drawn, have reliable transportation to attend all in-person assessments, have a working phone number, and plan to remain in the Kansas City area for the full duration of the trial.

Dual users:

COPD ≥21 years old, speak and understand English, smoke on ≥15 days of the last 30 days for the past 3 months, willing to switch from cigarettes and their own e-cigarette to the study e-cigarette for the duration of the study, use an EC on >15 days of the last 30 days for the past 3 months, have tried but failed to quit smoking in the last year, unwilling to make a pharmacotherapy-assisted quit attempt in the next 30 days, willing to complete six in-person study visits, willing to have blood drawn, have reliable transportation to attend all in-person assessments, have a working phone number, and plan to remain in the Kansas City area for the full duration of the trial.

2. Exclusion criteria:

Smokers:

Use of tobacco products other than cigarettes including e-cigarettes in the past 30 days, current use of cessation medications, pregnant, planning to become pregnant, or breastfeeding, recent history of cardiovascular or pulmonary events in the past 3 months, household member current or previously enrolled in the study, weekly use of an EC over the last 6 months

Dual Users:

Use of tobacco products other than cigarettes and e-cigarettes in the past 30 days, current use of cessation medications, pregnant, planning to become pregnant, or breastfeeding, recent history of cardiovascular or pulmonary events in the past 3 months, household member current or previously enrolled in the study

3. Withdrawal/Termination criteria:

Participants will be instructed to present to the lab nicotine deprived (12 hours abstinent) for the first study visit. If participants present to the first study visit with an eCO >12 ppm or they report other nicotine use on two separate study visits, they will be withdrawn from the study (i.e., participants will be rescheduled one time).

4. Participants will not be allowed to participate in another research study that aims to alter their tobacco use during this research study.

E. Specific methods and techniques used throughout the study

1. Laboratory tests: At the beginning and end of the vaping session at Human Lab visits 1, 2, and 3 (~week 12), blood will be collected for nicotine analysis via a blood draw from the participant's arm. If deemed necessary by the study nurse (CRU staff) or by the participant, an IV catheter may be placed for blood draws. Blood sampling for changes in nicotine levels will occur at -5 minutes (pre-vaping session) and +30 minutes

(immediately post-session). No more than 7 mL of blood will be drawn per draw (≤14 mL per visit). Blood will be processed and analyzed for nicotine and cotinine levels.

Human Laboratory Assessments (see Table 1 for timing):

Topography will be used to objectively and passively measure EC puff patterns. Topography is a measure of substance self-administration[11,12] and has been used successfully by our team in past trials.[13-16] Topography will be used in three ways: 1) in lab-based EC vaping sessions as an outcome variable, 2) within the intervention as outlined above, and 3) in the natural environment throughout the RCT.

Table 1. Measures by timepoint

		Human Lab				RCT	
Measure	**SCRN**	**V1**	**V2/W0**	**W4**	**W8**	**W12**	**V3**
Topography*		X	X	X	X		X
Nicotine boost		X	X				X
eCO	X	X	X	X	X	X	
7-day TLFB	X	X	X	X	X		X
Health effects							
Spirometry		X					X
COPD Gold Staging	X						X
CAT	X			X	X		X
Pulse wave velocity		X					X
Beat to beat blood pressure		X					X
6MWD		X					X
Other self-report							
Cigarette craving/withdrawal		X	X				X
mCES				X			X
Subjective effects of EC		X	X				X
Behavioral intentions	X			X			X

Notes. Topography measured throughout 12-week switching period

Nicotine boost. At all three visits, blood samples will be collected at -5 (baseline) and +30 minutes (post-session). Samples will be analyzed according to standardized methods by Dr. Na Zhang at KUMC. Blood will be analyzed for nicotine levels to assess nicotine "boost" (i.e., change in nicotine level pre- to post-session) achieved during the EC sessions.

eCO will be measured at final screening and all human lab visits. A >50% reduction in eCO from initial screening will indicate compliance with 12-hour abstinence from smoking.[17] eCO is collected by having the participant take a deep breath in and hold it for 15 seconds and then exhaling into a straw.

