Mass General Brigham

Institutional Review Board
Intervention/Interaction Detailed Protocol

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Project Title: Assessing e-cigarettes for tobacco harm reduction in the context of lung cancer screening

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Version Name/Number: 1

For Intervention/Interaction studies, submit a Detailed Protocol that includes the following sections. If information in a particular section is not applicable, omit and include the other relevant information.

1. Background and Significance

Cigarette smoking is the leading cause of preventable death in the US,[1] and lung cancer is the leading cause of tobacco-attributable cancer mortality, with a 5-year survival of 21%.[2,3] Annual lung cancer screening (LCS) reduces lung cancer mortality and is recommended by U.S. Preventive Services Task Force guidelines for current smokers age 50-80 years with ≥20 pack-year of smoking or former smokers who quit within 15 years.[4]

The Lung Cancer Screening (LCS) test provides a teachable moment at which to offer a smoking cessation intervention to older, heavy smokers at high risk for lung cancer. Adult smokers' motivation and readiness to quit significantly increase after having LCS.[5] An NCI-funded MGH-based randomized trial, Screen ASSIST (R01CA218123; PIs: Elyse Park, Nancy Rigotti, Jennifer Haas; IRB#2018000539) is currently identifying the effective components of a smoking cessation intervention to be offered at the teachable moment of LCS.[6] Using a Multiphase Optimization Strategy (MOST), it tests the effectiveness of 3 components of a smoking cessation intervention offered to smokers scheduled for LCS at 11 sites in the Mass General Brigham health care system. Participants are randomized with a 3-factor fully-crossed factorial design to combinations of 3 conditions: cessation counseling (4 vs. 8 weeks), nicotine replacement therapy (2 vs. 8 weeks), and systematic screening for social determinants of health with referral to community resources (yes vs. no).[6] Preliminary Screen ASSIST data show that across all conditions 14% of participants report past 7-day smoking abstinence at 6-month follow-up; therefore, 86% of participants continue to smoke despite receiving an evidence-based smoking cessation intervention. Smokers undergoing LCS who are unable to quit after an evidence-based smoking cessation intervention are a group in whom innovative approaches are needed to reduce tobacco health harms by promoting abstinence from combustible tobacco products.

While complete cigarette abstinence is the ultimate cancer prevention goal for smokers, older smokers are less likely to be interested in quitting, to make a past-year quit attempt and to successfully quit,[7] even when using evidenced-based cessation methods. As a result, the overall decreasing prevalence in cigarette use occurring in the general population is

not being seen among older adults. While smoking prevalence declined 22-46% for those 18-64 years old from 2000-2015, it declined only 2.1% among adults ≥65 years old.[7] In 2021, the age group with the highest smoking prevalence was adults aged 45-64 years (15%), and 8.3% of adults aged ≥65 years smoked.[8] The smallest decrease in smoking prevalence from 2019[9] to 2021[8] occurred among those eligible for LCS. These smokers need new strategies to reduce tobacco-related health harms.

E-cigarettes (EC) offer an opportunity for tobacco harm reduction among smokers who are unable to quit using evidence-based methods.[10] EC are battery-powered devices that heat a nicotine-containing liquid to create an aerosol that users inhale ("vape"). EC could be a particularly helpful harm reduction tool as these products have sufficient appeal and satisfying nicotine delivery to displace CC.[11] Several RCTs have also shown EC's efficacy for smoking cessation.[10] There is strong evidence that EC are significantly less harmful than CC.[10,12–14] Exposure to toxic substances from combustible cigarettes (CC) is significantly lower in EC, and completely switching from CC to EC results in reduced exposure to carcinogens, as well as lower levels of biomarkers of tobacco exposure and oxidative stress.[12,14–17] RCTs have shown that even smokers who only partially switch from CC to EC ("dual users") benefit.[14,17,18] CC smokers who became dual users during an EC switching intervention had a significant decrease in the number of cigarettes smoked per day, CO levels, respiratory symptoms and NNAL levels, compared to baseline.[18] Nicotine levels remained stable among dual users, showing that they are not using higher levels of nicotine.[18] Encouraging smokers undergoing LCS who are unable to quit using evidence-based treatment to fully switch to EC could reduce tobacco-related harms.

Older smokers' use of and perceptions of ECs. The prevalence of current EC use is lower among age groups eligible for LCS than in younger age groups. Adult EC prevalence in the U.S. is 2.7% in those aged 45-64 years and 0.9% in those aged ≥65 years, compared to an overall 4.5% adult prevalence.[8] Evidence about the perceptions of EC risk or benefits among older adults is limited. One of the few studies found that older adults were more likely than younger adults to misperceive the health risks of EC vs CC, rating EC as equally or more harmful than CC.[19] Another found that older adults see EC as a viable choice for smoking cessation.[20] However, these studies included both smokers and non-smokers. More rigorous research is needed to understand older smokers' perceptions regarding EC benefits and risks, and willingness to use ECs for harm reduction.

