Medical University of South Carolina
Protocol

PROTOCOL TITLE
Comparing the Effects of Augmented Doses of Nicotine Replacement Therapy on Quitting Cigarettes and E-cigarettes

PRINCIPAL INVESTIGATOR
Amanda M. Palmer, PhD

1.0 Objectives / Specific Aims

Tobacco use is one of the leading preventable causes of cancer-related morbidity and mortality in the US, and therefore remains a top priority for public health and cancer prevention research. The landscape of tobacco product use has shifted over the past decade, and research efforts should accommodate for these changes. Whereas smoking rates are declining, the use of electronic (e-)cigarettes is increasing. Although e-cigarettes may be used to help smokers quit cigarettes, many continue to use e-cigarettes without quitting smoking, thus identified as "dual users." For these individuals, nicotine delivery from multiple product sources may increase nicotine dependence, which may result in more challenges with quitting both products. Importantly, any level of combustible tobacco use is detrimental to health and should be discouraged. Results from large representative surveys have estimated that over 60% of dual users want to quit; yet, there is a lack of data and intervention research to determine the most effective and acceptable treatments for dual smoking and e-cigarette cessation. Our prior pilot study showed that a standard dose (21mg patch, 4mg lozenge) of nicotine replacement therapy (NRT) may be an acceptable treatment option for users to quit e-cigarettes; however, dual users were unable to quit both products using this dose alone. The purpose of the present study is to determine if augmented doses of NRT will facilitate dual use cessation among a community sample of dual users. Dual users enrolled in the intervention will receive 1 of 3 NRT treatment doses: Arm A (21mg patch + 4mg lozenges); Arm B (21mg patch + 14mg patch + 4mg lozenges), or Arm C (2X21mg patches + 4mg lozenges). Results from this study will 1) provide preliminary data regarding which NRT dose may be appropriate for dual use cessation, 2) demonstrate the feasibility and acceptability of this intervention within the target population of interest.

Aims and Hypotheses
Aim 1: Evaluate, in a preliminary manner, the effect of augmented doses of NRT, compared to a standard dose, on outcomes from a dual use cessation attempt.
Hypothesis: Higher instances of dual use abstinence days will be observed in the augmented dose groups (Arms B & C) as compared to the standard dose group (Arm A).
Aim 2: Evaluate the feasibility, acceptability, and engagement with the treatment intervention.
Hypothesis: There will be sufficient interest to complete study recruitment and procedures within the time limits of the funding.

Results from the "CAN-DOSE: **C**essation with **A**ugmented **N**icotine for **D**ual use **O**f **S**moking and **E**-cigarettes" study will provide preliminary insight into the effectiveness of NRT with a dual use population, and specifically, which dosage is best tolerated and utilized. These data will inform a future R-series application for a clinical trial for dual use cessation through enhanced doses of NRT. Treatment interventions to reduce the incidence of combustible tobacco use will benefit public health outcomes through cancer prevention.

2.0 Background

Over the past several decades, tobacco control efforts have succeeded in reducing cigarette smoking prevalence, which has reduced the negative health effects of smoking on the population including cancer incidence and mortality[1,2]. Recent estimated from the Centers for Disease Control (CDC) Morbidity and Mortality Weekly Reports (MMWR) suggest that smoking prevalence among adults was down to 12.5% in 2020[3]. However, overall prevalence of tobacco use has not declined as substantially, partially due to increasing rates of use of novel, alternative tobacco products. Specifically, use of electronic nicotine delivery systems (ENDS; i.e., electronic [e-]cigarettes, vaping) has been increasing. Both optimism and concern has arisen regarding the effect of these new products and their potential effects on public health[4,5].

E-cigarettes were initially marketed as an alternative to or means for smoking cessation, and they became popular amongst those currently smoking. Systematic reviews of the evidence show there is here is high certainty that e-cigarettes are just as effective as nicotine replacement therapy (NRT) for smoking cessation[6]. However, consistent with existing smoking cessation treatments, there is substantial room for improvement in quit rates. An unfortunate consequence of e-cigarette use, which differs from NRT outcomes, is that individuals who smoke and try to quit with e-cigarettes may progress to become "dual users" of both products[7]. Some individuals who smoke may initiate e-cigarette use for reasons other than cessation, or alternatively, exclusive e-cigarette users may initiate cigarette smoking. It is estimated that in 2020, 39% of US e-cigarette users also smoked cigarettes, amounting to at least 2 million dual users[3,8]. Most recently, devices containing salt-based, high nicotine solutions dramatically overtook the e-cigarette market by 15,000% from 2017-2022[9,10], which has likely increased the number of e-cigarette users and dual users.

Cigarettes, on average, contain about 1.2mg of nicotine (~24mg per pack of 20 cigarettes). Nicotine-containing e-cigarette liquids may range anywhere from 3mg/ml to 50mg/ml and higher (common in disposable and cartridge devices); therefore, 1ml of nicotine liquid (a typical amount for one e-cigarette or refill) may contain more nicotine than a pack of cigarettes. Nicotine absorption pharmacokinetics is similar to that of smoking with some devices[11]. Whereas cigarettes are, in general, smoked one at a time during smoking sessions, e-cigarettes may be vaped throughout the day in several smaller sessions or used in longer puffing sessions similar to smoking.[12]

Both cigarettes and e-cigarettes deliver nicotine, a highly addictive substance, which contributes to sustained smoking and vaping behaviors. Adults who use e-cigarettes report health concerns, dependence, financial burden, social stigma, and discomfort with industry influence as reasons for wanting to stop their e-cigarette use[13-15]. Studies show that over half of adult cigarette smokers are interested in quitting[16], and our has shown that 64.7% of dual users have plans to quit e-cigarette use[17]. Given that e-cigarette use is not completely harmless[18,19], and any level of combustible tobacco use is harmful[20] and poses a risk for the development of cancer, dual users should be a priority population for treatment. At minimum, the priority should be abstinence from combustible cigarettes, but abstinence from both products is ideal as to reduce any negative health effects that might occur. A specific emphasis on smoking relapse prevention is also warranted for this population. Our systematic review of e-cigarette cessation interventions showed that although it is clear that the majority of dual users want to quit, there are no empirically-supported interventions for dual use cessation[21]. In fact, most dual users attempt to quit unassisted ("cold turkey") and are unsuccessful[14]. There is an urgent need to develop evidence-based e-cigarette and smoking cessation interventions for this high priority population.

In order to address the critical need for treatments to help people quit ENDS, clinical scientists may draw upon best practices for smoking cessation as a foundation for intervention development. Pharmacotherapy is a well-established mechanism to promote long-term rates of smoking cessation[22]. Combined nicotine replacement therapy (NRT), which includes daily use of a patch alongside either lozenges or gum for breakthrough cravings, has demonstrated promise in enhancing smoking cessation outcomes[23] and may be especially well-suited to help manage dual use withdrawal symptoms. That is, many dual users might significantly benefit from the combination of an extended-release nicotine patch and the ease of access to lozenges to help mitigate nicotine withdrawal symptoms in the moment.