Cigarette craving/withdrawal. The self-reported Tiffany-Drobes Questionnaire on Smoking Urges – brief (QSU-brief)[18,19] and Minnesota Nicotine Withdrawal Scale (MNWS)[20] will measure changes in cigarette craving and nicotine withdrawal from pre- to post-session.

Other self-report assessments. The modified self-reported Cigarette Evaluation Scale (mCES)[21] will assess subjective effects and sensory experiences at the end of each session. Participant's intentions for future use (e.g., purchase, use) of ECs will be assessed using a 4-item measure.

RANDOMIZED TRIAL OF EC TRAINING

RCT Assessments (see Table 1 for timing):

Cigarette smoking. Cigarette smoking will be assessed at W0, W4, W8, and W12 using the Timeline Followback (TLFB)[22,23] in which individuals report on number of cigarettes per day (CPD) in the past 7 days.

eCO levels will be used to biochemically confirm smoking status. eCO <6 ppm will indicate a complete switch.[24]

Respiratory health and lung function. The COPD assessment test (CAT)[25] is a COPD-specific 8-item questionnaire designed to assess impairment in health status of COPD patients. Participants will complete the CAT at baseline and Wks 4, 8, and 12 to assess changes in self-reported respiratory health. Lung function will be assessed via spirometry.

6-minute walk distance (6MWD)[26,27] will assess changes in functional activity. The 6MWD assesses an individual's overall ability to conduct everyday activities and will be conducted at baseline, W4 and W12. This measure is particularly responsive to change in smokers with COPD. Specifically, improvements in 6MWD have been found within xx weeks of smoking reduction in smokers with COPD [ref].
Changes in cardiovascular functioning will be measured using Pulse Wave Velocity,[28,29] a sensitive measure of arterial stiffness that shows rapid (~1 month) changes with switching to ECs, at baseline and W12. In addition, we will assess changes in beat-to-beat blood pressure from baseline to W12. Beat-to-beat blood pressure is a sensitive measure of blood pressure and vascular elasticity. Measures of cardiovascular functioning will be conducted by Dr. Sandra Billinger and her team. These measures are sensitive to changes in smoking and vaping status and are associated with downstream health outcomes that result from smoking, such as cardiovascular disease.

2. Study Procedures:
    a. **Initial Screening:** The initial screening will review inclusion/exclusion criteria by phone or online screener. Those eligible will be scheduled to complete an in-person visit within 14 days.
    b. **Final Screening (Day 0):** Participants will be instructed to smoke and vape as they normally would before the final screening. Final eligibility screening will be conducted in-person and will consist of a pregnancy test, exhaled carbon monoxide (eCO), providing evidence of EC use (bring EC to visit; dual users only), and obtaining informed consent. Participants will complete carbon monoxide (CO) measurement to confirm current smoking status (CO > 12 ppm). CO is collected by a simple, non-invasive breath test that involves the participant holding their breath for ~15 seconds and then exhaling into a straw connected to the CO monitor. Cigarette smoking will be assessed using the Timeline Followback (TLFB) in which individuals report on number of cigarettes per day (CPD) in the past 7 days. To assess baseline self-reported respiratory health, participants will complete the COPD assessment test (CAT). The modified Cigarette Evaluation Scale (mCES) will assess subjective effects and sensory experiences at the end of the session. Participant's intentions for future use (e.g., purchase, use) of ECs will be assessed using a 4-item measure. Participants will sample two e-liquid flavors (Menthol and Tobacco) to establish preference. Participants will go home with their device and e-liquid of choice to practice at home. Participants will complete baseline measures. Participants will be compensated $10 for the final screening.
    c. **Human Lab Visit 1 (1-14 days after Final Screening):** At Human Lab Visit 1, participants will be re-screened according to inclusion/exclusion criteria. Pregnancy exclusion will be confirmed at each visit. They will be instructed to remain nicotine abstinent for 12 hours prior to the visit. Participants will complete CO measurement to confirm tobacco/nicotine abstinence. Participants will be provided with an overview of the study, and complete additional baseline self-report measures. Self-report will be used for EC abstinence, as there is currently no objective, reliable measure to verify non-use of these products within the time the participants will be in the lab. Cigarette smoking will be assessed using the TLFB in which individuals report on number of CPD in the past 7 days. Participants will be provided the device of their choice and pre-filled pod of their preferred e-liquid flavor. Participants will puff ad libitum for 30 minutes to establish baseline topography levels. Throughout the session, pre-intervention puff topography will be measured via a pressure sensor attached to the device/product and by the integrated topography software within the EC. This will not require anything additional of the participant. Blood sampling for changes in nicotine levels will occur at -5 minutes (pre-vaping session) and +30 minutes (immediately post-session). Self-reported levels of cigarette craving and withdrawal will be measured