Summary of the literature gap and impact. Older long-term smokers who are eligible for LCS are a high priority population for tobacco cessation.[21] However, they are less likely than younger smokers to quit smoking even with evidence-based smoking cessation interventions. They could benefit from tobacco harm reduction strategies, which could be offered in the context of LCS. However, the acceptability and efficacy of tobacco harm reduction strategies among older smokers is not known.[21] This project will fill this critical literature gap. Studies such as the one we propose are needed to assess older smokers' perceptions of risk and benefits related to EC, their willingness to substitute CC with EC and to assess if EC can serve as a harm reduction tool for smokers at high risk for lung cancer who are unable to quit. If so, ECs could be incorporated as part of harm reduction and cessation interventions offered to smokers in the context of LCS. The information gained will also provide critical preliminary data to support a future application to test, in a fully powered RCT, whether switching from CC to EC could reduce tobacco-related health risks for older smokers.

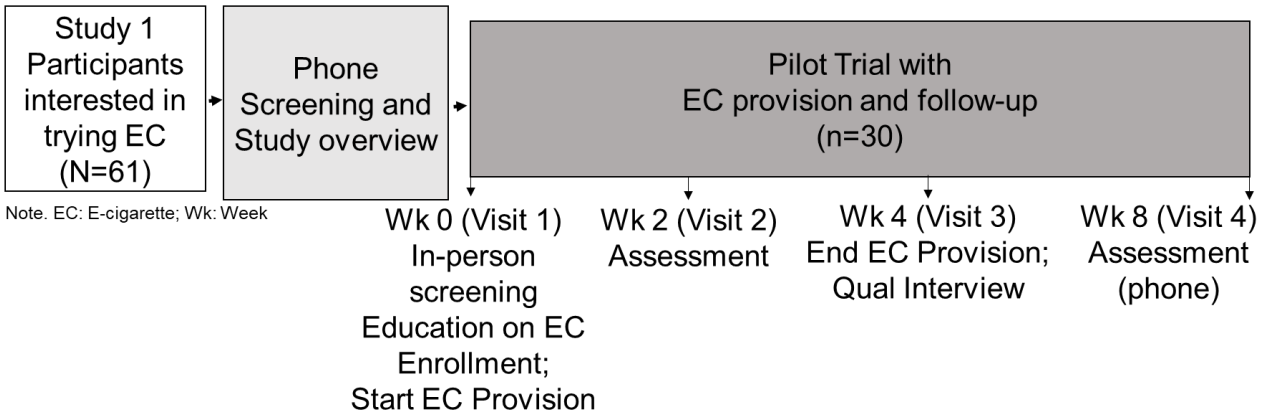
2. Specific Aims and Objectives

Aim: Assess the feasibility, acceptability, and short-term effects of providing ECs for 4 weeks to encourage switching from cigarettes to e-cigarettes by individuals who did not quit after smoking cessation treatment provided in the context of LCS and do not currently plan to quit.

Hyp 1: (i) > 40% of eligible smokers who are offered participation in the trial will enroll. (ii) > 75% of enrollees complete the trial.

Hyp 2: Participants will report fewer CPD at the end of 4 weeks of EC provision, relative to their baseline values.

Figure 1. Study design



3. General Description of Study Design

This is an open-label single-arm pilot clinical trial testing the feasibility, acceptability, and effects of a 4-week EC substitution intervention in 30 current smokers. Approach: Participants will be asked to switch from CC to the NJOY ACE electronic cigarette (EC) for 4 weeks. They will receive counseling to develop a plan to fully substitute CC for EC and to increase EC adherence. Follow-up assessment at 8 weeks will determine whether participants continue to use EC, return to cigarette smoking, or use both products. The primary outcomes are study feasibility (participant enrollment and retention) and change in cigarettes per day from baseline to week 4 (primary outcome). Secondary outcomes include change in exposure biomarkers (expired air CO, urine cotinine and anabasine) from baseline to week 4, product acceptability and tolerability (days of EC use, adverse events) and change in CC and EC use after EC provision ends. At the end of EC provision (week 4), we will conduct exploratory qualitative exit interviews in a purposive subsample to explore their experiences participating in the study and switching from CCs to ECs.

4. Subject Selection

Inclusion Criteria

a) Participants in the Screen Assist study (IRB#2018P000539) who self-reported smoking cigarettes at the end of the study and were asked to complete a subsequent Screen Assist survey to ascertain their potential interest in a research study to test the effects of switching from CC to EC. Individuals who expressed interest in a future research study about EC on that survey are eligible for this study.
b) Smoked ≥5 cigarettes/day in past month
c) Willingness to try switching to EC for 4 weeks
d) Own a mobile telephone
e) Smoking status at study entry confirmed by breath carbon monoxide (CO) ≥ 6ppm
f) English speaking
g) Willingness to travel to the MGH main campus for 3 in-person visits

Exclusion Criteria

a) Plan to quit smoking and have set a quit date in the next 30 days
b) Current EC use on >2 days in the past 30 days
c) Hospitalization for acute coronary syndrome, unstable angina, CHF, stroke, pneumonia or COPD/asthma exacerbation in the past 1 month
d) Be willing not to smoke marijuana in the 24h before each study visit

Current cannabis use will be assessed but users will not be excluded if they agree to abstain from smoking cannabis for 24 h before each study visit. Rationale: smoking any combusted product will increase the level of the biomarker of expired air carbon monoxide (CO). Individuals excluded from the RCT because they plan to make a quit attempt in the next 30 days will be referred to the free Massachusetts telephone quit line for assistance.