Additional benefits of NRT are that it is seldom used for longer than 1 year after quitting smoking[24] and is generally well-tolerated. Our pilot trials of NRT for e-cigarette cessation and dual use cessation[21,25] have shown promise for NRT for vaping cessation; however, it was unclear if this dose of NRT was sufficient for dual users (see preliminary results below for a full explanation of the findings). Of note, we know of no other researchers conducting pharmacotherapy trials for dual users, making the proposed work especially novel.

The purpose of the present study is to further investigate the successful smoking cessation intervention, NRT, for dual use cessation. Specifically, given the results of our prior pilot studies (described later in *Preliminary Findings*), the aim is to evaluate whether an augmented (increased) dose of NRT might be more effective in helping dual users achieve abstinence from both products. Prior research has shown that an increased NRT dose is an effective, well-tolerated treatment option for individuals who had not yet achieved abstinence from smoking[22,26]. Dual users who are interested in quitting will be randomized to receive 1 of 3 NRT treatment doses: Arm A (21mg patch, *qd* + 4mg lozenge *prn* [minimum of 5 & up to 20 per day]); Arm B (21mg patch + 14mg patch *qd* + 4mg lozenge *prn* [minimum of 5 & up to 30 per day]), or Arm C (2X21mg patches *qd* + 4mg lozenges *prn* [minimum of 5 & up to 40 per day]). Throughout the course of treatment, dual users will report their tobacco use, medication use, and any side effects. Results from this preliminary study will give insight into NRT dosages that may be appropriate for future clinical trials of dual use cessation, as well as feasibility, acceptability, and engagement data for undergoing this type of treatment and the effects on cessation outcomes.

Innovation

This study includes several innovative elements that align with ACS and NCI's aims to reduce cancer incidence and mortality. **1)** As the previous literature has shown, many dual users who have tried to quit endorsed unsupported, "cold turkey" methods with limited success[14,21]. This project will serve as a foundation for future dual use cessation intervention development work. **2)** Although testing an existing smoking cessation treatment (NRT) is not inherently novel, it is the best foundation for starting research on dual use cessation, which has a critical need for treatment development. Additionally, the augmented NRT doses have not, to our knowledge, been tested on dual users, thus representing a potentially significant impact in the treatment literature.

Proof-of-concept.

Proof-of-concept. We conducted a proof-of-concept feasibility study[27] with 30 participants interested in quitting e-cigarettes (both dual and mono-users; for the purpose of this application, we will discuss results related to the dual users). This study included a qualitative interview followed by enrollment in a pilot trial. In the qualitative interview, participants were asked about why they were interested in quitting vaping and smoking. Primary motives for dual use included major themes surrounding health, cost, perceptions of friends and family, negative consequences of dependence, and stigma. Participants were then randomized (at a 1:2 ratio, respectively) to 4-weeks of either 1) referral to the Quitline or 2) NRT + booklet of tips for quitting. The NRT dosage was the standard dose for someone smoking 1 pack of cigarettes per day: 4 weeks worth of 21mg patches and 4mg lozenges. The booklet was a rudimentary adaptation of standard smoking cessation materials from the MUSC Tobacco Treatment Program[28]. Participants completed assessments

Table 1. Abstinence outcomes

	Intervention (N=18)		**Control** (N=12)	
	Mono Use (N=10)	**Dual Use** (N=8)	**Mono Use** (N=5)	**Dual Use** (N=7)
End of Treatment (Day 28)				
E-cigarette abstinence	4 (40%)	2 (25%)	0	0
E-cigarette change				
Reduced	2 (33.3%)	3 (50%)	1 (20%)	3 (42.8%)
No change	4 (66.7%)	3 (50%)	4 (80%)	4 (57.1%)
Increased	0	0	0	0
Smoking abstinence	-	0	-	0
Smoking change				
Reduced	0	1 (12.5%)	0	1 (14.2%)
No change	10 (100%)	7 (87.5%)	5 (100%)	5 (71.4%)
Increased	0	0	0	1 (14.2%)
Follow-up (Day 56)				
E-cigarette abstinence	3 (30%)	2 (25%)	1 (20%)	1 (14.2%)
E-cigarette change				
Reduced	3 (30%)	2 (33.3%)	0	4 (57.1%)
No change	4 (40%)	4 (66.7%)	4 (80%)	3 (42.8%)
Increased	0	0	0	0
Smoking abstinence	-	0	-	0
Smoking change				
Reduced	0	2 (25%)	0	2 (28.5%)
No change	10 (100%)	6 (75%)	5 (100%)	4 (57.1%)
Increased	0	0	0	1 (14.2%)

reporting e-cigarette use and smoking at end of treatment (EOT) and 1-month follow up. In 6 months, we enrolled 30 participants; 24 (80%) of whom completed the EOT survey and 18 (60%) who completed follow-up. As shown in **Table 1**, following treatment, **33.3% (6/18) of the intervention group that received NRT was able to quit vaping** whereas 0% in the control group did (3-day point prevalence). Notably, no dual users quit smoking; that is, some discontinued their e-cigarette use but continued to smoke. Some dual users were able to reduce their e-cigarette use and/or smoking, and only one had increased their smoking. Another important observation from this study was that individuals who achieved abstinence from vaping self-reported using NRT more than those who were not abstinent (see **Table 2**).

Table 2

Intervention (N=18)	**Abstinent** (N=6)	**Not abstinent** (N=12)	**Abstinent vs Not** T , *p*, d
# days using any NRT	22.67 (2.88)	7.83 (8.67)	**-5.36, <.001, -2.01**
# days using NRT patch	19.50 (4.76)	6.58 (4.76)	**-3.23, <.01, -1.61**
# days using NRT lozenge	11.33 (7.06)	3.91 (5.96)	**-2.35, <.05, -1.17**
# days using combined NRT	8.16 (6.49)	2.66 (5.75)	-1.83, .08, -0.92

Altogether, these preliminary studies support the current application in 1) There is substantial interest in quitting dual use, as evidenced by results from national surveys as well as the recruitment and retention in the proof-of-concept study; 2) It is unclear what dose of NRT might be the most beneficial for those wishing to quit smoking and vaping; 3) Participants who achieved abstinence from vaping tended to use more NRT, which suggests a dose-response relationship between medication use and outcomes; 4) adherence to dual NRT was low and needs to be explicitly encouraged.