using the Tiffany-Drobes Questionnaire on Smoking Urges – brief (QSU-brief) and Minnesota Nicotine Withdrawal Scale (MNWS) pre- and post-session. The mCES will assess subjective effects and sensory experiences at the end of each session. Participant's intentions for future use (e.g., purchase, use) of ECs will be assessed using a 4-item measure. At the end of the baseline vaping session, participants will be randomized and enrolled (stratified on EC history) to one of three study arms in a 1:1:1 fashion: 1) Brief Advice, 2) Single Episode Training, 3) Enhanced EC Training. See the Training Guild for Researcher for specific training. For the Brief Advice study arm, participants will be given brief advice to switch to the EC and basic instructions on use of the EC and refilling pods. Participants will view their topography post-intervention via the Escribe software while they puff. Based on our preliminary data, trained research staff will give feedback on puff parameters shown to differ between complete switchers and switch "failures" – puff duration, flow rate, inter-puff interval, and puff number. The session will last ~30 minutes. For the Enhanced EC training study arm, participants will receive the same training as the Single Episode Training arm. Participants will be asked to set a switch date using the Action Planning form. Participants will take the EC device home and use it as much or as little as they would like before the next visit. Lung function will be assessed via spirometry. At the end of the visit, a 6-minute walk distance (6MWD) test will be done to assess the participant's overall ability to conduct everyday activities. Baseline cardiovascular functioning will be measured using Pulse Wave Velocity, a sensitive measure of arterial stiffness that shows rapid (~1 month) changes with switching to ECs. Baseline beat-to-beat blood pressure will be measured to assess blood pressure and vascular elasticity. Participants will be compensated $50 for this visit.

d. **Human Lab Visit 2 / RCT Visit – Week 0 (1-5 days after Human Lab Visit 1):** Human Lab Visit 2 will occur 1-5 days after Human Lab Visit 2. Human Lab Visit 2 will be identical to Visit 1 but will not include any training, 6MWD test, or cardiovascular assessment. The purpose of this visit is to assess changes in topography following training at visit 1. Participants will be compensated $50 for this visit.
e. **Between Week 0 and Week 4:** Participants will be provided with the device of their choice and pre-filled pods to use between visits for the real-world switch period. If chosen, the Evolv Reflex EC device will collect and store 4 weeks of data on the participant's EC use patterns and puffing topography. The JUUL and Vuse devices do not collect data. Research staff will conduct a brief phone check in with all participants on their switch date. During this call, a trained research assistant will assess tobacco and nicotine use since the last visit and will briefly trouble shoot barriers to switching to the e-cigarette.
f. **RCT Visit – Week 4:** At Week 4 topography data will be downloaded from the EC and reviewed. In addition, participants will return their used and unused pods which will be weighed to assess e-liquid consumption between visits. Those in the Brief Advice and Single Session Training arms will not receive additional training. For those in the Enhanced Training arm, they will receive additional real-time feedback on their puff patterns. This arm is intended to mimic the level of support provided to smokers making a quit attempt using traditional quit smoking strategies and to determine the minimum level of support necessary to achieve a pattern of predominant EC use. Our approach with this arm is intentionally flexible to match the needs of each participant over the course of behavior change. For the purposes of rapport-building and continuity of care, attempts will be made to have participants meet with the same staff member each session. For participants in all study arms, the following will be done. Topography will be used to objectively and passively measure EC puff patterns. Participants will again complete eCO measurement to confirm smoking status. Cigarette smoking will be assessed using the TLFB in which individuals report on number of CPD in the past 7 days. To