Recruitment Methods

Participants will be recruited by re-contacting participants who previously completed the Screen ASSIST trial and had given informed consent (IRB#2018P000539) to allow re-contact after the study ended. As part of the Screen Assist protocol, we conducted a cross-sectional survey of former Screen ASSIST participants who were smoking at the end of that study. Of the 209 individuals who completed the survey, 124(59%) indicated they would be interested in hearing about a future research study about EC . These potential participants will be contacted by mail and phone call and invited to participate in this study by the study research assistant. Up to 3 outreach contacts will be attempted per participant. All potential participants who contacted for recruitment in this study have already given us permission to contact them again by phone, mail, or email.

5. Subject Enrollment

Study staff will call potentially eligible patients (Screen Assist participants who were still smoking and said they were interested in a switching trial at when surveyed at the end of the Screen Assist Study). During the initial call, study staff will offer patients the opportunity to participate in a 10-minute virtual informational session with a tobacco treatment counselor to learn more about what is an electronic cigarette and what participation in the study entails. Patients will only

be agreeing to complete the informational session and can decline study participation after completing the session.

For patients who complete the informational session and express interest in participating in the study, study staff will offer them the opportunity to confirm study eligibility at that time or will schedule a time in the upcoming days for them to be called. If patients are not interested in participating in the study after completing the session, study staff will provide relevant resources for quitting smoking. We will attempt to reach patients three times before assuming lack of interest in study. Patients who screen eligible via the pre-screener will be scheduled for an in-person visit (Visit 1) to confirm eligibility (CO verification). Eligible participants will complete the written informed consent form at the start of the in-person visit. A trained research assistant, or the PIs, will obtain informed consent.

Prior to consent, the PI or research assistant will explain study procedures in detail, discuss potential risks and benefits of participation, and remind patients that the study is completely voluntary and that their choice to participate will not impact the care they are receiving currently at MGH or care they may wish to seek in the future. They will be informed that they can choose to withdraw their participation at any time and may also choose not to answer any questions or submit any other data (e.g., urine samples) that they are not comfortable with. Patients will also be informed of the limits of confidentiality, including expressed risk of harm to self or others (see protocol below for details). They will receive the PI's contact information and that of the MGH IRB to contact with any additional questions or concerns. The RA will assess participant's ability to provide informed consent and route any questions about the participant's capacity to the PI to weigh in on or assess further prior to enrolling the participant. The participant will be provided with a copy of their signed consent form to keep for their records. Patients' signatures will be documented on our study consent log and all physical study consent forms will be kept separately from study data and will be locked in a filing cabinet in a locked office within the PI's research office suite. Once patients have been consented, they will be enrolled in the study and receive baseline assessments.

6. STUDY PROCEDURES

	Phone Screening	EC Provision					F/U
		In person screening / In Person Baseline	Phone Call	In person Visit	Phone Call	In Person Visit	Phone Call
	-14	Week 0	Week 1	Week 2	Week 3	Week 4	Week 8
Screening and Enrollment							
Tobacco history since survey completion: past 30-day CC and EC use, plan to quit smoking in the next 30 days	X						
Other screening items	X						
Breath Carbon Monoxide		X					
Baseline Measures							
Current medical history		X					
Alcohol use screening		X					
CC and EC Use							
Recent CC quit attempts		X	X	X	X	X	X

Current CC Use: Past 7-day use (Yes vs.no) and 7-day timeline follow back interview (TLFB)		X	X	X	X	X	X
Current EC use: Past 7-day use (Yes vs.no) and 7-day timeline follow back interview (TLFB)		X	X	X	X	X	X
EC pod collection/count				X		X	
Nicotine, CC, and EC Perceptions							
Absolute and comparative health and addiction risk perceptions of EC, CC and Nicotine		X				X	X
EC Acceptability							
E-Cigarette Sensory Effects and Appeal Ratings				X		X	
Electronic cigarette rating scale				X		X	
Electronic Cigarette Smoking Consequences Questionnaire				X		X	
Readiness to switch to EC							
Electronic cigarette taste and feel compared to cigarette				X		X	
Dependence, Withdrawal and Craving							
Time to first cigarette, number of cigarettes smoked per day; short-form PROMIS Nicotine Dependence Item Bank		X		X		X	
Penn State e-cigarette dependence index				X		X	
Minnesota Nicotine Withdrawal Scale (MNWS)		X		X		X	
Brief Questionnaire on smoking urges		X		X		X	X
Biomarkers							
Breath carbon monoxide (CO)		X		X		X	
Urine Cotinine		X		X		X	
Urine Anabasine		X		X		X	
Adverse events							
Adverse events			X	X	X	X	
Respiratory symptoms: American Thoracic Society questionnaire		X	X	X	X	X	
Exit qualitative interview						X	

