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E-cigarettes as harm reduction tools in smokers who fail to quit with traditional methods

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1 ABSTRACT

The majority of smokers try to quit each year, and the majority of quit attempts fail, even when the most effective FDA-approved pharmacotherapies are used. Non-combustible tobacco products emit fewer harmful chemicals than cigarettes, and thus for smokers who cannot quit smoking, switching completely to a less harmful product is likely to improve their risk of cancer and other deleterious health outcomes. E-cigarettes, the most commonly used non-cigarette tobacco product, have been shown to deliver sufficient nicotine, be appealing to smokers, and reduce cigarette smoking when provided to smokers to use ad libitum. For smokers who have failed to quit with traditional methods, trying to switch to a less harmful product may be more likely to help them stop smoking than trying to quit using tobacco altogether repeatedly with pharmacotherapy. The proposed trial evaluates the potential of e-cigarettes to serve as substitutes for current smokers who have already tried, and failed, to quit with traditional methods. Current smokers who failed to quit with FDA-approved pharmacotherapy within the past year (N=30) will be randomly assigned to either 1) switch completely to e-cigarettes (Switch Group, n=20), or 2) try to quit again using pharmacotherapy (Meds Group, n=10). Thus, our design is strengthened by a strong active control group. Participants will select a Target Switch / Quit Date on which they will stop smoking. Participants in the Switch group will receive a 5-week supply of NJOY ACE e-cigarettes, an FDA-authorized product. Participants in the Meds Group will receive a 5-week supply of combination nicotine replacement therapy (transdermal nicotine patch and short-acting nicotine lozenge). Participants will use 1-week of their e-cigarette or medication ad libitum while continuing to smoke in advance of their Target Switch / Quit Date, and 4-weeks as instructed following a Target Switch or Quit Date. Behavioral outcomes of interest include partial switching (daily use of e-cigarettes or NRT and smoking reduction > 50%) and complete switching (daily use of e-cigarettes or NRT and biochemically-confirmed abstinence from cigarette smoking at 4-weeks). The proposed trial addresses a highly significant research question using a rigorous design and is supported by a strong investigative team.

2 OBJECTIVES

2.1 OBJECTIVES

Primary Aim: Test a switching approach and a standard quitting approach among smokers who have previously failed to quit with traditional methods to assess feasibility and acceptability.

Hypothesis: The interventions will be feasible to implement among the target population. Those who receive the e-cigarette will rate the intervention as acceptable. The primary outcome is the percentage of participants who complete the 4-week assessment, and secondary outcomes include the percentage of eligible and contacted participants that enroll, and the percentage of participants that complete at least 80% of their daily diaries.

Secondary Aim: Completely a preliminary assessment of the impact of a switching approach on switching to inform sample size estimates for a larger clinical trial.

Hypothesis: The key outcome for this aim is biochemically-confirmed partial switching (daily use of e-cigarettes or NRT and >50% reduction in cigarette smoking), and a secondary outcome is complete switching (daily use of e-cigarettes or NRT and biochemically-confirmed abstinence from cigarette smoking at the 4-week visit).

3 BACKGROUND AND SIGNIFICANCE

Most smokers want to quit smoking and current FDA-approved pharmacotherapies fall short.
Although the prevalence of smoking has declined over several decades, 34.1 million adults in the US are still smoking[1]. Most smokers want to quit—68% of smokers are interested in quitting, and 55.4% try to quit smoking each year[2]. However, only 7.4% are successful[2]. FDA-approved pharmacotherapy for smoking cessation can help[3, 4]. Transdermal nicotine patch along with short-acting nicotine replacement therapy (i.e., combo NRT), can increase rates of quitting to 36.5%[3]. However, even with our best methods the majority still return to smoking[5].

Many smokers try to quit repeatedly.
Many smokers try to quit repeatedly before they are successful—on average smokers try 30 times or more before they successfully quit[6]. Unfortunately, the probability of success decreases with each subsequent quit attempt[6], and smokers report fatigue with trying and failing to quit[7, 8]. Smokers who have failed to quit within the past year are less likely to achieve abstinence on their next attempt compared to smokers making their first attempt[9]. Although pharmacotherapy is helpful, repeatedly trying to quit with the same pharmacotherapy has been shown to decrease success[10]. In sum, there are large numbers of smokers who want to quit, and who repeatedly try to quit, but for whom our current treatments continue to fail them. Alternative strategies that can reduce death and disease are needed.

3.1 INTERVENTION TO BE STUDIED (E-CIGARETTES AS HARM REDUCTION TOOLS)

Non-cigarette tobacco products as harm reduction products.
Without question, most of the harm from smoking comes from the combustion of tobacco. Over the last decade, many novel tobacco products have been designed to deliver nicotine without tobacco combustion—resulting in the delivery of fewer toxicants than cigarettes. These products are marketed as alternative products for addicted smokers with the goal of reducing harm. Indeed, the harms associated with tobacco are best viewed on a continuum, with combustible cigarettes and abstinence at polar ends, and alternative products in between[11, 12]. NRT would be close to the abstinence end of the spectrum, and non-combustible tobacco products, like e-cigarettes lie somewhere between. The discussion around alternative products has driven an intense debate in the public health community, with some emphasizing risks[13] and others potential benefits[14, 15]. We recognize that these products likely have ***both*** benefits and harms, and our goal is to understand whether they have the potential to serve as harm reduction tools for smokers who have already tried to quit.

E-cigarettes as potential harm reduction tools.
The most popular non-combusted tobacco products are e-cigarettes[1]. E-cigarettes have risen rapidly in prevalence, with more than 10.9 million US adults currently using them[1]. The long-term health effects of e-cigarettes are still largely unknown, but they are not harmless. E-cigarette aerosols contain numerous irritants and toxicants[16]. However, e-cigarettes deliver much lower levels of toxicants than cigarettes[17-21], and exclusive e-cigarette users are exposed to lower levels of toxicants than cigarette smokers[16, 19, 22], suggesting that **switching completely from cigarettes** is likely to improve health outcomes[21, 23]. Exposure to harmful constituents is likely to be improved even if switching is incomplete (i.e., dual use) if there is a reduction in cigarette use [22].