assess changes in self-reported respiratory health, participants will complete the CAT. Lung function will be assessed via spirometry. Self-reported levels of cigarette craving and withdrawal will be measured using the Tiffany-Drobes QSU-brief and MNWS. The mCES will assess subjective effects and sensory experiences at the end of each session. Participant's intentions for future use (e.g., purchase, use) of ECs will be assessed using a 4-item measure. At the end of the visit, participants will be provided another 4-week supply of pre-filled pods and encouraged to continue their switch. Participants will be compensated $20 for this visit.

g. **Between Week 4 and Week 8:** Participants will be provided with another 4-week supply of pre-filled pods to use between visits for the real-world switch period. The Evolv Reflex EC device will collect and store 4 weeks of data on the participant's use and puffing topography. The JUUL and Vuse devices do not collect data.
h. **RCT Visit – Week 8:** Procedures at the Week 8 the visit will closely mirror Week 4 visit. Used and unused returned pods will be weighed. Topography data will be downloaded and reviewed. Those from the Enhanced EC Training study arm that have not achieved optimal topography or predominant EC use will receive real-time feedback on their puff patterns. Participants will again complete eCO measurement to confirm smoking status. Cigarette smoking will be assessed using the Timeline Followback (TLFB). To assess changes in self-reported respiratory health, participants will complete the CAT. Lung function will be assessed via spirometry. Self-reported levels of cigarette craving and withdrawal will be measured using the Tiffany-Drobes Questionnaire on Smoking Urges – brief (QSU-brief) and Minnesota Nicotine Withdrawal Scale (MNWS). The modified Cigarette Evaluation Scale (mCES) will assess subjective effects and sensory experiences at the end of each session. Participant's intentions for future use (e.g., purchase, use) of ECs will be assessed using a 4-item measure. Participants will be compensated $20 for this visit.
i. **Between Week 8 and Week 12:** Participants will again be provided with 4 weeks of pre-filled pods to use between visits for the real-world switch period. The Evolv Reflex EC device will collect and store 4 weeks of data on the participant's use and puffing topography. The JUUL and Vuse devices do not collect data.
j. **RCT Visit – Week 12:** Participants will smoke and vape as they normally would. Participants will complete eCO measurement to confirm smoking status. Because the eCO is the only measure needed for this visit, visit location will be flexible. Visits will be conducted as determined by location and abilities of the study participant. Participants will be compensated $10 for this visit.
k. **Human Lab Visit 3:** Human Lab Visit 3 (Week 12) will be identical to Visit 1 (above) but will not include any training. The visit is intended to measure longer-term changes in EC puff patterns. Participants will be instructed to remain abstinent from nicotine and tobacco for 12 hours prior to the study visit. Participants will complete eCO measurement to confirm tobacco/nicotine abstinence. To assess changes in self-reported respiratory health, participants will complete the CAT. Lung function will be assessed via spirometry. Self-reported levels of cigarette craving and withdrawal will be measured using the Tiffany-Drobes QSU-brief and MNWS. The mCES will assess subjective effects and sensory experiences at the end of each session. Participant's intentions for future use (e.g., purchase, use) of ECs will be assessed using a 4-item measure. At the end of the visit, a 6-minute walk distance (6MWD) test will be done to assess the participant's overall ability to conduct everyday activities. Baseline cardiovascular functioning will be measured using Pulse Wave Velocity, a sensitive measure of arterial stiffness that shows rapid (~1 month) changes with switching to ECs. Baseline beat-to-beat blood pressure will be measured to assess blood pressure and vascular elasticity. Participants will be compensated $50 for this visit.

l. Monthly for 3 months post active study completion – phone follow up with participant.