Selection and provision of electronic cigarettes: Participants will receive a two-week supply of the NJOY ACE e-cigarette (NJOY, LLC). This product was selected because it is a 4th generation nicotine salt-based pod EC and is a commercially available consumer product that was granted a Premarket Tobacco Product Authorization (PMTA) from the FDA's Center for Tobacco Products (CTP) in 2022. This authorization required that FDA CTP decide that the product met the standard of being "appropriate for the protection of the public health," defined as it having net public health benefits that exceed its net public health risks. A tobacco product with a PMTA designation is not considered by FDA CTP to be an investigational device and does not need to obtain certification from the CTP's Investigational Tobacco Products (ITP) Program when it is used in a research study. We have confirmed the accuracy of this statement with an email communication with Jaime Tosh of the FDA CTP's IPT Program (dated July 11, 2024).

The NJOY ACE contains a device and sealed pods available with 5% nicotine and is tobacco flavored. Each pod is equivalent to ~20 cigarettes, and participants will receive an EC pod supply equivalent to their average cigarette smoking rate at baseline. The supply of pods provided will be adjusted as needed to ensure the adequate amount to substitute cigarette use.

Participants will receive written and verbal instructions on how to use the device and be provided with written educational materials used in previous research trials to help vapers quit smoking. They will be instructed to use the EC instead of their usual CC brand, encouraged to switch completely to the EC by the end of the first week and try to use only the EC for the rest of EC provision period. All devices and pods will be labeled for investigational use only. Dispensing and collection logs will be used to track devices and pods. We will collect and count used and unused pods at visits.

Schedule of Assessments:

a) Initial Phone Screening: Telephone screening will determine initial eligibility. Initial screening will query on all inclusion and exclusion criteria, except for CO. For those who meet the initial eligibility criteria, a research assistant (RA) will explain the purpose and procedures of the study, provide information on confidentiality, answer questions, and invite participant for an in-person final eligibility visit.
b) Baseline visit (Consent, Final eligibility, baseline data collection and product provision): Participants will receive a study overview. Informed consent for the study will be obtained. Final in-person eligibility will be confirmed with an exhaled carbon monoxide via Bedfont Micro Smokerlyzer. Participants meeting final eligibility will be enrolled in the study. Baseline data collection will immediately follow screening at the same visit. Measures will be completed per the schedule of measures above (see Table 1), broadly including: recent CC and EC use, cigarette dependence; respiratory symptoms; intentions to quit smoking; and biomarkers of tobacco use and inflammation. Biological assessments involving urine sample collection will be performed by the RA.

   Following completion of all scheduled measures, participants will be provided with a complimentary NJOY ACE device, information on its storage and use, and disposable cartridges in the tobacco flavor. Participants will be provided with a number of pods comparable to 150% of their weekly consumption of nicotine based on their responses to the baseline timeline follow-back (TLFB). This quantity will ensure that participants have adequate pods to fully substitute combustible cigarettes within a reasonable margin of error (e.g., timing/scheduling of the next session) should they choose to do so. As each standard 5% NJOY ACE pod provide an amount of serum nicotine delivery in ideal use conditions comparable to one pack of cigarettes (i.e., 20 cigarettes), we will compute participants' average weekly cigarette consumption in packs and provide 1.5x that number of cartridges.
c) Phone call visits at Weeks 1 and 3: These visits will be conducted by phone. Participants will be assessed for their cigarette, tobacco, and EC use. Participants will also be assessed for any quit attempt or adverse event and will be asked for any issues using the product and reminded to use the EC instead of the CC every time they want to smoke.
d) In person Visit at Week 2: Participants will attend an in-person visit at Week 2 to receive a new 2-week supply of pods, return used and unused pods to measure EC use, complete assessments and troubleshoot device or other study-related issues.
e) In person Visit at Week 4: Participants will attend an in-person visit at Week 4 when product provision will end and all baseline assessments will be repeated.
f) Exit Qualitative interviews: A purposive subsample of 8 trial participants (4 who switched fully or partially to EC and 4 who switched minimally or not at all to EC) will receive a semi-structured exploratory qualitative interview at Week 4 to assess study and EC acceptability. Domains include general thoughts about the study procedures, description about EC use

experience (sensation, emotional aspects of use, flavor, taste, smell, side effects, etc.) and barriers to EC use during the study or to continuing EC use.

g) Phone call visit at Week 8: A phone call at Week 8 will assess CC and EC use after product provision ends and repeat other assessments.