The impact of non-combusted products on cigarette smoking.
There are now numerous studies, including our own, demonstrating that e-cigarettes reduce cigarette smoking, at least under certain circumstances. Most of these studies are non-randomized, observational survey or cohort studies. In a recent special issue of the *American Journal of Health Behavior*, industry scientists from JUUL reported data from 17,986 adult smokers who purchased a JUUL starter kit. Across a variety of demographic subgroups, complete switching rates were near 50%[24]. Further, the effect of e-cigarettes grew over time—at 1-month, 27.2% of participants reported switching, while at 12-months, 51.2% of participants reported switching[25]. Although these data come from industry scientists and should be viewed with skepticism, they demonstrate the potential for e-cigarettes to disrupt smoking. In line with these data from other groups, multiple randomized trials from our group have now demonstrated that providing e-cigarettes to current smokers and allowing them to use them ad libitum decreases cigarette smoking and dependence[26-29]. These data show that even without instructions to switch completely, e-cigarettes have the potential to reduce cigarette smoking.

Non-combusted tobacco products as harm reduction tools for smokers who cannot quit?
FDA-approved pharmacotherapies should be the first line intervention for smokers who want to quit. For smokers who have tried to quit using these methods and failed, one could argue that research should be devoted to optimizing these options. We do not disagree. However, because e-cigarettes are now the most used aid to try to quit smoking,[30] ***we need to know if e-cigarettes work as substitutes for cigarettes***. We especially need to know if they work in the group for whom they are most appropriate—smokers who have tried to quit using safer interventions, and failed to be successful. Although switching to a non-combustible product is clearly more harmful than quitting altogether, it could reduce the harms of tobacco on a population level if smokers are more likely to switch than they are to completely quit using traditional methods.

We know relatively little about the use of non-combusted tobacco products for promoting complete switching. Existing data are limited in several ways. First, most trials recruit smokers regardless of motivation to quit and participants are told to use the products ad libitum rather than switch completely. Non-cigarette tobacco products would likely produce greater reductions in cigarette smoking and greater switching rates if smokers made an intentional effort to switch completely.

Further, the greatest health benefits are likely to come from complete switching, rather than ad libitum use while continuing to smoke (i.e., dual use).

Second, most trials investigating the impact of e-cigarettes on smoking lack a comparison to pharmacotherapy. Thus, they cannot provide information about whether e-cigarettes are more (or less) likely to promote abstinence through switching compared to traditional cessation products. Published trials that utilize a pharmacotherapy comparison group in motivated smokers come almost exclusively from outside the US. Two trials deserve attention –one clinical trial of 885 treatment-seeking smokers in the UK found that e-cigarettes led to greater cessation compared to NRT (18% vs. 9.9%)[5]. A second trial of 1124 smokers in New Zealand found that receiving an e-cigarette along with nicotine patches increased smoking cessation compared to receiving patches alone (7% vs. 2%)[25].

Third, there are almost no data in switching to non-cigarette products in smokers who have previously failed to quit using traditional methods. Only one published trial is relevant here. Smokers from the UK who recently failed to quit using a stop smoking program (N=135) were assigned to either receive an 8-week supply of NRT or a starter pack of e-cigarettes[31]. All participants set a date to quit or switch. As compared to smokers given NRT, smokers provided with e-cigarettes were more likely to be biochemically confirmed abstinent at 6-months (19.1% vs. 3%), and more likely to have reduced their smoking by >50% (26.5% vs. 6%). One other relevant trial is now underway in the US, in which smokers who failed to quit using the Quitline (N=372) will be randomly assigned to either 1) a nicotine-containing e-cigarette, 2) a placebo e-cigarette, or 3) an assessment only control group. This study will be informative, but it lacks a comparison to FDA-approved pharmacotherapy of any kind, and enrolls participants who may or may not have previously tried to quit. FDA-approved pharmacotherapy should always be recommended first because complete abstinence from tobacco results in the biggest health gains.

Together, these data demonstrate that e-cigarettes may be more effective for stopping smoking through switching than traditional methods which promote quitting tobacco altogether. However, most published trials 1) focus on ad libitum use of e-cigarettes rather than complete and intentional switching among smokers motivated to quit, and 2) are conducted outside the US.

Clinical and public health significance.

Even though e-cigarettes have risen in prevalence over the last decade, data on the use of these products as harm reduction tools for smokers who try to switch completely is lacking. The paucity of data is problematic for several reasons. 1) Clinicians cannot provide clear guidance to smokers who may be interested in switching. One analysis of conversations on a digital message board between patients and medical providers found that the frequency of e-cigarette questions was increasing; in 2011, only 1.2% of tobacco-related questions were about e-cigarettes, but by 2015, this percentage rose to 5.3%. Moreover, 20% of responses were positive towards e-cigarettes and 40% were negative towards e-cigarettes[32], reflecting the confusion about these products even among medical professionals. 2) Smokers who fail with traditional methods are continuing to smoke cigarettes, the most harmful tobacco product available. E-cigarettes have the potential to reduce the burden of disease and death from tobacco for these individuals, but more data are needed on whether they can effectively do so. 3) Public health organizations are providing mixed messages about the health risks of non-cigarette tobacco products, leading to misperceptions about the health risks of e-cigarettes and continued use of cigarettes. A recent Cochrane review of e-cigarettes for the purpose of stopping smoking ranked the confidence of evidence that e-cigarettes are effective for smoking cessation as low, particularly given the low number of trials[33]. The review also underscored the need for additional data on this topic, especially data comparing e-cigarettes to pharmacotherapy. Public health organizations have offered mixed recommendations on the use of non-cigarette products for smoking cessation—with some not recommending their use at all (The American Cancer Society, American Lung Association)[34, 35], and some acknowledging that complete switching to e-cigarettes would reduce health risks compared to continued smoking, but not recommending the use of these products over traditional methods (Centers for Disease Control, Food and Drug Administration)[12, 36].