3. Due to COVID-19 and the need to keep patients and researchers safe, we may use Zoom, a HIPAA compliant, university approved video conferencing software, during the visit. This will allow the participant to smoke freely (unmasked) while the researcher can watch and communicate with the participant via video conferencing from outside the clinic room. We will only enter the room when necessary and will ensure the participant is masked when research staff are present.
4. All procedures, tests, and visits are being performed solely for research purposes and are not billable to insurance.
5. Samples will be labeled with a unique participant and study identification numbers, participant initials, visit date, and timepoint (-5, +30) and only members of Dr. Leavens and Zhang's teams will have access to the samples. Samples will be disposed of one month after the final report is sent out to the Principal Investigator.
6. Timeline: We anticipate that this study will last 1 year (12 months; See Table 2 for timeline). We expect to recruit 5 participants in the third month of Q1 and 18 participants in each Q2 and Q3 and 4 participants in the final quarter. This accrual rate is commensurate with our past studies.

Table 2. Study timeline by quarter

Quarters (3 months)	Q1	Q2	Q3	Q4	Post-award
Staff training, REDCap, IRB	X				
Participant recruitment (N = 45)	5	18	18	4	
Human Lab Visits	X	X	X	X	
RCT	X	X	X	X	
Processing/sample analysis				X	
Data analysis				X	X
R01 preparation			X	X	X
Dissemination				X	X

F. Risk/benefit assessment:

1. Physical risk: The potential risks for this study are minimal. There is a slight risk of discomfort, bruising and infection with blood draw. Blood will be drawn by trained research staff. IVs will be placed and blood draws will be conducted by an RN or LPN. Sterile instruments will be used for blood draws, the participants skin will be cleaned with an alcohol wipe at the site of the needle stick. Participants will complete no more than two study visits in a seven-day period.
2. Psychological risk: Risks for participants include those associated with the inconvenience of participation including answering surveys, providing blood samples, and completing multiple visits. To minimize the inconveniences associated with study participation we will review all data collection instruments and study procedures to minimize the number of items in our instruments and improve the accessibility and convenience of our study procedures. We may use several methods to enhance convenience to participants, including offering study visits throughout the day. Another risk is feeling pressured to be in the study, which we will track in order to monitor and will report as an adverse event. Finally, although very unlikely, some questions may make participants uncomfortable; participants are not required to answer questions they do not wish to.
3. Social risk: None
4. Economic risk: None
5. Potential benefit of participating in the study
    a. There are no direct benefits to participants for participating in this study
    b. If shown to be effective, our study could, in the future, benefit smokers with COPD who are unable to quit smoking using FDA-approved medications by helping them switch to a potentially less harmful product.

c. The researchers hope that the information gathered from this research may be useful in informing interventions for smokers unable to quit and to therefore benefit public health.

G. Location where study will be performed: All study visits will be completed at the Clinical Research Unit – Rainbow. During study visits where cardiovascular functioning is measured, participants will also visit Dr. Billinger's laboratory (KUMC campus; Hemenway Bldg; G002). All data will be directly entered into an electronic data capture system (i.e., RedCap or CRIS), therefore minimizing the use of paper records. If paper records are generated, they will be stored in locked file cabinets. Only study staff will have access to the locked records and the secure online electronic data capture system.