Texting for Visit Reminders & Assessments

Participants that consent to receiving text messages will receive messages reminding them of their upcoming in-person visits (baseline in-person visit, week 2 in-person visit, week 4 in-person visit)

Quantitative measures:

a) Measures already collected by Screen ASSIST trial and survey[6]: Sex, age, race/ethnicity, education, past medical history (lung cancer, CVD, COPD), alcohol use screener, tobacco use history (year started, pack-years, CPD, prior quit attempts, quit methods used) self-reported smoking status at end of study and household income.
b) Screener measures: past 30-day CC and EC use, recent quit attempts, quit methods used, plan to quit smoking in the next 30 days.
c) Recent tobacco use and quit attempts: past 7-day CC and EC use, recent quit attempts,
d) Current medical history: self-report of diagnosis of cancer, CVD, COPD and other chronic diseases made by a physician.
e) Alcohol use screener: Audit-C short form.
f) Current CC Use: Assessed with a 7-day timeline follow back interview (TLFB) during in-person or phone visits.[22]
g) Current EC Use: We will only quantify EC use as yes vs.no for each day of assessment. We will not quantify the amount of EC use.
    --Daily EC use (yes/no) assessed with 7-day TLFB at in-person & phone visits.
    --EC pod collection/count: EC use will be estimated with the number of used and unused pods returned at 2 and 4 weeks (end of EC provision).
h) EC and CC related harm perceptions: Measures from PATH to assess absolute and comparative addiction perceptions of EC and CC;[23] the perceived health and addiction risk assessment scales will be used to assess risk associated with nicotine, CC and EC.[24,25]
i) EC Acceptability: Subjective effect of EC (e.g. satisfaction, psychological reward, craving reduction) using the modified E-Cigarette Sensory Effects and Appeal Ratings and the Electronic cigarette rating scale0;[26] beliefs and behaviors related to EC measuring nine positive expectancies and seven negative expectancies related to EC using the Electronic Cigarette Smoking Consequences Questionnaire;[27] Participants will also be asked to compare the taste, satisfaction and helpfulness for managing cravings of the study e-cigarette to the usual cigarette they smoked before the study.
j) Cigarette and e-cigarette dependence: Time to First Cigarette and Time to First EC of the Day measured with the Fagerstrom Test of Cigarette Dependence (FTCD);[28] and its e-cigarette adaptation.[29] Patient Reported Outcomes Measurement Information System (PROMIS) Nicotine Dependence Item Bank.[30,31] The Penn State electronic cigarette dependence index will also be included to assess e-cigarette dependence.[33]
k) Nicotine Withdrawal Symptoms: Minnesota Nicotine Withdrawal Scale (MNWS)[34], which assess both the desire to smoke and withdrawal symptoms.
l) Smoking Urges: Questionnaire of smoking urges-brief.[35]

m) Biomarkers of Exposure: Exhaled breath samples measured as concentration of Carbon Monoxide (CO) in parts per million. Cotinine and Anabasine measured in the urine sample. Cotinine is the major metabolite of nicotine. It is found in both CC and ECs. It will be measured to assess EC safety. Cotinine may or may not change with a CC to EC switch, depending on degree of substitution.[36] Anabasine is a tobacco alkaloid that reflects exposure to combustible tobacco products and should fall with reductions in CPD.[36] Urine samples will be collected and stored at MGH and analyzed at Mayo Clinic laboratories.
n) Respiratory Symptoms: Assessed with the American Thoracic Society questionnaire.[37]
o) EC Adverse Events: self-reported adverse events with open-ended questions about new symptoms since the last visit, then symptom checklist of common vaping side effects,

Remuneration: Remuneration will be provided via gift cards purchased on an MGB Corporate Card. Participants will receive gift cards for their participation. Participants will receive $50 for attending the baseline in-person visit, $50 for attending the Week 2 visit, and $80 for attending the Week 4 in-person visit, and $30 for a Week 8 phone visit. Participants will receive $15 for completing the phone visits at Weeks 1 and 3. Total possible compensation is $240. Compensation will not be contingent on EC or CC use status.

7. Risks and Discomforts

a) E-cigarette use:

E-cigarettes are devices that heat nicotine to produce an aerosol that users “vape.” The health effects of e-cigarettes are still unclear, but preliminary data suggest that using e-cigarettes is generally less harmful than smoking tobacco cigarettes in that e-cigarettes expose users to fewer toxicants than cigarettes,[12] and emerging data suggest that smokers who switch completely from conventional cigarettes to e-cigarettes will likely reduce their risk of tobacco-related health harms (the goal of the present study). Most exclusive e-cigarette users have lower nicotine levels than when they smoked regular combustible cigarettes. Some e-cigarette users, especially those who use both e-cigarettes and regular tobacco cigarettes, as well as youth and young adults, can have increased nicotine levels, though recent data suggests that on average, exclusive vapers, exclusive cigarette smokers and dual users of both products have similar levels of daily nicotine intake.[38] In some rare cases, these use patterns have been associated with seizures. Whether this would occur with individuals instructed to switch completely to e-cigarettes from cigarettes is unclear but based on prior data we would hypothesize highly unlikely to occur in the present study. E-cigarette users very often maintain an addiction to nicotine, but this addiction appears to be somewhat less than that from tobacco cigarettes. Abruptly quitting e-cigarettes could cause withdrawal symptoms similar to those from quitting tobacco cigarettes but slightly less severe. The most common side effects include dry mouth, irritation of the throat and mouth, and mild cough.