The proposed trial

The goal of the proposed study is to provide one of the first well-designed, randomized, controlled trials that addresses whether alternative tobacco products have the potential to serve as harm reduction tools in a critical population—smokers who have tried to quit using FDA-approved pharmacotherapy and failed. We will utilize the most popular non-cigarette tobacco product for adult smokers—e-cigarettes. Importantly, we include a strong active control group (FDA-approved pharmacotherapy for smoking cessation).

4 ELIGIBLITY CRITERIA

4.1 INCLUSION CRITERIA

To be eligible for this study, the participant must meet all of the following criteria:

a) At least 21 years old
b) Smoking at least 5 cigarettes per day for 1 year (baseline CO>8ppm)
c) A quit attempt using an FDA-approved pharmacotherapy (varenicline, nicotine replacement therapy, bupropion) in the past year that resulted in abstinence of at least 24 hours
d) Intention to quit smoking within the next month
e) Access to daily e-mail or a smartphone that receives text messages (necessary for diary completion)

4.2 EXCLUSION CRITERIA

To be eligible for this study, the participant CANNOT meet any of the following criteria:

a) use of e-cigarettes on 9 or more days in the past 30 days
b) current use of pharmacotherapy for smoking cessation
c) pregnant, breastfeeding, or trying to become pregnant
d) household member currently enrolled in the study
e) contraindicated for NRT
f) planning to move out of the area within the next 6 months.

5 PROCEDURES

Design Overview: Smokers who have tried to quit within the past year using an FDA-approved pharmacotherapy and remain interested in quitting will be randomly assigned to either 1) receive FDA-approved pharmacotherapy (Meds Group, combination transdermal and short-acting NRT), or 2) receive e-cigarettes (Switch Group). Participants will choose a Target Switch/Quit Date within 1 week. Participants will be instructed to try their assigned medication or product before their Target Switch/Quit Date, continuing to smoke if they wish. This lead-in period allows for pre-quit use of NRT, which has been shown to increase quit rates[37]. Use of assigned non-cigarette tobacco products prior to switching completely allows participants to learn to operate and acclimate to their device before switching. Participants will complete weekly assessments and daily electronic diaries cataloging their tobacco use across the 4-weeks.

Experimental Design: Study design follows our prior and ongoing studies, and all procedures, including diaries, are well established. Prior to attending the in-person screening session, participants will complete an online screening questionnaire to determine preliminary eligibility and may be consented remotely (see below for details). If consent is not completed remotely, it will be completed in person at the Screening/Baseline Session prior to collection of any data.

Screening/Consent/Randomization. Potential participants will be directed to a REDCap screening tool. Those meeting eligibility criteria will be sent an electronic copy of the consent form, and a consent session will be scheduled. In a virtual consent session, the participant and staff member will be able to talk with each other (and see each other, using one method; see below) and review the consent form together, but with added ability to electronically share, sign, and return the consent form. After participants complete the virtual consent, we will schedule the in-person Screening/Baseline visit. At the Screening visit, we will collect an expired CO sample, ensuring that our sample is indeed comprised of smokers. Participants will be randomized. Participants will be enrolled in daily electronic diaries at the end of the Baseline. Participants will receive study product / medication and instructions for dosing (Meds Group) or how to operate their device (Switch Group). Participants in the Meds and Switch Groups will choose a Target Quit / Switch Date. Participants will be instructed to either quit smoking completely on their Target Quit Date (Meds Group) or to switch completely to their assigned non-cigarette product on their Target Switch Date (Switch Group). They will be told that if they are unable to quit completely, they should reduce smoking as much as possible. Note that for Switch Group participants who do not switch completely, use of both

products (i.e., dual use) is a likely outcome. The health impact of dual use is dependent on the decrease in cigarette smoking (i.e., health will be improved if smoking is reduced). We will measure and report the percentage of participants in the Switch Group who engage in sustained dual use and the percentage reduction in cigarette smoking. Participants who engage in dual use, but do not decrease cigarette smoking by > 50% will be referred to additional treatment at the final visit.

Target Switch/Quit Date. Participants will receive text messages on the date before and on the day of their Target Quit/Switch Date reminding them to use their assigned medication and abstain from smoking (Meds Group), or switch completely to their assigned product (Switch Group).

Follow-up Assessments. Participants will complete follow-up assessment each week during the 4-week medication and product period. Participants will return to the lab to provide breath samples at Week 4. Other assessments (Week 1, Week 2, Week 3) will be completed over the phone with study staff.

Compensation. Participants will receive $50 each for the in-person assessments (Baseline, Week 4), $25 each for the phone assessments (Week 1, Week 2, Week 3), and a $100 completion bonus if they complete all assessments ($275 total). Participants who are not eligible at the Baseline visit will receive $15 for their time. In addition, participants can receive up to $25 for completing each week of daily diaries ($125 total for 5 weeks of diaries). Participants who complete all diaries and all assessments can earn $400.

5.1 CONSENT PROCESS

All research personnel have up to date CITI Certification for Protection of Human Subjects and will keep this training current throughout the course of the study. Study participants will be recruited through local media outlets (e.g., craigslist, flyers, print ads, Facebook). Participants will complete an online redcap survey to determine initial eligibility. When participants click the link for this survey, they will see a brief description of the research study. Once participants have been determined to be initially eligible, they will be invited to participate in the consent process.