3.0 Interventions to Be Studied

The purpose of the present study is to further investigate the successful smoking cessation intervention, NRT, for dual use cessation. Specifically, given the results of our prior pilot study, the aim is to evaluate whether an augmented (increased) dose of NRT might be more effective in helping dual users achieve abstinence from both products. Prior research has shown that an increased NRT dose is an effective, well-tolerated treatment option for individuals who had not yet achieved abstinence from smoking[20,24]. In this intervention study, participants who are dual users of cigarettes and e-cigarettes who are interested in quitting both products will be recruited. Participants will be randomized into 1 of 3 treatment conditions, each receiving a 4-week (28 day) supply of NRT: Arm A (21mg patch, *qd* + 4mg lozenge *prn* [minimum of 5 & up to 20 per day]); Arm B (21mg patch + 14mg patch *qd* + 4mg lozenge *prn* minimum of 5 & [up to 30 per day]), or Arm C (2X21mg patches *qd* + 4mg lozenges *prn* [minimum of 5 & up to 40 per day]). Additionally, participants will receive a supportive booklet, adapted from smoking cessation materials currently in use by the MUSC Tobacco Treatment Program, with tips and strategies for how to go about quitting vaping and smoking. Participants will complete weekly surveys to report on their medication use, tobacco use, and other quitting-related variables. Following completion of the 28-day treatment, participants will be sent follow-up surveys at 1 month (Day 56). Results from this preliminary study will give insight into NRT dosages that may be appropriate for future clinical trials of dual use cessation, as well as feasibility, acceptability, and engagement data for undergoing this type of treatment and the effects on cessation outcomes.

4.0 Study Endpoints.

Primary Endpoint:
Days of dual use abstinence (Day 28, Day 56): The primary outcome of interest is the number of days participants self-report abstinence from both e-cigarettes and smoking. These data will be derived from daily surveys that query about the previous day's e-cigarette use (yes/no, estimated number of times

vaped, estimated amount of cartridge/refill used) and cigarette smoking (yes/no overall, number of cigarettes smoked). Non-responders and missing data will be coded as not abstinent.
Secondary Endpoints:
Reduction (Day 28, Day 56): In addition to number of days of complete dual product abstinence, we will use baseline and daily survey data (described above) to calculate the reduction of e-cigarette use and smoking between groups from baseline to end of treatment.
Safety (Day 28): To further assess differences in acceptability and response to the treatment doses, adverse events between groups will be evaluated. NRT side effects will be captured during daily diary assessments using the Systematic Assessment for Treatment Emergent Events (SAFTEE)[29].
Feasibility/Acceptability (Day 28): Feasibility and acceptability endpoints will be determined by the proportion of eligible subjects able to be contacted who subsequently enroll, the proportion of enrolled subjects who complete the Day 28 survey, and the proportion of enrolled subjects who complete ≥80% of their daily surveys during the treatment period. Participants will report satisfaction and helpfulness of the intervention at the end of treatment (Day 28).

5.0 Study Population / Inclusion and Exclusion Criteria

We aim to recruit 45 participants (15 in each group: A, B, and C). Inclusion criteria include: 1) age 18+; 2) daily nicotine-containing e-cigarette user (25+ days per previous month); 3) e-cigarette use 5+ times/day; 4) e-cigarette use > 1year; 5) smoking >1 cigarette on 5-7 days per week 6) interest in quitting smoking and e-cigarette within the next month (>7 on 10-point scale); 7) willingness to use NRT; 8) able to receive text messages/email, and 8) mailing address in SC.

Exclusion criteria includes medical conditions contraindicated to NRT use (including pregnancy, past month myocardial infarction, current cardiac arrhythmia, current angina, uncontrolled vascular disease, or medical conditions in which consumption of phenylalanine is contraindicated, including Phenylketonuria [PKU] and allergy to phenylalanine), individuals reporting current use of other nicotine-containing products and/or smoking cessation medications, those who vape non-nicotine substances, and individuals unable to consent (e.g. significant cognitive deficit, non-English speaking). These criteria were used in the proof-of-concept study[25] which recruited at an acceptable pace. Exclusion criteria, including health information, will be ascertained via self-report on the online pre-screener. We have requested a waiver of signed consent for this assessment.

Pregnancy status will be ascertained via self-report on the online pre-screener. In addition, we will ask participants if they are sexually active and if they are using any type of contraceptive method (with a list of available options). If female participants are deemed eligible (i.e., not pregnant and not engaging in unprotected sex) and schedule an intake, they will be mailed a pregnancy test. They will be told they will not complete the test until after they have consented to the study and agree to continue. During consent, discuss the exclusion criteria for pregnancy, as well as review risks of medication use as it pertains to pregnancy. Following consent, during the initial intake assessment, we will conduct the pregnancy test. The participant will perform the pregnancy test at home and report results to the research staff via sending a photo of the test (if doing consent over phone) or showing the test on video (if consenting via video call). If the test is negative, we will continue with the rest of the study procedures.

We will not be enrolling vulnerable populations, specifically pregnant women, children, prisoners, or institutionalized individuals. We also will not enroll subjects incapable of providing their own consent. Should a potential subject present where there is a concern about their ability to understand study procedures and provide meaningful consent, their cognitive status and understanding of the study will be evaluated by the investigative team. If there is any concern that the individual may be impaired, they will not be eligible for participation and not enrolled in the study. The rationale will be provided to

the individual as well as his or her family members. Referrals for further evaluation, including urgent or emergent evaluation, will be made as needed and clinically warranted.

6.0 Number of Subjects
We aim to recruit 45 participants (15 in each group: Arm A (21mg patch, qd + 4mg lozenge prn [minimum of 5 & up to 20 per day]); Arm B (21mg patch + 14mg patch qd + 4mg lozenge prn [minimum of 5 & up to 30 per day]), or Arm C (2X21mg patches qd + 4mg lozenges prn [minimum of 5 & up to 40 per day]). We will use all possible methods to recruit until each arm is full.

7.0 Setting
We will use exclusively remote/telehealth procedures as detailed below. Data will be stored on MUSC Box or OneDrive folders which will only be shared with study staff. Any paper copies of data will be stored in a locked office in the HCC building.

8.0 Recruitment Methods
Advertising will be done online through a variety of media outlets seeking dual users motivated to quit. Participants will be screened online for eligibility. Potential participants will complete a pre-screening survey that is linked in the ad. If the individual is deemed eligible, the research staff will conduct a screening appointment via the web/mobile phone with the participant to confirm eligibility. After confirming eligibility, the research staff will conduct a full consent and intake via the tele-consent platform (i.e., Doxy.me or other HIPAA compliant tele-video conferencing software) or a link to a REDCap consent form.

This research study will use remote/telehealth procedures as detailed below, consistent with our Tobacco Treatment Program procedures at our institutions.

9.0 Consent Process

When interested participants enter into the online screening survey via REDCap, they will be provided with information about the purpose of the screening survey, including what information will be collected, and how it will be kept private. Participants will be aware that they will be providing contact information and health information on this survey, which will only be used for research study eligibility purposes and will be kept secure. Participants have the option to stop the screening survey at any time. Upon review of the provided information, participants will provide consent to screening by selecting the appropriate option on REDCap, which will be recorded as consent (signature waived). Eligible participants will be contacted following the screening to consent into the study as outlined below.