Patients may have heard that e-cigarettes, or "vapes," can explode and seriously injure people. Study staff will instruct patients that although they are rare, these explosions are dangerous. The exact causes of these incidents are not yet clear, but some evidence suggests that battery-related issues (reported with older device types not under investigation in the present study) may lead to vape explosions. To prevent e-cigarette related injuries, patients will be instructed to keep their e-cigarettes away from other metal objects, not charge the device with a phone or tablet charger, and not charge the e-cigarette overnight or leave it charging unattended, and to stop using the e-cigarette immediately if the batteries get damaged or wet.

Patients will also be instructed to always keep e-cigarette liquid pods out of children's and pets' reach (although our EC pods are sealed and non-refillable thus e-liquid is not accessible) and sight after use. If the study staff learns about additional risks of e-cigarettes during the study, patients will immediately be informed of these risks.

Additionally, in August 2019, a concern about the safety of commercial e-cigarettes arose when cases of severe pulmonary illness associated with vaping (EVALI) were reported. However, the Centers for Disease Control and Prevention (CDC) have since reported that: 1) vitamin E acetate, an additive in some THC-containing e-cigarettes, was strongly indicated as the primary cause of EVALI, 2) data suggests that most EVALI patients obtained these products from informal source such as friends, online, or in-person dealers, and, 3) there have been significant declines in new EVALI cases since September 2019.[39] Further, in 2022, the FDA Center for Tobacco Products (CTP) authorized for sale as a consumer product a pod-mod e-cigarette device type (NJOY, LLC). This authorization required that FDA CTP decide that it met the standard of being "appropriate for the protection of the public health," defined as net public health benefits exceed net public health risks. The Director of the CTP recently co-authored a publication indicating that adult smokers who switch to e-cigarettes to reduce their health risks should use one of the "authorized" products with include the NJOY ACE device that we propose to use as our e-cigarette product for the present study.[40] This e-cigarette will provide a device that produces a consistent, well-characterized aerosol and sealed pods to reduce concerns about device tampering during the study. Thus, use of the NJOY ACE e-cigarette is not expected to be harmful or elevate risk beyond the risk expected from smoking combustible cigarettes, and below we detail our plan for monitoring risks including any increases in nicotine use from baseline.

All patients will receive detailed verbal and written instructions (at Baseline) about how to properly use e-cigarettes, safely charge and store the devices, and instructions to reach out to study staff at any time during the study with any questions or concerns about e-cigarette use. To minimize the risks outlined above, we will also instruct patients on the nicotine content of the e-cigarettes compared to their regular daily cigarette and provide e-cigarette pod supplies using this calculation (adjusted as needed), as well as instruct patients on the signs/symptoms of too much or too little nicotine. We will closely monitor for symptoms of nicotine increase from baseline, nicotine overdose or withdrawal, and respiratory symptoms at scheduled visits and in-between visits as necessary. We will advise patients to report all adverse events (assessed at each visit), and arrangements will be made for urgent visits with the patient's primary care provider, our study physicians, or the emergency department depending on the nature of the event. We will exclude individuals with severe medical complications as mentioned above. See Data Safety Monitoring Plan for additional details on safety monitoring and adverse event reporting.

b) *Loss of confidentiality:* Loss of confidentiality is another potential risk, though unlikely, for questionnaire items. We have never had any confidentiality issues in any of our related trials and overall risks from loss of confidentiality are expected to be minimal. We will ensure that maximal care is taken to preserve participant confidentiality to the highest extent possible. Questionnaire data will be collected and stored electronically using secure systems (e.g. REDCap; Research Electronic Data capture; http://project-redcap.org) and questionnaire data will not include any identifying information. Consent forms will be stored in a separate, locked filing cabinet within the PI's locked office on a locked floor at MGH. Additionally, access to patient identifiers will be limited to necessary study staff on a password protected encrypted network drive on MGH's secure server. A separate file will link study ID with patient contact information. All digital audio recordings for the qualitative interviews will be immediately uploaded to the PI's MGH-encrypted computer and the file will then be deleted

from the recording device. All participant assessment visits will be held in-person in a standard confidential medical conference room. The pre-screening visit and qualitative interview will be conducted via telephone and the RA will use confidential standard office space in the MGH Division of General Internal Medicine's Tobacco Research and Treatment Center and ensure that the patient is in a space that they are comfortable completing the interview. Only IRB approved study staff will have access to any research or personally identifying data.