H. Collaboration (with another institution, if applicable): N/A

I. Single IRB Review for a Multi-site study (if applicable): N/A

J. Community-Based Participatory Research (if applicable): N/A

K. Personnel who will conduct the study, including:

1. Indicate, by title, who will be present during study procedure(s):
   Personnel on the project include: Eleanor Leavens (PI), Nikki Nollen (co-I), Edward Ellerbeck (co-I), Sandra Billinger (co-I), Jennifer Woodward (co-I and study physician), Matthew Mayo (biostatistician), Tricia Snow (lead study coordinator), Terri Tapp (research assistant), Olivia Funk (research assistant), Leah Lambart (GRA), Dan Li (regulatory staff), CRU staff
2. Primary responsibility for the following activities, for example:
   a. Determining eligibility: Eleanor Leavens, Nikki Nollen, Tricia Snow, Leah Lambart, Olivia Funk
   b. Obtaining informed consent: Eleanor Leavens, Leah Lambart, Olivia Funk
   c. Providing on-going information to the study sponsor and the IRB: Eleanor Leavens,
   d. Maintaining participant's research records: Eleanor Leavens, Tricia Snow, Matt Mayo, Olivia Funk, Leah Lambart
   e. Completing physical examination: N/A
   f. Taking vital signs, height, weight: CRU staff, Sandra Billinger and staff
   g. Drawing / collecting laboratory specimens: CRU staff
   h. Performing / conducting tests, procedures, interventions, questionnaires: Eleanor Leavens, Tricia Snow, Leah Lambart, Olivia Funk, CRU staff
   i. Completing study data forms: Eleanor Leavens, Tricia Snow, Leah Lambart, Olivia Funk
   j. Managing study database: Matt Mayo, Tricia Snow, Eleanor Leavens, Nikki Nollen, Leah Lambart

L. Assessment of Subject Safety and Development of a Data and Safety Monitoring Plan

1. Elements of the plan include:
   The current study does not pose more than minimal risk. We continue to closely monitor the situation. To address this concern, we will obtain informed consent, closely monitor AEs and SAEs and promptly report any that occur. Dr. Woodward will provide medical oversight. The Evolv Reflex EC will be used for the proposed study. The Reflex device is a commercially available pod-based device and is compatible with nicotine salt and freebase nicotine e-liquid. We will use commercially available nicotine salt e-liquid in ~5% nicotine concentration. If participants cannot tolerate the Evolv Relfex, we will offer

a choice of JUUL or Vuse devices. JUUL and Vuse are pod based systems. We will offer menthol or tobacco flavors in 5% or 3% concentration.

2. We will protect participants and minimize risks by using the strict exclusion criteria and careful monitoring of AEs. AEs will be tracked during regularly scheduled visits or through spontaneous reports made by participants. Drs. Leavens, Nollen, and Woodward will be made aware of unexpected or serious AEs within 24 hours of the first report by participants; all other AEs will be reviewed weekly by Dr. Leavens and discussed at regular meetings with Dr. Woodward. SAEs will be reported to the KUMC IRB within 24 hours of first awareness of the event. Unexpected adverse events that are related to the study products will be reported to KUMC IRB within 5 working days of first awareness of the event if the event is not serious and within 24 hours of first awareness if the event is serious. Unexpected adverse events that are unrelated to the study products will be reported to the KUMC HSC during yearly routine event reporting. Dr. Woodward will determine relatedness for each reported AE. SAEs will be defined as any event experienced by a study subject while using the study device that is fatal, life-threatening (subject was at risk of death from the event as it occurred), disabling or incapacitating, requires inpatient hospitalization or prolongs a current hospitalization, or required intervention to prevent permanent impairment or damage.
3. In the case of AEs, participants will be reminded of the voluntary nature of the study and be allowed to discontinue participation without negative consequences. In the case of SAEs related to use of study products, participation will be discontinued.
4. We will follow up with participants three months post treatment.