Participants will have 2 options to consent into this study: 1) remote consent via a virtual procedure (i.e., Doxy.me or other HIPAA compliant tele-video conferencing software), or 2) remote electronic consent (e-consent) via REDCap combined with a phone call. Informed consent will be maintained in each, allowing (requiring) discussion with study staff to ensure full understanding. In each option, participants will schedule a remote consent “visit” with research staff and will be encouraged to be in a private location during the call. Participants will be provided with a copy of the consent form electronically, which they can review on their own. Research staff will review the consent form with participants during the visit, allowing for any participant questions to be answered. The participant will be encouraged to take as much time as needed to review the consent form prior to enrolling in the study. Participants will also be notified that they will receive a signed copy of the consent form for their personal records to reference in the future.

Remote consent via doxy.me: This essentially is video or telephone facilitated live discussion with study staff and potential study participant. After the initial determination of study eligibility, assessed online in

our secure survey, participants will be asked about their capacity for doxy.me procedures, including access to a computer with a webcam and speakers, and compatible internet browser (doxy.me is currently optimized for Google Chrome & Firefox, with planned expansion to additional browsers). For those who have the required hardware and software for doxy.me, we will offer this option and follow IRB-approved procedures as per precedent. All doxy.me signed consent forms will be saved as pdf files within our study records; the participant also gets an electronic copy. Research staff will then have the participant complete the baseline questionnaire.

Remote e-consent via REDCap: This is similar to above doxy.me procedures but without the video connection, replaced by live phone call. Participants will link to a REDCap-delivered consent document and will have a concurrent phone discussion with study staff who will provide further details on the study and answer any questions. Like doxy.me procedures above, these will likely be scheduled with potential participants in advance, i.e., through a consent appointment. The individual would electronically sign the consent form, and this then becomes a part of the research record, and like above the participant is given an electronic version of the consent to retain.

For all the above procedures, and throughout the study, we maintain a phone line to support anyone who calls with questions. Anyone who completes a consent form will comprise the consented sample. However, the sample is reduced further to those with whom we can establish phone contact (Day 0; weekly follow-up surveys will begin the following day); i.e., the enrolled sample. This enrolled sample is the intent-to-treat sample.
Although the mode of consent may differ across participants (i.e., doxy.me vs. teleconsent) we have taken steps to ensure that all participants will be fully informed of study procedures, including risks/benefits of participation, prior to providing signed consent. We ensure that all potential participants discuss the study with an IRB-approved consenter prior to providing signed consent.

10.0 Study Design / Methods

A target of 45 dual users across South Carolina will be recruited through various media outlets. Advertising will solicit vapers motivated to quit. Dual users will consent to be screened online for study eligibility, including potential for pregnancy. Pregnancy status and health conditions contraindicated to NRT (past month myocardial infarction, current cardiac arrhythmia, current angina, uncontrolled vascular disease, or medical conditions in which consumption of phenylalanine is contraindicated, including Phenylketonuria [PKU] and allergy to phenylalanine) will be ascertained via self-report on the online pre-screener. In addition, we will ask participants if they are sexually active and if they are using any type of contraceptive method (with a list of available options). If female participants are deemed eligible (i.e., not pregnant and not engaging in unprotected sex) and schedule an intake, they will be mailed a pregnancy test. They will be told they will not complete the test until after they have consented to the study and agree to continue. During consent, we will discuss the exclusion criteria for pregnancy, as well as review risks of medication use as it pertains to pregnancy and the aforementioned medical conditions.

If the participant qualifies, research staff will schedule a time to complete the interview and baseline assessment battery. Following consent, during the initial intake assessment, we will conduct the pregnancy test on applicable participants. If the test is negative, we will continue with the rest of the study procedures. Participants will then be randomized to study arm (Arm A (21mg patch, qd + 4mg lozenge prn [minimum of 5 & up to 20 per day]); Arm B (21mg patch + 14mg patch qd + 4mg lozenge prn [minimum of 5 & up to 30 per day]), or Arm C (2X21mg patches qd + 4mg lozenges prn [minimum of 5 & up to 40 per day]). Participants will be provided with a 28-day supply of NRT by mail and a self-help booklet (which includes instructions for medication use) and instructions to select a target quit date within 1 week. Research staff will contact the participants upon receipt of the materials and obtain the

target quit date. Participants in both groups will receive a brochure with information for contacting the SC QuitLine. During the 28-days of treatment, participants will be sent daily monitoring surveys asking about e-cigarette use, cigarette smoking, NRT, and quit attempts during the previous day. One month following the receipt of the materials, participants will complete an assessment battery. All assessment procedures will be completed via approved remote data collection platforms (e.g. REDCap). Participants will have the option to receive all study-related surveys (through REDCap) via text message or via email. No identifying information will be included on the texts/emails.

Randomization. Participants will be randomized to one of the following NRT conditions: Arm A (21mg patch, *qd* + 4mg lozenge *prn* [minimum of 5 & up to 20 per day]); Arm B (21mg patch + 14mg patch *qd* + 4mg lozenge *prn* [minimum of 5 & up to 30 per day]), or Arm C (2X21mg patches *qd* + 4mg lozenges *prn* [minimum of 5 & up to 40 per day]). Randomization to the intervention groups will be stratified on dependence score as follows: Participants will complete both the Roswell ENDS Nicotine Dependence Scale (Roswell eND[30]; e-cigarette dependence) and the Fagerström Test for Nicotine Dependence (FTND[31]; smoking dependence). Both scales have score ranges from 0 (no dependence) – 10 (high dependence). Consistent with cutoffs for the Roswell eND scale, participants will be stratified by low dependence (0-5) or high dependence (6-10) based on their highest score on either scale.

Treatments. All treatment procedures will be conducted remotely (e.g., online, through mail).

Intervention: Following randomization, participants will be instructed to select a quit day (Day 0) within the next week at which time they will commence using NRT. Participants will be sent a supportive text message reminder on that date *("Today is your quit date! Make sure to use your medications and written materials to help you. You got this!").*

NRT medications. Following consent, participants randomized to the combined intervention will be mailed their 28-day supply of NRT. All participants will be encouraged to use the highest dose sent to them based on their randomization. A specific emphasis will be made on instructing participants to use both patches and lozenges concurrently. We will allow participants to engage in dose reductions naturalistically if they feel they need to, which will be captured through the daily surveys. Although this medication has not been formally tested for ENDS cessation, with the exceptions of our small pilot studies[19,23], it is the first line treatment for cigarette cessation. For this reason, we believe it is a safe and acceptable pharmacotherapy to use for this intervention. We will monitor adverse events.

Behavioral Support. A brief, informational booklet will be provided to participants that discusses how to plan and engage in a quit attempt of all tobacco products used. This will be adapted from currently used treatment manuals utilized by the MUSC Tobacco Treatment Program with clinical patients. This booklet will also provide information regarding the SC QuitLine, a freely available public service that provides tobacco cessation counseling and medication over the phone or through mobile/web platforms. Participants will be informed about the services the QuitLine offers as well as how to contact this service.

Daily Monitoring. During the 28-days of treatment, all participants will be sent daily monitoring surveys (described later). All assessment procedures will be completed via approved remote data collection platforms (e.g., texting via Redcap). To increase retention, we will call participants who do not respond for ≥3 days.