The consent process will take place via one of the following modalities: 1) Remote electronic consent (e-consent) via REDCap facilitated with a discussion over the phone, 2) Remote consent via doxy.me (video), or 3) in-person consent (in-person visit at start of Baseline). Options 1 and 2 are functionally the same (remote teleconsent prior to attending Baseline), but utilize different platforms (doxy.me vs. REDCap), and we have built in the option to use both platforms in case of technicality difficulties with one platform. During COVID-19 restrictions, all consenting will be done remotely (not in-person). We have included the option for electronic consent to reduce the length of the first in-person visit, while still providing ample time for the consent process. During the teleconsent process, the participant and staff member will be able to talk with each other and review the consent form together. When participants sign the consent form (details below), the form can be downloaded by study staff and saved in a secure REDCap/Box folder (details below).

All participants will be provided with a hard copy and/or electronic copy of the consent form. Participants will be given time to review the consent documents, as well as given a detailed description of the consent documents by study staff. After participants have read the documents and the documents have been described by the study staff, participants will demonstrate that they understand key aspects of the study by verbally answering questions from study staff about participation (e.g., “Can you tell me what the risks of participation are?”). Participants will sign the consent form only after both the participant and the study staff member are confident that the participant understands their participation and the risks associated with participating. Consent/HIPAA signatures may be collected electronically. When consent is collected electronically in person, our study team has a combination laptop/tablet that will be used for the eProcess. No information will be stored locally on the laptop/tablet; all information will be stored securely in REDCap/Box folder if captured electronically. Instead of signing on paper, a participant will enter his/her name, date, and sign electronically (with mouse or finger) in REDCap. Dr. Smith will supervise all aspects of the recruiting process. During COVID-19 restrictions, all consenting will be done remotely through Redcap or doxy.me.

5.2 SETTING

The Medical University of South Carolina will be the only study site. In-person lab sessions will take place in the Center for Research Evaluating Smoking and Tobacco located at 30 Bee Street in Charleston, or at similar lab spaces on the MUSC Florence and MUSC Lancaster campuses. We currently use this lab space for a number of other lab-based studies. This space includes three testing rooms for conducting participant visits, and these testing rooms are ventilated to allow

smoking/tobacco use inside the room. The lab also has a bathroom for collecting urine specimens, and a control room where staff can see and talk to participants while they complete smoking procedures in the testing rooms.

5.3 RECRUITMENT METHODS

Potential participants will be recruited from the Charleston, Florence, and Lancaster SC communities using standard recruitment methods (craigslist, TV, radio, newspaper, social media) using IRB-approved flyers and ads. Potential participants will be directed to a REDCap screening questionnaire for determination of preliminary eligibility. All appropriate approvals will be obtained if/as needed prior to posting any flyers/advertising in the community.

5.4 SPECIMEN COLLECTION AND BANKING

We will collect spot urine samples at baseline. These urine samples are collected for the purposes of pregnancy testing. Specimens will not be stored, and will be discarded after conducting the pregnancy test.

5.5 MODIFIED PROCEDURES TO BE IMPLEMENTED DURING COVID-19 RESTRICTIONS:

For interview-administered questionnaires, we will call participants in advance of in-person visits and complete the questionnaire over the phone via interview with study staff. For questionnaires that are completed independently by the participant, we will send them a RedCAP link prior to the visit and request that they complete the questionnaires on their own. If participants fail to complete these questionnaires on their own or we are unable to reach them to complete the questionnaires, we will ask the participant to complete them at the visit in the lab.

For all visits, participants will be called 24 hours prior to all visits to confirm they are not experiencing any symptoms of COVID-19. All participants for each visit will be required to wear a mask and remain six feet away from the research staff and others when possible. When staff and participants must interact (for CO collection and product disbursal), at least six feet of distance will be maintained by placing materials on a desk/table six feet away from the participant and then staff stepping away while the participant approaches to retrieve materials. All surfaces will be sanitized prior to the visit and after the visit.

6 STUDY

Timepoints	Screening / Baseline	Week 1 Call	Week 2 Call	Week 3 Call	Week 4 visit
Assessments					
Online Screening	X				
Informed Consent	X				
Demographics	X				
Carbon Monoxide	X				X
Physiological and Medical History	X				
Tobacco Use History	X				
Randomization	X				
Adverse Event Monitoring		X	X	X	X
Timeline Followback	X	X	X	X	X
Stages of Change / Contemplation Ladder	X				X
E-cigarette Reasons for Use	X				
Fagerstrom Test for Nicotine Dependence	X				X
Penn State Cigarette Dependence Index	X				X
Penn State E-cigarette Dependence					X
Brief Wisconsin Inventory of Smoking Dependence Motives	X				X
Questionnaire of Smoking Urges	X	X	X	X	X
Respiratory Health	X	X	X	X	X
Cigarette Evaluation Scale	X	X			X
Product Evaluation Scale (E-cigarette)		X			X
Perceived Health Risks (UB)	X	X			X
Perceived Health Risks (E-cigarette)	X	X			X

Electronic Daily Diaries	**Enroll→**	**→**	**→**	**→**	**→Unenroll**

7 RISKS AND BENEFITS

The research protocol calls for smokers assigned to the Meds group to use nicotine replacement therapy, and those assigned to the Switch group to use NJOY ACE e-cigarettes. Nicotine Replacement Therapy is FDA-approved to be safe and effective, and e-cigarettes are no more harmful than conventional cigarettes. Indeed, various studies suggest that e-cigarettes may offer reduced harm. Questionnaires and interviews are all non-invasive and involve minimal risk to study participants.

7.1 RISKS TO SUBJECTS

Potential risks are as follows:

1) Use of nicotine replacement therapy
2) Use of e-cigarettes
3) Concurrent use of cigarettes with medication or non-cigarette tobacco products
4) Non-smokers in the home (i.e., children) experimenting with non-cigarette tobacco products
5) Loss of confidentiality

Use of nicotine replacement therapy

For our study, participants assigned to the Meds group will be given nicotine replacement therapy (combination transdermal and short-acting lozenge).