REDCap: REDCap is a secure, web-based application that was developed by researchers at the Vanderbilt University. Locally hosted by Mass General Brigham/MGH Research Computing, REDCap allows for secure, electronic data collection and management of clinical research study data.

c) *Emotional discomfort:* There is minimal emotional discomfort or psychological risk associated from discussion of tobacco use and related symptoms proposed in this study. It is possible that patients may be uncomfortable answering questions about their tobacco use due to stigma associated with use. However, these questions are not anticipated to cause significant embarrassment or emotional distress based on our prior work in this population. Study staff will instruct patients that they do not have to answer any questions or provide any samples that make them uncomfortable.

d) *Adverse Events:* As outlined in our Data Safety Monitoring Plan, in the event of any adverse or other serious events that require immediate medical, psychiatric, or other professional intervention, the research assistant, under the supervision of the PI, will triage the patient to the appropriate emergency services.

e) *Urine biomarker analysis*: Patient's urine samples will also be identified solely by patient's unique study ID and they will be kept in a secure MGH freezer until they are shipped in batches to the Mayo Clinic for analysis.

8. Benefits

There is a possible direct benefit to participants. Patients will be instructed to reduce their combustible daily cigarette use and to substitute e-cigarette use for cigarette use. This aims to facilitate reductions in cigarettes smoked per day, reduced tobacco smoke exposure and eventual increase in health benefits (e.g., improvement in dyspnea). Even if e-cigarettes are found to not reduce exposure to toxins, cigarettes per day, or if respiratory symptoms were to worsen with their use (which is not anticipated), this study will still provide valuable data about the need for patients to avoid e-cigarette products. The data from this trial will be clinically informative and inform policies on regulating and marketing e-cigarettes. A systematic review of randomized controlled trials indicates that e-cigarettes are more effective than nicotine replacement products for helping cigarettes smokers to quit smoking.[10] Quitting smoking is associated with a rapid reduction in tobacco-related health risks, even in older individuals who have smoked enough to qualify for lung cancer screening, as our study population does.[41]

In the qualitative interview, participants will also discuss their attempts to reduce their cigarette use and barriers and facilitators to e-cigarette substitution which may be useful for increasing participants' awareness of their cigarette use, what maintains use, and obstacles to stopping use which could be useful for eventual cessation of cigarette use.

9. Statistical Analysis

Aim: Assess the feasibility, acceptability, and short-term effects of providing ECs for 4 weeks to encourage switching from cigarettes to e-cigarettes by individuals who did not quit after smoking cessation treatment provided in the context of LCS and do not currently plan to quit.

Hypothesis 1: (i) ≥ 40% of eligible smokers who are offered trial enrollment. (ii) ≥ 75% of enrollees complete the trial

Primary Outcomes H1: Study enrollment (% screened of those who completed our study 1 survey, % eligible of those screened; % enrolled of those screened eligible); retention (% of patients who complete the trial, defined as completing the final follow-up assessment and >50% of the study visits). We will also document reasons for ineligibility and exclusion to inform future trial protocols.

Analysis H1: Descriptive statistics using data from study recruitment and enrollment records will test hypotheses.

H2b: Participants will report fewer CPD at the end of the 4-week EC switch period, relative to their baseline values.

Primary Outcome H2: Change in mean cigarettes smoked per day (CPD) between baseline and 4 weeks.

Analyses H2: Paired sample t-tests will be used to compare mean differences in past 7-day CC use from BL to Week 4. Linear mixed models will also be used to test differences in CPD and CO levels over the study period (using data from all observed time points observed). Primary analysis will be conducted among completers and multiple imputation will be used for a sensitivity analysis.

Additional Planned Analyses: Analyses of other secondary outcomes will include EC acceptability measures and changes from baseline to week 4 in the levels of: EC use days, levels of biomarkers of exposure (CO, anabasine, cotinine). The qualitative interviews will be audio-recorded, transcribed, and iteratively analyzed using the framework method of content analysis (both inductive and deductive) in Dedoose 8.3 qualitative software. The trained research assistants will separately review each transcript and develop a coding framework. The coders will meet weekly with the PIs to review results for agreement.

Power: If 40% (n=30) of 75 screened eligible subjects agree to participate, the width of the 95% CI will be limited to 11.1% on each side. If at least 24 of the 30 subjects complete the study, the width of the 95% CI will be limited to 14.7% on each side. Hyp 2b: Participants will report fewer CPD after 4 weeks of EC provision relative to their baseline values. Results from PI Avila's recent study[42] found a significant reduction in mean CPD in the EC arm (N=18) from 14.8 cigarettes per day to 4.4 in week 4 (Change SD: 3.81) (p-value <0.01) (Cohen's d=1.6). With a sample size of 30 and a 25% attrition rate, we expect at least 24 of the 30 subjects will provide data on CPD reduction. The study will have 80% power to detect a more conservative Cohen's d of 0.60 with a two-sided type-I error of 5%. A Cohen's d of 0.60 will translate into a mean change of 3 CPD (SD of change=5).