Follow-up. At the end of treatment (Day 28), research staff will contact the participant to complete an assessment battery. Four weeks after this (Day 56), a final follow-up assessment battery will be administered. Those who report abstinence from smoking will be mailed a remote carbon monoxide monitor (iCO) to complete and return. To increase retention, surveys will be sent via text and email, and we will call participants who do not respond within 1 week.

Measures. Dual users who enroll in the study will first complete an assessment battery.

Assessments

- Demographics (Baseline): Demographics will include sex, gender, sexual orientation, race, ethnicity, age, income, education, marital status, and health insurance status.
- E-cigarette Use History (Baseline): At baseline participants will report e-cigarette use history (length of e-cigarette use, device, flavor, why they started, past quit attempts), current weekly use rates (days per week, estimated times per day, estimated puffs per day, length that a cartridge/refill lasts) and details about their specific product typically used (type, flavors, nicotine content, size of cartridge/refill).
- Cigarette Use History (Baseline): Participants will report retrospective (lifetime) and current weekly (past 7-day) use of cigarettes, including length of time smoking, brand smoked, cigarettes per day, and quit attempts.
- Motivation and Confidence to quit (Baseline, Days 28, 56): Participants will be asked to rate on a scale of 1-10, 10 being highest, their level of motivation and confidence in their upcoming quit attempt. If still using ENDS/smoking at end of treatment or follow-up, this will be re-assessed.
- Expectancies (Baseline). Expectancies for e-cigarette use will be measured using the Short Form Vaping Consequences Questionnaire (S-VCQ)[32] and expectancies for smoking will be measured using the Smoking Consequences Questionnaire (SCQ)[33].
- Dependence (Baseline, Days 28, 56). Participants will complete the Roswell eND Scale[30], which has been validated to measure dependence on individuals seeking to quit ENDS use, as well as the Fagerström Test of Nicotine Dependence (FTND)[34].
- Daily monitoring survey (Treatment [Days 1-28]): In addition to the primary endpoints above, daily surveys will ask about the previous day: attempts to quit e-cigarettes/smoking, cravings to vape (Vaping Craving Questionnaire[35]), cravings to smoke (Questionnaire of Smoking Urges[36]), and NRT use (number of patches and/or lozenges used). Participants will also be asked if they used the supportive booklet or engaged with the Quitline, and length of each interaction.
- Withdrawal (Treatment [Days 1-28]): Symptoms of withdrawal will be measured using the Brief Wisconsin Inventory of Smoking Dependence Motives (WISDM) scale[34].
- Timeline Follow-Back (TLFB; Days 29-56): On Day 56, a study staff member will conduct a TLFB[37] assessment to capture vaping, smoking, and NRT use over the previous month.
- Carbon Monoxide (Day 28, Day 56): Participants who report abstinence from cigarette smoking will be sent an iCO to provide samples at each timepoint. TLFB data will be used to cross-reference self-reported product use.

Participant compensation. Participants will be compensated $25 for each the baseline, end of treatment, and follow-up assessments. Participants can earn up to $60 more for daily survey completion (biweekly payments as follows: $10 for 1-4 completed, $15 for 5-6, $20 for 7-11, $25 for 12, $30 for 13-14). Participants will be compensated with $20 for each CO sample provided (up to 2). To improve retention, participants who complete >85% (27 out of 31) of assessments will receive a bonus payment of $25. The maximum that someone in this study can earn if they complete all aspects of the study is $200. Participants will be offered electronic payments via ClinCard.

# of Assessments Completed in 2 weeks	Amount paid (Bi-weekly)
1-4	$10
5-6	$15
7-11	$20
12	$25
13-14	$30

11.0 Data Management

Power analyses were performed using PASS 2022 v 22.0.4. Forty-five subjects will be randomly allocated 1:1:1 to treatment arm (A, B or C) using permuted block randomization with block sizes of 3 or 6. Randomization will be stratified by level of dependence (low vs high). The primary endpoint is a binary indicator of abstinence (yes or no) measured daily for 28 (56) days from treatment initiation. Generalized estimating equations (GEEs) will be used to model the log odds of abstinence as a function of treatment arm. Separate models will be fit to evaluate abstinence in the first 28 or 56 days. Following best practice for covariate adjustment, level of dependence (stratification variable) will be included as a model covariate. We will assume a compound-symmetric working correlation structure, but all final estimates and inference will be based on the robust sandwich estimator. Finally, we will conform with the intention-to-treat principle and therefore anticipate no issues secondary to missing data. The probability of abstinence in each treatment arm, differences in abstinence probabilities between treatment arms, and corresponding 90% confidence intervals will be estimated based on the fitted model. These estimates will then be used to construct model-based point and interval estimates of the average number of days abstinent in the first 28 (56) days from treatment initiation by multiplying by a factor of 28 or 56 as appropriate. As an additional analysis, we will include time (continuous) and arm-by-time interaction to evaluate temporal trends. Finally, we will investigate gender-related treatment effect heterogeneity by including sex and arm-by-sex interaction terms. However, sample size is small, and we consider such models to be purely exploratory. **Fig 1** shows the power to detect a difference in the probability of abstinence between two groups of size 15 measured at 28 timepoints, where the probability of abstinence in group 1 is 10% (**Fig 1A**) or 15% (**Fig 1B**), the probability of abstinence in group 2 ranges from 30% to 50%, and inference is based on GEE Wald tests with two-sided $\alpha = 0.1$. Null abstinence rates ranging from 10 to 15% are justified based on preliminary data presented in this application. With no preliminary data to estimate the intra-cluster correlation (ICC), we considered a broad range of ICC values (0.2 to 0.5).

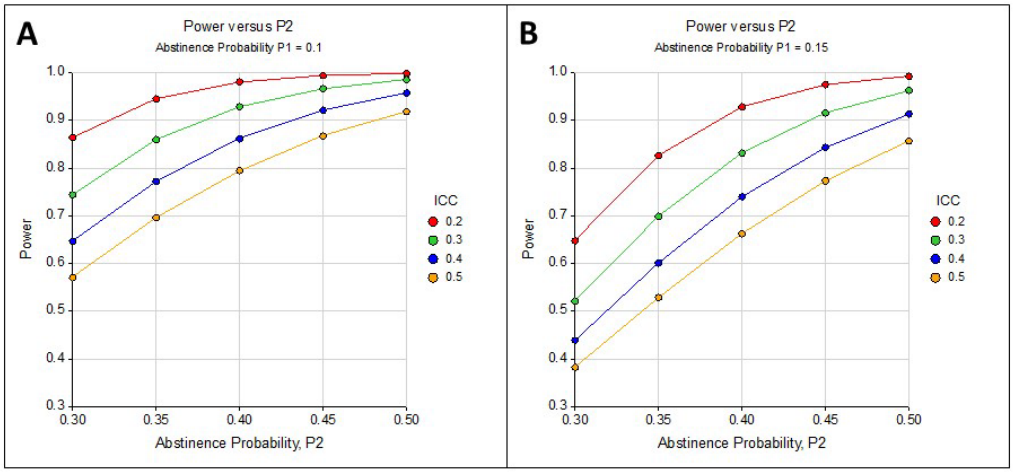

Fig. 1 Power to detect a two-group difference in abstinence (P2 – P1) for (A) P1 = 0.1 or (B) P1 = 0.15 across ICC values ranging from 0.2 to 0.5.