Nicotine lozenge

In a prior trial of the particular lozenge we will be using, 68% and 71% of 2 and 4 mg users of nicotine lozenge reported an adverse event (AE) vs. 54% of placebo users [38, 39]. With both active doses of the lozenge, 7% dropped out due to AEs and 7% dropped out due to AEs on placebo. With both active doses, 1.6% reported a serious AE which was not different than that for placebo. There were no deaths or irreversible injuries deemed possibly due to lozenge. The most common AEs were nausea, flatulence and upper respiratory tract infection [38]. The current labeling on OTC lozenge states pregnant and breast-feeding women, those less than 18 years of age, those using a prescription medication for depression or asthma or a smoking cessation medication and those with heart disease, recent heart attack, irregular heartbeat, high blood pressure not controlled by medication, stomach ulcers or diabetes should consult a provider before using the lozenge.

In a recent trial of placebo vs. single vs. multiple medications for smoking cessation [40], the three most common adverse events within the lozenge group were 1) nausea: 7.8%, compared to 4.4% within placebo group, 2) mouth/throat irritation: 6.7%, compared to 3.3% within placebo group, and 3) hiccups: 6.2%, compared to 0.3% within placebo group. All other adverse events occurred <5%. In a recent trial from our group that used the nicotine lozenge, which was not placebo-controlled, the most common adverse events were nausea (23% of all adverse events), throat irritation (17%), and hiccups (13%).

Dependence on the lozenge has not been well studied. The pharmacokinetics of the lozenge most closely matches that of nicotine gum. With gum used for abrupt cessation, the estimated incidence of dependence is 1-3% [41].

Nicotine patch

The most common side effects from nicotine patch are skin irritation, insomnia, and headache or nausea. In an early but seminal placebo controlled test of patch [42], there were few systemic side effects of patch use: 21% vs. 15% of smokers in the patch and placebo groups respectively reported a side effect during the treatment period. The most frequent symptoms with the patch as compared with the placebo patch were headache (4 vs. 4 percent), nausea (4 vs. 1 percent), and vertigo (4 vs. 0 percent). Transient mild itching was reported by 14% of the subjects in the patch group and 1% in those in the placebo group after the first week ($P<0.001$). At each visit, 4.5% to 7.3% of the remaining subjects in the patch group reported erythema, as compared with 2.3% to 6.7% of those in the placebo group. Acute eczema persisting for several days in the area of the patch caused 1.4% of the subjects in the nicotine group and 0.7% of those in the placebo group to stop using the patch.

In a separate but similar study comparing bupropion vs. patch vs. combined bupropion/patch vs. placebo [43], the most common adverse events reported by patch participants were 1) insomnia (30% in active patch group vs. 20% in placebo),

2) headache (28% in active patch group vs. 33% in placebo), 3) application site reactions (19% in active patch group vs. 7% in placebo), and 4) dream abnormalities (18% in active patch group vs. 3% in placebo).

Finally, in a recent trial of placebo vs. single vs. multiple medications for smoking cessation [40], the two most common adverse events within the patch group were 1) skin irritation: 14.7%, compared to 2.7% within placebo group, and 2) disturbed sleep: 11.3%, compared to 5.6% within placebo group. All other adverse events occurred <5%. Seven percent of patch users vs. 4% of placebo users discontinued medication due to adverse events.

Combined patch & gum

Combination treatments are often suggested for more dependent smokers and/or smokers with chronic medical conditions [44-46]. One review in particular [44] provides significant rationale by which combined NRT should not incur significant risks, since NRTs provide lower doses per unit or per hour than are typically obtained by cigarette smoking, and the rate of nicotine administration for all NRT products is substantially slower than that from an inhaled cigarette.

In a recent trial of placebo vs. single vs. multiple medications for smoking cessation[40], the four most common adverse events within the combined patch/lozenge group, were 1) disturbed sleep: 9.0%, compared to 5.6% within placebo group, and 2) skin irritation: 8.9%, compared to 2.7% within placebo group, 3) nausea: 7.9%, compared to 4.4% within placebo group, and 4) mouth/throat irritation: 5.7%, compared to 53.3% within placebo group. All other adverse events occurred <5%.

Use of e-cigarettes

E-cigarettes are not fully combusted, and as a result, they deliver lower levels of toxicants than cigarettes. We will verify smoking status at study onset, and thus, we will not provide e-cigarettes to anyone to whom it would present increased risk.

E-liquid will contain propylene glycol, which some suggest may be harmful. E-liquid also contains a variety of flavor constituents, and their long-term effects upon inhalation are unknown.

As for e-cigarette adverse events, these are usually mild. We report here on 3 moderate-to-large surveys assessing e-cigarette adverse events. In the first[47], 3 side effects were reported by >20% of respondents: headaches (21%), cough (27%), and increased phlegm (25%). In the second[48], the most common negative effect of e-cigarette use was throat and mouth irritation, and fewer than 3% "reported a high level of side effects." Finally, the largest online survey to date[49] did not fully assess adverse events but reported that 26% of e-cigarette users reported burning in throat. A recent cohort study reported that the most reported adverse event was mouth irritation (6.1%)[50]. In a cross-over study of 40 smokers given e-cigarettes for 4 days[51], the 4 most common adverse events (within highest dosage group) were mouth/throat irritation (38%), nausea (29%), vertigo (21%) and headache (22%). All other adverse events were rare (<5%). We have no expectation that NJOY ACE-specific adverse events will be markedly different than general e-cigarette adverse events. However, given the higher nicotine content of NJOY ACE, it is possible that it could result in higher rates of headache, nausea, or insomnia.

In the recent RCT from New Zealand[52], there was a higher number and proportion of adverse events among active e-cigarette group, but the event rate did not significantly differ as compared to nicotine patches. In a RCT from Italy[53] there was no differential rate of adverse events among high, medium, or placebo e-cigarette groups. The 5 most common adverse events were dry cough, mouth irritation, shortness of breath, throat irritation, and headache, with no serious adverse events. The study also reported no significant changes in body weight, resting heart rate, or blood pressure.