III. Subject Participation

A. Recruitment:

1. Our team has a record of successful recruitment of smokers that spans three decades. Our team has completed 7 large-scale, NIH-funded trials and recruited over 3,000 smokers in the past decade. Moreover, according to TUKHS patient database, there are over 3,700 smokers with COPD within Family Medicine alone. Based on this history and the available patient population, our enrollment goal of 45 smokers and e-cigarette users is comfortably feasible. Participants will be recruited through clinic (KUMC Department of Family Medicine), community-based efforts (e.g., flyers, face-to-face), and social media platforms including Facebook, Instagram, and Craigslist. Flyers will be placed around KUMC/TUKHS for patients to take. We will use the KUMC HERON and KUMC KUCC C3OD databases and the TMC/O2 electronic medical records to identify smokers. We will then send letters to patients on behalf of physicians (with prior physician approval) informing them of the study. In the letter, participants will be given the option to opt out of future study contact. Potential participants that do not opt out will be contacted by phone to assess interest in study enrollment/eligibility. We will also use the Frontiers registry to identify adult smokers who have agreed to be contacted for research. We will also use radio ads, word of mouth, and our existing pool of participants from prior studies. We will post the study to the KUMC Intranet list of current studies for KUMC employees. Additionally, participants are currently being screened for other research studies conducted by our team. Those who have completed studies or who are ineligible for other studies being conducted will be informed about the current study and offered the opportunity to be screened.

2. Recruitment methods are described above. Recruitment will be conducted by members of the study team. Recruitment will be overseen by Dr. Leavens. Initial screening will be conducted over the phone and by redcap survey.

3. Advertisements and flyers that will be used for recruitment are attached. Advertisements and flyers will be handed out to potential participants by the study team and will be placed in clinics at KUMC/TUKHS.

4. Letters sent on behalf of physicians will be mailed directly to patients to inform them of the study. Within one week of mailing letters, study staff will make follow-up calls to patients who did not opt out and offer initial screening.

B. Screening Interview/questionnaire: The screening will be conducted by self-report via a redcap survey and eligibility will be verified by phone and at the initial in-person study visit (i.e., final enrollment). Participants will also have the option to complete initial screening completely by phone. The screening questionnaire will address the general inclusion/exclusion criteria as listed above. Only participants who have expressed interest will be screened. Prior to screening, participants will be given a brief overview of the study and informed that we need to collect some information to learn whether they may be eligible for the research. They will be informed that completion of the screening interview is voluntary, and they can discontinue screening at any time. Participants will be asked to provide consent for screening.

C. Informed consent process and timing of obtaining of consent

1 Consent procedures will be conducted by trained members of the research team. Prior to consent, participants will be provided a detailed and comprehensive overview of study procedures.

2 Individuals interested in the proposed study and deemed to be initially eligible will meet the research assistant at the Clinical Research Unit – Rainbow. Each individual will be given a copy of the consent form and as much time as they need to review its contents. After the consent form is read, both the individual and the research assistant will review the consent form together and the potential participant will be encouraged to ask questions. Each individual will be reminded that participation in the study is completely voluntary. The consenting process will take place in a private location.

3 We do not anticipate recruitment of subjects with compromised cognitive abilities and/or decisional impairment. However, if questions regarding a participant's ability to provide informed consent arise, Dr. Leavens will determine whether the subject is able to give informed consent.

D. Alternatives to Participation: The alternative to participation is not participating, continuing to smoke cigarettes as usual, obtaining EC on their own, attempting to quit using FDA-approved pharmacotherapy, attempting to quit cold turkey.

E. Costs to Subjects: There are no costs to participants. All tests, procedures, and visits are being performed solely for research purposes and are not billable to insurance companies.

F. How new information will be conveyed to the study subject and how it will be documented: We have plans to publish data from this study in aggregate but will not provide any individualized feedback to patients.

G. Payment, including a prorated plan for payment: Participants will receive $10 for final screening. Eligible participants who complete study procedures will receive $50 for each of the human lab visits, and $20 for each of the week 4 and 8 RCT visits. In addition, participants will be compensated $10 for the week 12 visit. Participants who complete all study procedures will earn $210.