All studies:
Several steps will be taken to safeguard the confidentiality of subjects and their data. From the original data collected from participants, any identifying information will be removed, put into another file (described later), and all participants will be given a study number. Coded data will be stored in digital databases (Box folder). The names of participants will not be associated with this data and assessments will be maintained according to participant study number. A master list connecting participant study numbers to participant names and other identifying data will be kept in a locked file cabinet where it can only be accessed by senior level project staff. OnCore records will be maintained for each participant. Any information published as a result of the study will be such that it will not permit identification of any participant.

Right to privacy for participation in this research will be protected through coding of data and proper storage of research records. Consistent with mandated reporting requirements for health providers, we advise participants that in the case of child abuse or neglect, threat of injury to self or others, or intention to destroy property, that we may need to intervene and report that information to the proper authorities. Subjects will be informed of this limit to confidentiality as it is stated in the informed consent document.

The data will be stored in a locked room for 6 years after the final data is collected. The PI and the research staff will have access to PHI. Organizations that have a responsibility for protecting human participants, including the MUSC IRB, may have access to subjects' records containing PHI. Additionally, the funding source may have access to subjects' records containing PHI.

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects
Sources of Material: Forty-five individuals will be enrolled in the current project. The assessments will be collected only after obtaining informed consent, and for research purposes only. These records will be kept by Dr. Palmer in password protected confidential electronic files with restricted access.

Confidentiality Procedures: As the PI, Dr. Palmer will assure all procedures protecting study data designed to guard subject confidentiality conform to the MUSC Research Protection Program requirements. Additionally, the MUSC IRB must approve all procedures before the study can begin. All data will be stored securely in locked offices or laboratories accessible only by study staff. Further, all information that could potentially identify a subject directly is removed from all study data. This will be replaced with a unique identifier code. The key to linking the code to subject identity will be kept

separately from study data, in a locked file. Only study staff involved in clinical recruitment and assessment will have access to individually identifiable private information. All other study staff will only have access to the coded identifier.

Adverse Events:
Given that this is a very low risk study assessing a behavioral intervention and a medication (nicotine patches and lozenges) that is so safe it has been available over-the-counter since 1996, we do not expect serious adverse events. Please see section 14 “Risks to Subjects” for more research on the safety of NRT, augmented doses of NRT, and NRT for vaping cessation.

Adverse Events:

Participants will have the phone numbers of the PI Dr. Amanda Palmer (843-792-1413) and will be prompted to contact her if an adverse event occurs. If a participant contacts the research team due to an adverse event, the event will be appropriately addressed, and the event will be reported per the IRB standard procedures and criteria below. Adverse events will also be tracked via daily and monthly assessments, where they will be able to rate the incident as mild, moderate, or severe. The research staff, with the guidance of Dr. Palmer and Dr. Emily Ware will track the relatedness of the incident to study medication. The variables that we will encourage the pharmacist and PI to assess include severe reports of the following symptoms (listed symptoms of nicotine overdose per package insert): nausea, salivation, abdominal pain, sweating, headache, diarrhea, dizziness and weakness. We will determine if any adverse events result in dropouts or are serious according to FDA guidelines. Following the report of an adverse event and consultation with Dr. Ware, the participant will be contacted to discuss modifying their NRT usage.

Adverse events will be defined and graded for risk as follows:

Coding of Severity:
0 = No adverse event or within normal limits
1 = Mild adverse event
2 = Moderate adverse event
3 = Severe, resulting in psychiatric or medical hospitalization
4 = Life-threatening adverse event
5 = Fatal adverse event

Coding of Attribution will be made for adverse events grade 3 and above (ie, serious adverse events):
1 = Unrelated to study interventions
2 = Unlikely relationship to study interventions
3 = Possible relationship to study interventions
4 = Probable relationship to study interventions
5 = Definite relationship to study interventions

The FDA’s definition of serious adverse events (21 CFR 312) will be used. Serious Adverse Events include any untoward medical occurrence that at any dose results in death or the immediate risk of death, hospitalization, or the prolonging of an existing hospitalization, persistent or significant disability/incapacity or a congenital anomaly/birth defect, new cancer, or medication overdose.

Serious adverse events, whether unanticipated or anticipated, will be reported immediately (within 24 hours) to the MUSC Institutional Review Board. The PI will evaluate the adverse event and determine whether the adverse event affects the Risk/Benefit ratio of the study and whether modifications to the protocol or the consent procedures are required.

Unanticipated problems involving risk to subjects or others (defined as an event that is is 1] unexpected, 2] related or possibly related and 3] serious) will be reported to the IRB no later than 10 working days after the event or notification to the research team that the event has occurred. The reported information will include: a description of the event, the date of occurrence, whether it is a local or outside report, how the event affected the rights, safety or welfare of the subject or others, current status of MUSC subjects, and any planned changes or modifications to the project as a result of the event.

Any participants' experiences of unanticipated adverse events will be reported on an annual basis to the MUSC Institutional Review Board.

14.0 Risks to Subjects

The main study procedures include completion of questionnaires and using NRT, both of which are generally considered minimal risk procedures. Although these procedures do carry slight risk, the primary risks of the study is loss of confidentiality. There is also a risk that the treatment the study participant is randomized to may prove to be less effective than the other study treatment or other available treatments.

1. Breach of confidentiality: There is the potential risk of breach of confidentiality of laboratory information. The Co-PIs have experience as an investigator dealing with such sensitive information and has experience assuring that data is adequately protected. Safeguards to protect confidentiality include locked records and firewalls around password-protected electronic data, and all study data being coded, with the key linking the code with a subject's identity being kept in a separate, locked file.

2. NRT

   Daily diary surveys will monitor for AEs related to the NRT. If a participant endorses an adverse side effect, they will be contacted by research staff to determine the degree of the event and make recommendations regarding continuing product use as recommended by the TTP Clinical Pharmacist Dr Emily Ware. These will be recorded as a part of the study file.

   2.1 Nicotine patches and lozenges: Exclusion criteria will include endorsement of history of any of the following medical conditions that are contraindicated for patch use: myocardial infarction, arrhythmias, angina, vascular disease, or medical conditions in which consumption of phenylalanine is contraindicated.

   The most common side effects from nicotine patch are skin irritation, insomnia, and headache or nausea. Nicotine lozenges may cause side effects, including sore throat, indigestion, gas, and nausea.