In 2019, there was widespread concern about rates of lung injury among adolescents and adults who used vaping devices, and this injury was named EVALI (e-cigarette and vaping product use associated lung injury)[54]. However, more recent data revealed that these injuries were related to Vitamin E Acetate, an ingredient often found in THC-containing e-liquid, but sometimes found in nicotine-containing e-liquid purchased from unofficial sources (i.e., black market e-liquid)[54]. Since this discovery, the rates of EVALI have dropped dramatically[54], so much so that the CDC has not updated their EVALI webpage since February of 2020. We will purchase all e-liquids that we provide to participants from commercial sources, avoiding the risk of EVALI.

Concurrent use of cigarettes with medications or e-cigarettes

Our study includes a one-week lead in period before the target date when participants are instructed to try their assigned product before quitting or switching. During this time, participants will be smoking and using their assigned product. After the target date, participants are told to stop smoking completely. However, it is likely that many participants will not be able to stop completely or will relapse after a period of abstinence from cigarettes. We will instruct participants to continue their assigned medication or product and reduce their use of cigarettes as much as possible. Thus, there is likely to be some

concurrent use of cigarettes along with medication, or concurrent use of cigarettes with a non-cigarette tobacco product (i.e., dual use).

Combined use of cigarettes and medication

It was previously thought that using NRT at the same time as cigarettes could result in nicotine intoxication; i.e. nausea, dizziness, headache, stomachache, etc [55]. An early anecdotal report suggested concomitant use of NRT and smoking could induce heart attacks, but several large empirical studies since then have failed to confirm this observation [55]. For example, in the LHS study [56] and in a prior study from our group [57], large numbers of smokers concurrently smoked and used nicotine gum or other NRT products and the incidence of any significant AEs was < 1%. Recent research now demonstrates that starting nicotine patch prior to stopping smoking increases quit rates relative to starting patch at the time of cessation[58, 59].

Combined use of cigarettes with e-cigarettes

If smokers use cigarettes along with another tobacco product, the major concern will be intake of nicotine, and too much of it. Symptoms of nicotine intoxication include nausea, dizziness, headache, and stomachache[55]. In prior studies from our lab where participants used e-cigarettes and many smoked concurrently, there was no evidence of nicotine intoxication, nor have we seen serious adverse events[60, 61].

The bulk of the evidence surrounding these products suggests that smokers who engage in dual use with e-cigarettes can titrate their nicotine intake. That is, they reduce their use of 1 product when they increased use of another product to avoid excessive nicotine intake. Thus, it is unlikely that concurrent use of cigarettes along with NJOY ACE would result in nicotine intoxication.

Some researchers have expressed concern that dual use may result in increased overall dependence on tobacco products. Dependence on a novel product isn't necessarily a health concern if participants reduce use of cigarettes, which is a more harmful product than e-cigarettes[62]. Further, it is unlikely that participants will develop dependence on a novel product in the short sampling period. Nonetheless, we also assess dependence on all products (cigarettes, e-cigarettes,), and for participants who increase their dependence on any product during the study without reducing cigarette smoking by >50%, we will refer them to seek treatment for tobacco dependence at the final follow-up assessment.

Use of non-cigarette tobacco products among non-participants and non-smokers, including children. Whenever a product is given to a smoker to take home and use, there is potential that the product will be used by someone else, inclusive of non-smokers and even children. This would be the case for a local in-person study or a remote study. In Dr. Carpenter's recently completed snus trial in which he mailed tins of smokeless tobacco to smokers all over the country, such "diversion" was not a problem, nor has it been observed in his ongoing R01 of e-cigarettes. We will verify smoking status at the study outset and will advise participants who receive e-cigarettes to keep them out of reach of children and pets.

Confidentiality. A final risk is breach of confidentiality.

2. Adequacy of protection against risks.

2.1 Informed consent. All research personnel have up to date CITI Certification for Protection of Human Subjects and will keep this training current throughout the course of the study. Study participants will be recruited through local media outlets in each recruitment city (e.g., craigslist, flyers, print ads, tv, Facebook). Participants will be directed to an online REDCap screening questionnaire for determination of initial eligibility. We have a system in place for REDCap to flag potential duplicate entries, ensuring we are able to exclude participants who might try to complete the screener multiple times to gain entry to the study. Participants who are determined to be eligible will be sent the informed consent document to review on their own before scheduling an informed consent teleconsent session or coming to the lab to review the consent document in person. During the consent session, study staff will review the consent document with participants, and answer any questions the participants may have. Participants will demonstrate that they understand key aspects of the study by verbally answering questions from study staff about participation (e.g., "Can you tell me what the risks of participation are?"). Participants will sign the consent form only after both the participant and the study staff member are confident that the participant understands their participation and the risks associated with participating. Consent signatures will be collected electronically during teleconsent or on our study tablet if in person. No information will be stored locally on the laptop/tablet; all information will be stored securely in REDCap. We will abide by all HIPAA regulations as set forth by our institution. Dr. Smith will supervise all aspects of the recruiting process.

2.2 Protection against risk.

Use of nicotine replacement therapy

We will exclude individuals based on standard FDA contraindications for NRT use (pregnancy, recent cardio trauma). Participants will be encouraged to contact the Study PI as soon as possible for serious AEs and for those conditions that OTC labeling suggests seeing a provider. We will withdraw participants who have a serious AE. For other AEs, if the study physician, the participant's physician or the participant wishes it, the participant will be withdrawn from the study.

Use of e-cigarettes.