H. Payment for a research-related injury: N/A

IV. Data Collection and Protection

A. Data Management and Security: Confidentiality will be maintained by assigning each participant a study identification number and numerically coding all data. The association of the ID-code and the participant's name will be kept by Tricia Snow in a locked file cabinet. The screening questionnaire and all survey data will be directly entered into RedCap or CRIS and accessible only by study staff. Any paper copies of records will be kept in a locked filing cabinet in offices that are kept locked when unoccupied. Only summaries of group data will be reported in any publications or presentations, with no identification of individuals. Because identifiable information will be collected, participant privacy will be maintained throughout the duration of the study by adhering to the regulations set forth by the HIPAA Privacy Rule. More specifically, identifiable information will not be released without written authorization of the participant. Mobile devices will not be used for data collection or storage. Identifiable data will not be sent outside of KUMC.

B. Sample / Specimen Collection: No more than 7 mL of blood will be collected per blood draw (7 mL per draw x 2 draws per visit x 3 visits = 42 mL total during study). All samples will be de-identified and labeled with a study identification number. Blood samples will be aliquoted into two separate vials. Samples will be stored at the Bioanalytical Laboratory at the Rainbow Clinical Research Center. Samples will be accessible only to members of the study team. Results from biomarker analyses will be de-identified and shared only with members of the research team. Any resulting publications will present the data in aggregate; individual participants will not be identified. Samples will be disposed of one month after the final report is sent out to the Principal Investigator.

C. Procedures to protect subject confidentiality: Confidentiality will be maintained by assigning each participant a study identification number and numerically coding all data. All biological samples and survey data will be labeled with the study identification number and never with the participants name or other identifiable information. The association of the ID-code and the participant's name will be kept by Dr. Leavens in a locked file cabinet and will only be accessible to members of the study team.

D. Quality Assurance / Monitoring: All data will be directly entered into our electronic data capture system (i.e., RedCap or CRIS) that contains edit checks to control the quality and completeness of data entry. Completeness of data entry will be automatically verified before each assessment is completed. The electronic data capture system is behind the KUMC secure firewall with role-based access that is HIPAA and human subjects compliant. There are no plans for ongoing third-party monitoring.

V.Data Analysis and Reporting

A. Statistical and Data Analysis: The purpose of this pilot is to build a body of preliminary evidence and determine effect sizes for a fully powered R01 trial. To assess Aim 1, we will obtain means and SD for each variable at V1 and V2 and calculate mean change and SD of the change. Given that there is no difference at this stage in singe and enhanced training arms, data for these arms will be combined. We will then construct 95% CIs on the change of each of these variables for treated and control groups. Obtain CI on the difference in the change between the two groups on each of these variables which will allow us to determine the short-term impact of training on outcome variables. To assess Aim 2, we will be able to estimate the proportion of subjects that fall into each of the switch patterns across the three treatment groups. Specifically, we will construct CIs on the proportion of predominant EC users. This would give us the data to determine effect sizes for the fully powered R01 trial. We will obtain means and SDs for each variable (i.e., health effects, puff patterns) at Wk0 and Wk12 and calculate mean change and SD of the change. We will then construct 95% CIs on the change of each of these variables for the three arms. We will obtain CI on the difference in the change between the three groups on each of these variables which will allow us to determine the longer-term impact of training on the outcome variables. Given the pilot nature of the study, we have limited ability to assess variables that may affect our

endpoints of interest, but initial correlations and associations will be examined to see if any of the variables (e.g., stratification variables including EC use history, gender) are related to our endpoints of interest.

B. Outcome: The primary study endpoint is changes in puff duration from pre- to post-EC training/brief advice between smokers who received brief advice versus EC training (single episode and enhanced EC training arms combined). We hypothesize that smokers who receive EC training will show greater increases in puff duration compared to brief advice, greater reductions in cigarette craving compared to brief advice, and greater increases in nicotine exposure compared to brief advice. Additionally, enhanced EC training will result in the greatest proportion of predominant EC users, the greatest reduction in COPD-related health effects, and the greatest increases in puff duration.

C. Study results to participants: Study results will not be shared with research participants.

D. Publication Plan: We plan to publish results in appropriate tobacco and public health journals such as Addiction, Tobacco Control, Nicotine and Tobacco Research, etc. In addition, results will be presented at regional, national, and international conferences.

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