   2.2 Combined use of any NRT product and tobacco product
   Our study allows participants to sample individual NRT products while attempting to quit smoking and vaping. Thus, participants could be using NRT products concurrently (same day) as smoking or

vaping. This could result in nicotine intoxication; i.e. nausea, dizziness, headache, stomachache, etc[38]. In a prior study for cigarette smokers, participants completed a nicotine intoxication scale, and Drs. Toll and Carpenter found no evidence of nicotine intoxication when gum and cigarettes were In a review of prior smoking reduction studies, it was found that most participants did not have higher than normal cotinine levels with concurrent use of cigs and NRT, and there were few AEs reported[39].

Our participants will be encouraged to avoid vaping and smoking at the same time as wearing the patch or using the lozenge.

2.3 Augmented doses of NRT

This study utilizes augmented doses of NRT; that is, participants may be recommended to a dosing schedule that is higher than the labeled recommendations on the box. One reason for doing this is to address the elevated levels of nicotine consumption seen in dual users of cigarettes and e-cigarettes. One study[40] asked dual users about how their dependence changed from smoking only to dual use. Most dual using participants reported feeling higher nicotine dependence and believed themselves to be using more nicotine than when they were exclusively smoking. For this reason, it makes sense to utilize higher doses of NRT than standard recommended doses for exclusive smoking cessation. In fact, for some individuals who are heavy smoking or have difficulty quitting, higher doses of NRT have been endorsed in the literature.

The Cochrane review[41] of NRT showed benefit for increasing NRT doses above the standard dose, particularly for those smoking at higher rates or who have failed to quit in the past repeatedly. A 2013 review of methods for enhancing NRT efficacy found that increasing the dosage of NRT or adjusting the dosage based on higher dependence showed favorable outcomes for smoking cessation[23]. Other reviews[42] and studies[26,43] have also demonstrated favorable outcomes of high-dose NRT compared to controls, some utilizing doses as high as 84mg[43]. Importantly, these studies and reviews failed to show increased incidents of serious adverse events related to increased NRT use. Results of studies of high-dose NRT have been so consistently reported that clinical practice guidelines[22] for smoking cessation recommend higher doses of NRT for individuals who smoke based on characteristics such as dependence (See Chapter 6, part B: Medication Evidence and Table 3.8). Given the recent proliferation of e-cigarette use in the US (e-cigarettes are the second most common tobacco product used among adults, with nearly half of those using e-cigarettes also reporting smoking), it is important to continue extending these findings to dual tobacco product users as is called for in the reviews[23,42].

Some (but not all) studies of high dose NRT have shown an increased prevalence of non-serious side effects, including sleep disturbance, nausea, dizziness, headache, and skin irritation at patch application site[42]. Participants will be encouraged to report any adverse effects to the research staff, who will consult with our Clinical Pharmacist and provide recommendations for dosage alterations as appropriate. We will record all AEs and have plans to evaluate differential safety profiles of each dosage arm (see section 4.0; *Secondary endpoints*).

2.4 NRT for e-cigarette use

Recently published reviews[21,44,45] of vaping cessation interventions provide preliminary evidence for the effectiveness, acceptability, and safety of NRT for e-cigarette use. Also see proof of concept study[25] for which the present proposal was based off of and showed minimal adverse events of NRT for dual use cessation.

Nicotine replacement therapy is a recommended treatment for pharmacists by the Therapeutic Research Center[46]. Dr. Ware uses these guidelines to treat patients in the Tobacco Treatment Program at MUSC.

Our participants will be encouraged to report any adverse effects to the research staff, who will consult with our Clinical Pharmacist and provide recommendations for dosage alterations as appropriate. We will record all AEs and have plans to evaluate differential safety profiles of each dosage arm (see section 4.0; *Secondary endpoints*).

3. Randomization. There is a risk that the treatment the study participant is randomized to may prove to be less effective than the other study treatment or other available treatments.
4. Pregnancy. NRT use is contraindicated during pregnancy. Participants will be aware that they should discontinue use of NRT medications if they become pregnant during the course of the study. Participants will be instructed to inform research staff if they become pregnant during the course of the study. They will be permitted to continue in other study procedures (e.g., surveys) but will be explicitly discouraged from continuing to use study medications.

16.0 Drugs

The NRT for research participants will be stored at room temperature in a location accessible to research staff. Once a participant enrolls into the study, the medication, in the original packaging, will be mailed in the to the participant (overnight via fedex) after they have completed the baseline assessment. We will include medication instruction sheets that detail how to properly use the medications and what to do about side effects. If side effect are reported, either through the daily surveys or directly to research staff, suggested alterations of dosages will be done with the MUSC HCC TTP Clinical Pharmacist Dr. Emily Ware.

REFERENCES

1. Holford TR, Meza R, Warner KE, et al. Tobacco control and the reduction in smoking-related premature deaths in the United States, 1964-2012. *JAMA.* 2014;311(2):164-171.
2. Creamer MR, Wang TW, Babb S, et al. Tobacco product use and cessation indicators among adults—United States, 2018. *Morbidity and Mortality Weekly Report.* 2019;68(45):1013.
3. Cornelius ME, Loretan CG, Wang TW, Jamal A, Homa DM. Tobacco product use among adults—United States, 2020. *Morbidity and Mortality Weekly Report.* 2022;71(11):397.
4. Balfour DJK, Benowitz NL, Colby SM, et al. Balancing Consideration of the Risks and Benefits of E-Cigarettes. *Am J Public Health.* 2021;111(9):1661-1672.
5. Palmer AM, Toll BA, Carpenter MJ, et al. Reappraising Choice in Addiction: Novel Conceptualizations and Treatments for Tobacco Use Disorder. *Nicotine Tob Res.* 2022;24(1):3-9.
6. Hartmann-Boyce J, McRobbie H, Lindson N, et al. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev.* 2021;4(4):CD010216.
7. Coleman SRM, Piper ME, Byron MJ, Bold KW. Dual Use of Combustible Cigarettes and E-cigarettes: a Narrative Review of Current Evidence. *Current Addiction Reports.* 2022;9(4):353-362.
8. Mayer M, Reyes-Guzman C, Grana R, Choi K, Freedman ND. Demographic characteristics, cigarette smoking, and e-cigarette use among US adults. *JAMA network open.* 2020;3(10):e2020694-e2020694.
9. Huang J, Duan Z, Kwok J, et al. Vaping versus JUULing: how the extraordinary growth and marketing of JUUL transformed the US retail e-cigarette market. *Tob Control.* 2019;28(2):146-151.