Participants will be screened for general medical precautions (cardiovascular disease), and all participants will be monitored for adverse events during the study period. We will clearly advise against use of any tobacco product during pregnancy and breastfeeding. Participants will be educated about potential risks of tobacco use, including risks specific to e-cigarettes, and concurrent use of these products with cigarettes. Any serious or unexpected adverse events will be reported to the IRB. The most likely adverse event (potential for nicotine overdose) is anticipated to be rare (<5%) and mild (mouth/throat irritation, cough, headache, nausea, headache), and will be handled quickly (i.e., advice to participant to reduce or stop e-cigarettes). Lab studies of toxicant exposure (above) suggest that e-cigarettes confer no greater risk to health than do conventional cigarettes.

Concurrent use of cigarettes with medications or e-cigarettes,

The consent form will discuss the anticipated negative consequences of nicotine intoxication (nausea, headache) and advise participants to discontinue one or both products should they arise. We will track adverse events at every study contact and will have a toll-free number available for participants to call if they experience an adverse event (AE). All study contacts will remind participants of this number. Participants will be encouraged to contact Dr. Smith as soon as possible for serious events. If they wish, they may contact their local MD. We will withdraw participants who have a serious AE, become pregnant or begin breastfeeding. For other AEs, if the participant's physician or the participant wishes it, the participant will be withdrawn from the study.

It is unlikely that e-cigarette users will become addicted to the product in the 5-week period of prescribed use. We will assess dependence on all products used, and for participants whose dependence increases for any product without a corresponding decrease >50% in cigarettes per day, we will refer them to seek treatment for tobacco dependence.

Use of non-cigarette tobacco products among non-participants and non-smokers, including children. We will verify smoking status prior to randomization to ensure that we do not provide non-cigarette tobacco products to a non-smoker for whom these products would represent increased health risks. We will strongly advise participants that they are not to share the study product with others, and that they should store the product in a secure area that is out of reach of children and pets. We cannot directly assess any diversion/uptake from the perspective of adolescents, since that would require separate consent, and is a separate research question. Given the popularity of e-cigarettes among adolescents, we will stress to participants that they are not to share their product with anyone else.

Confidentiality. We will use the participant's name only on the screening and informed consent/HIPAA documents and these will be kept in electronically in REDCap, a secure database. Instead of signing on paper, a participant will enter his/her name, date, and sign electronically (with mouse or finger) in REDCap. The research materials will become part of the modern record keeping facility of the Institute of Psychiatry, which will minimize risks to the privacy of participants. All interviews, records, charts, rating scales, and other patient information will be kept in locked files at the Cancer Control Program of the Hollings Cancer Center, with limited access to the study personnel. All database files will include password protection to further ensure confidentiality.

7.2 POTENTIAL BENEFITS

Participants assigned to the Meds group will receive combination NRT, an FDA-approved pharmacotherapy for smoking cessation, free of charge.

8 DEFINITION OF ENDPOINTS

Screening: Participants will be directed an online screening form to determine eligibility before providing informed consent. Screening questions assess demographics, tobacco use, use of pharmacotherapy, quit attempts, motivation to quit, and medical history.

Baseline Assessments. Baseline assessments include items from the Population Assessment on Tobacco and Health (PATH) questionnaire, a tobacco use questionnaire to assess detailed history of cigarette and other tobacco use, quit attempts, history of pharmacotherapy use, and e-cigarette use. Reasons for Use of each product will be asked using a questionnaire we established from a review of the literature on most commonly reported reasons for use of non-cigarette tobacco products.

Daily Diaries. During the 1-week lead-in period and the 4-week treatment phase, all participants will complete a brief daily diary (1-2 min each). The diary will assess tobacco use—including cigarettes and e-cigarettes, but will also assess use of pharmacotherapy, craving to smoke, and withdrawal symptoms. We have now used these diaries in multiple studies, with compliance > 85%.

Tobacco Use and Use of Pharmacotherapy. At each assessment, participants will also complete a detailed timeline followback (TLFB) which will assess use of cigarettes, non-cigarette tobacco products (including e-cigarettes) and use of pharmacotherapy (including NRT). We will collect detailed information about number of quit attempts, duration of each attempt, point-prevalence abstinence from cigarettes, and continuous abstinence from cigarettes. At the follow-up assessments we will assess whether participants obtained more of their assigned medication or product, if so, where they obtained it.

Expired CO. We utilize biomarkers to verify changes in smoking, including abstinence from cigarettes, and reductions in smoking. Carbon Monoxide (CO) will be collected at 2 timepoints (Baseline, Week 4).

Respiratory Health. Changes in respiratory health will be assessed using a Respiratory Symptom Questionnaire[65] that asks participants to rate their cough, phlegm production, shortness of breath, and other respiratory symptoms on a scale from 0 to 10, with total score determined by adding the scores of each item.

Secondary outcomes. Changes in cigarette dependence will be assessed using established measures of smoking dependence, including the Fagerstrom Test for Nicotine Dependence[66], and the Wisconsin Inventory of Smoking Dependence Motives[67]. For participants assigned to non-cigarette tobacco products, we will assess dependence on their assigned product using modified version of the Penn State Dependence Scale[68], and all participants will receive the cigarette version of the Penn State Dependence Scale[68] to allow comparison of dependence across products. For participants who have not quit smoking, Motivation and Confidence to Quit will be assessed for all products using a modification of the Contemplation Ladder[69]. We will assess changes in the perceived health risks of cigarettes and e-cigarettes using a Perceived Health Risks questionnaire that is well-established in our laboratory.

We will assess perceived health risks of all tobacco products using a questionnaire that is well established in our studies. The questionnaire asks about the perception of personal health risks, perception of risk to others, perceived level of harmful chemicals, and product addictiveness. Withdrawal and craving to smoke will be assessed using the Minnesota Nicotine Withdrawal Scale[70] and the Questionnaire of Smoking Urges[71]. For participants assigned to non-cigarette tobacco products, the subjective effects of the products will be assessed using a modified version of the Cigarette Evaluation Scale[72] which assesses 5 subscales of subjective effects.