10. Monitoring and Quality Assurance

Training of all Study Personnel in the Responsible Conduct of Human Studies: Prior to recruiting subjects or handling study data, all study personnel will be required to pass the NIH approved course that reviews regulatory and informational documents on human subject protection and the responsible conduct of human studies. In addition, all study personnel will sign a statement of commitment to the protection of the rights and welfare of human subjects participating in research.

DATA SAFETY MONITORING PLAN

Overview: The PI will be responsible for monitoring safety throughout the trial and adhering to all reporting requirements. The PI will assume responsibility for reporting all adverse events that may arise to the IRB and/or federal funding agency, as required. Adverse events will be defined according to FDA's definition (i.e., any untoward consequence to study participants that may be related or possibly related to study procedures). Events may include, but are not limited to, worsening of psychiatric, emotional or physical symptoms; breaches in participant confidentiality, deviations from IRB-approved protocols (e.g., contacting participants to obtain survey data outside of IRB-approved time windows), or any participant safety concerns. Study recruitment, enrollment, and retention will be reviewed by the PI and research assistant (RA) weekly. Informed consents will also be reviewed weekly by the RA and PI, and monthly by the PI's mentors for the purposes of quality control. The RA will report on any issues or obstacles in recruitment, enrollment, survey administration, biospecimen collection, e-cigarette provision, and follow-up to the PI during weekly research team meetings. The RA will review all questionnaire and collected biospecimens (e.g., breath, urine) in real time to ensure data completion.

Safety monitoring plan: In this proposal, we will provide e-cigarettes to individuals who smoke cigarettes who are not ready to quit smoking. We will collect safety information related to the following categories: (1) worsening of respiratory symptoms, (2) symptoms of nicotine toxicity, and (3) adverse events of e-cigarettes previously reported to the FDA. This includes regular monitoring (every 2 weeks for all participants and more if needed determined on a case-by-case basis) of dyspnea and open-ended questions on any medical care (including hospitalizations or emergency room visits) since the last visit assessed at each study visit. While nicotine toxicity is rare in clinical trials, we will monitor breath CO levels at each study visit and also monitor for potential signs and symptoms of nicotine withdrawal. Adverse events related to e-cigarettes previously reported to the FDA include serious events such as hospitalization for pulmonary or cardiac causes, seizure, burns caused by e-cigarette devices/malfunction, and other adverse events such as headache, nausea/vomiting, dizziness, confusion, blurry vision, throat irritation, abdominal pain, and sleepiness. We will advise participants to stop e-cigarette use if necessary. A trained RA will collect all data. In the event of any adverse or other events that require immediate medical, psychiatric or other professional

intervention, the RA will immediately page the PI who will triage the patient to the appropriate emergency services (e.g., 911 or emergency room).

Attribution of adverse events: Adverse events are any side effect that occurs in a participant, while serious adverse events are those that are life-threatening, resulting in hospitalization, disability, or death. We will attribute adverse events that arise in the study to e-cigarettes according to the following scale: definite (clearly related to e-cigarettes), probable (likely related to e-cigarettes), possible (may be related to e-cigarettes), unlikely (likely not related to e-cigarettes), and unrelated (clearly not related to e-cigarettes).

Reporting of adverse events: We will report all adverse events to the Mass General Brigham (MGB) IRB and the NIH funding agency. We will also report serious adverse events, and any events requiring the trial to be stopped, to the FDA. Any complications that are deemed to be related to the study will be immediately reported to the study PI (within 24 hours). Any serious adverse events that arise throughout the course of the award period will be reported to the Mass General Brigham IRB submitted within 5 working days/7 calendar days of the date the investigator first becomes aware of the problem. All adverse events will be submitted annually for review by the MGB IRB.

11. Data and Research Material Sharing

A) Sending Data/Materials to Research Collaborators outside Mass General Brigham

Data, materials and personally identifying data will not be shared outside Mass General Brigham. The UMass Boston PI and research assistants have a non-employee research status at MGH and will work within the password protected encrypted network drive on MGH's secure server.

Receiving Data/Materials from Research Collaborators outside Mass General Brigham

De-identified data for the biomarker analysis will be received from the Mayo clinic, where the urine biomarkers will be analyzed. Mayo clinic will not be able to re-identify participants. Data will be transferred using an encrypted e-mail.

12. Privacy and Confidentiality

☒ Study procedures will be conducted in a private setting.
☒ Only data and/or specimens necessary for the conduct of the study will be collected.

- ☒ Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- ☒ Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- ☒ Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol.
- ☒ Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- ☒ All electronic communication with participants will comply with Mass General Brigham secure communication policies.
- ☒ Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research.
- ☒ All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens.
- ☒ The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research.
- ☐ Additional privacy and/or confidentiality protections

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