10. Ali FRM, Seaman EL, Crane E, Schillo B, King BA. Trends in US E-cigarette Sales and Prices by Nicotine Strength, Overall and by Product and Flavor Type, 2017-2022. *Nicotine Tob Res.* 2022.
11. Prochaska JJ, Vogel EA, Benowitz N. Nicotine delivery and cigarette equivalents from vaping a JUULpod. *Tobacco control.* 2022;31(e1):e88-e93.
12. Dowd AN, John L, Betts JM, Belsare P, Sazonov E, Tiffany ST. An Examination of Objective and Self-Report Measures of Ad Libitum Electronic Cigarette Use: Identifying Patterns of Puffing Behavior and Evaluating Self-Report Items. *Nicotine and Tobacco Research.* 2023;25(7):1391-1399.
13. Sanchez S, Kaufman P, Pelletier H, et al. Is vaping cessation like smoking cessation? A qualitative study exploring the responses of youth and young adults who vape e-cigarettes. *Addict Behav.* 2021;113:106687.
14. Klemperer EM, Villanti AC. Why and how do dual users quit vaping? Survey findings from adults who use electronic and combustible cigarettes. *Tob Induc Dis.* 2021;19:12.
15. Amato MS, Bottcher MM, Cha S, Jacobs MA, Pearson JL, Graham AL. "It's really addictive and I'm trapped:" A qualitative analysis of the reasons for quitting vaping among treatment-seeking young people. *Addict Behav.* 2021;112:106599.
16. Henley SJ, Asman K, Momin B, et al. Smoking cessation behaviors among older US adults. *Preventive Medicine Reports.* 2019;16:100978.
17. Palmer AM, Rojewski AM, Carpenter MJ, et al. Interest in quitting e-cigarette use by device type and smoking history in US adults. *Tobacco Control.* 2023:tc-2022-057710.
18. National Academies of Sciences Engineering & Medicine. *Public Health Consequences of E-Cigarettes.* Washington, DC: The National Academies Press; 2018.
19. Parrott AC. The Psychobiological Problems of Continued Nicotine Dependency in E-Cigarette 'Vapers'. Commentary: "Electronic Cigarettes". *Front Psychiatry.* 2015;6(123):123.
20. US Department of Health & Human Services. The health consequences of smoking—50 years of progress: a report of the Surgeon General. In: Atlanta, GA: US Department of Health and Human Services, Centers for Disease …; 2014.
21. Palmer AM, Price SN, Foster MG, Sanford BT, Fucito LM, Toll BA. Urgent Need for Novel Investigations of Treatments to Quit E-cigarettes: Findings from a Systematic Review. *Cancer Prev Res (Phila).* 2022;15(9):569-580.
22. Fiore M. *Treating tobacco use and dependence: 2008 update: clinical practice guideline.* Diane Publishing; 2009.
23. Carpenter MJ, Jardin BF, Burris JL, et al. Clinical Strategies to Enhance the Efficacy of Nicotine Replacement Therapy for Smoking Cessation: A Review of the Literature. *Drugs.* 2013;73(5):407-426.
24. Shahab L, Dobbie F, Hiscock R, McNeill A, Bauld L. Prevalence and Impact of Long-term Use of Nicotine Replacement Therapy in UK Stop-Smoking Services: Findings From the ELONS Study. *Nicotine Tob Res.* 2017;20(1):81-88.
25. Palmer AM, Carpenter MJ, Rojewski AM, Haire K, Baker NL, Toll BA. Nicotine replacement therapy for vaping cessation among mono and dual users: A mixed methods preliminary study. *Addict Behav.* 2023;139:107579.
26. Hatsukami D, Mooney M, Murphy S, LeSage M, Babb D, Hecht S. Effects of high dose transdermal nicotine replacement in cigarette smokers. *Pharmacology Biochemistry and Behavior.* 2007;86(1):132-139.
27. Palmer AM, Carpenter MJ, Rojewski AM, Haire K, Baker NL, Toll BA. Nicotine replacement therapy for vaping cessation among mono and dual users: A mixed methods preliminary study. *Addictive Behaviors.* 2023;139:107579.
28. Palmer AM, Rojewski AM, Chen LS, et al. Tobacco Treatment Program Models in US Hospitals and Outpatient Centers on Behalf of the SRNT Treatment Network. *Chest.* 2021;159(4):1652-1663.

29. Levine J, Schooler NR. SAFTEE: a technique for the systematic assessment of side effects in clinical trials. *Psychopharmacol Bull.* 1986;22(2):343-381.
30. Sheffer CE, Shevorykin A, Foulds J, et al. The Roswell eND scale: Brief, valid assessment of nicotine dependence adults seeking to discontinue e-cigarette use. *Drug Alcohol Depend.* 2023;243:109708.
31. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict.* 1991;86(9):1119-1127.
32. Morean ME, L'Insalata A. The Short Form Vaping Consequences Questionnaire: Psychometric Properties of a Measure of Vaping Expectancies for Use With Adult E-cigarette Users. *Nicotine Tob Res.* 2017;19(2):215-221.
33. Copeland AL, Brandon TH, Quinn EP. The Smoking Consequences Questionnaire-Adult: Measurement of smoking outcome expectancies of experienced smokers. *Psychological Assessment.* 1995;7(4):484-494.
34. Piper ME, McCarthy DE, Bolt DM, et al. Assessing dimensions of nicotine dependence: an evaluation of the Nicotine Dependence Syndrome Scale (NDSS) and the Wisconsin Inventory of Smoking Dependence Motives (WISDM). *Nicotine Tob Res.* 2008;10(6):1009-1020.
35. Dowd AN, Motschman CA, Tiffany ST. Development and Validation of the Questionnaire of Vaping Craving. *Nicotine Tob Res.* 2019;21(1):63-70.
36. Cox LS, Tiffany ST, Christen AG. Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine Tob Res.* 2001;3(1):7-16.
37. Sobell LC, Sobell MB. Timeline follow-back. In: *Measuring alcohol consumption.* Springer; 1992:41-72.
38. Pierce JP, Gilpin E, Farkas AJ. Nicotine patch use in the general population: results from the 1993 California Tobacco Survey. *J Natl Cancer Inst.* 1995;87(2):87-93.
39. Fagerström KO, Hughes JR. Nicotine concentrations with concurrent use of cigarettes and nicotine replacement: A review. *Nicotine & Tobacco Research.* 2002;4(Suppl_2):S73-S79.
40. Martínez Ú, Martínez-Loredo V, Simmons VN, et al. How does smoking and nicotine dependence change after onset of vaping? A Retrospective analysis of dual users. *Nicotine and Tobacco Research.* 2020;22(5):764-770.
41. Silagy C, Lancaster T, Stead LF, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. *Cochrane database of systematic reviews.* 2004(3).
42. Brokowski L, Chen J, Tanner S. High-dose transdermal nicotine replacement for tobacco cessation. *American journal of health-system pharmacy.* 2014;71(8):634-638.
43. Przulj D, Wehbe L, McRobbie H, Hajek P. Progressive nicotine patch dosing prior to quitting smoking: feasibility, safety and effects during the pre-quit and post-quit periods. *Addiction.* 2019;114(3):515-522.
44. Huerne K, Eisenberg MJ. Vaping Cessation Interventions in Former Smokers: A Review. *Canadian Journal of Cardiology.* 2023.
45. Amin S, Pokhrel P, Elwir T, Mettias H, Kawamoto CT. A systematic review of experimental and longitudinal studies on e-cigarette use cessation. *Addictive Behaviors.* 2023:107787.
46. Therapeutic Research Center. *Help Patients Break the E-Cigarette Habit.* 2019.