Adverse events will be assessed at each assessment using our Adverse Event Form. Prior research on pharmacotherapy and non-cigarette tobacco products suggests adverse events will be rare and mild.

9 STATISTICAL CONSIDERATIONS AND DETERMINATION OF SAMPLE SIZE

Thirty trial participants will be assigned in a 2:1 ratio to either e-cigarettes (n=20) or NRT (n=10) using permuted block randomization stratified by the number of cigarettes smoked per day (5-10 or 11+). The rationale for 2:1 randomization is to ensure sufficient sample size in the experimental (e-cigarette) arm to yield efficacy estimates with adequate precision. Although our trial is not powered to perform a head-to-head comparison of the two arms, we plan to use the data collected to appropriately power a randomized trial with an efficacy primary endpoint. Instead, we justify our sample size based on the precision of estimates of feasibility and acceptability where precision is based on the width of the corresponding exact binomial 95% confidence interval (CI). Key primary and secondary feasibility and acceptability endpoints include: the proportion of enrolled subjects who complete the 4-week assessment; the proportion of eligible and contacted subjects who subsequently enroll; and the proportion of enrolled subjects who complete ≥80% of their daily diaries. For each feasibility endpoint, we will construct point and interval estimates for the overall study population. We will also construct exact one-sided 80% intervals (equivalent to one-sided $\alpha = 0.1$) and consider the study to be sufficiently feasible and acceptable if the corresponding lower bounds exceed 50%. Table 1 summarizes precision and exceedance probabilities for target feasibility

rates of 70% or higher. Additionally, we will obtain preliminary measures of efficacy by estimating the proportion of enrolled subjects in each arm with biochemically confirmed partial switching (daily use of e-cigarettes or NRT and reduction in smoking (>50%)) and the proportion of enrolled subjects who completely switch (daily use of e-cigarettes or NRT and abstinence at the 4-week visit). Smith and colleagues[31] report a 4-week reduction in smoking of 43% and 24% for e-cigarette and NRT subjects, respectively. Table 2 summarizes precision and exceedance probabilities for target efficacy rates in the experimental arm ranging from 45% to 60%. Finally, we will construct all point and interval estimates separately for male and female subjects to evaluate sex-related heterogeneity.

Table 1: Precision of estimated proportions for feasibility and acceptability endpoints.				
N	Observed proportion	Exact binomial 95% CI of true proportion	CI width = upper bound (UB) – lower bound (LB)	Prob(LB > 0.5 given true proportion = observed proportion) (one-sided exact 80% CI)
30	21/30 = 0.7	(0.51, 0.85)	0.35	0.59
	24/30 = 0.8	(0.61, 0.92)	0.31	0.94
	27/30 = 0.9	(0.73, 0.98)	0.24	>0.99
Table 2: Precision of estimated proportions for efficacy endpoints in e-cigarette arm.				
N	Observed proportion	Exact binomial 95% CI of true proportion	CI width = upper bound (UB) – lower bound (LB)	Prob(LB > 0.24 given true proportion = observed proportion) (one-sided exact 80% CI)
20	9/20 = 0.45	(0.23, 0.68)	0.45	0.56
	10/20 = 0.50	(0.27, 0.73)	0.46	0.75
	11/20 = 0.55	(0.32, 0.77)	0.45	0.87
	12/20 = 0.6	(0.36, 0.81)	0.45	0.94

10 DATA COLLECTION AND MANAGMENT

Research material obtained from the participants include responses to surveys, collected directly by our research team and entered into REDCap, responses to surveys entered directly into REDCap by the participant themselves, and responses to electronic daily diaries, stored directly into REDCap. We will also collect CO, entered by study staff into REDCap at the in-person visits. Research data will be obtained specifically for research purposes. Every effort will be made to maintain subject confidentiality, in accordance with HIPAA.

11 PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS

This project involves two laboratory visits and three phone calls across five weeks. Participants will receive nicotine replacement therapy or e-cigarettes to take home with them for a five-week time period.

Dr. Tracy Smith has used a similar protocol before and she will train and closely monitor research assistants. She will discuss issues with research assistants at least weekly.

Any unexpected death or unanticipated problem involving risks to subjects or others will be reported to the IRB. Consistent with MUSC policy, we will report deaths within 1 day and unanticipated problems within 10 days. We have identified clear risks associated with the trial, which are related to potential breaches of confidentiality and use of nicotine replacement therapy and e-cigarettes.

12 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

12.1 INFORMED CONSENT

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

12.2 INSTITUTIONAL REVIEW

Adverse events will be handled in accordance with MUSC Human Research Protection Program (HRPP) policies. Any event that is unexpected, related or possibly related, and suggest that the research places participants at greater risk than was previously known will be reported to MUSC IRB. Serious adverse events (SAEs) are defined in Section 4.7 of MUSC HRPP as any adverse event temporarily associated with a participant's participation in research that results in death, is life-threatening, requires inpatient hospitalization, results in significant disability/incapacity, results in a congenital anomaly, or any other adverse event that requires immediate medical or surgical intervention. Consistent with IRB policy, any unexpected death will be reported within 24 hours and any unanticipated problem involving risk to subjects or others will be reported within 10 days.

13 DEVICE

The NJOY ACE devices and NJOY ACE pods used in this study are FDA authorized for commercial sale, and there is no FDA approval required to use the devices. NJOY ACE pods will be 5% nicotine and Classic Tobacco or Menthol Flavors. NJOY ACE was selected because it is FDA authorized, is a popular type of ECs, easy to use, has demonstrated nicotine delivery comparable to a combustible cigarette[73] and significantly lower levels of toxicant production compared to cigarettes and other ECs,[74, 75]. Devices and pods will be stores in a locked cabinet accessible to study staff only. Participants will be told to store the devices and pods out of reach from children and pets, and will be told that they are not share their products with anyone.

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