CLINICAL STUDY PROTOCOL

Interventional Drug or Biologic

Varenicline for treatment of e-cigarette dependence

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PRINCIPAL INVESTIGATOR:

Name Lisa Fucito, Ph.D.
Department Psychiatry
Telephone Number 201-341-8865
Email Address: lisa.fucito@yale.edu

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IND Holder: N/A

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Synopsis

Primary Objective The primary objective of this Phase 1 study is to determine whether varenicline reduces e-cigarette use in adults who regularly use e-cigarettes.
Secondary Objective (if applicable) The secondary objective[s] of this study is] to determine whether varenicline promotes vaping cessation at week 12.
Study Duration Participant duration in this study is 12 weeks. The entire study is expected to take about 2 year.
Study Design Randomized, Placebo-controlled, double blind pilot study
Number of Study Sites This is a dual site study that will be carried out at Yale and Medical University of South Carolina The study will use remote/telehealth procedures, as much as possible, as detailed below
Study Population This study will use various media outlets to recruit adults who report current e-cigarette use in South Carolina (for MUSC) and in Connecticut (for Yale). Advertising will target e-cigarette users who have a desire to quit and are willing to undergo treatment, set a quit date, and attempt to maintain e-cigarette abstinence. Mono-vapers will click the link in our Craigslist and social media ads which will open a screening survey through REDCap on their mobile devices. If the individual meets pre-screening eligibility, the research staff will call the participant to schedule an intake to confirm final eligibility for the study.
Number of Participants We plan to enroll 40 participants across two sites. As with previous studies, we will make every effort to maximize participant retention via a thorough informed consent process, careful screening, and other practices.
Primary Outcome Variables The primary outcome will be abstinence from vaping at week 8. Abstinence is defined as no vaping, not even a puff, every day for the last 7 days via self-report (i.e., 7 day point prevalent abstinence).
Secondary and Exploratory Outcome Variables (if applicable)

The secondary outcome will be abstinence from vaping at week 12. Abstinence is defined as no vaping, not even a puff, every day for the last 7 days via self-report (i.e., 7 day point prevalent abstinence).

Abbreviations

Abbreviation	Explanation

Glossary of Terms

Glossary	Explanation

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1 Introduction

1.1 Introductory Statement

This document is a protocol for a human research study. The purpose of this protocol is to ensure that this study is to be conducted according to ICH GCP guidelines, and according to CFR 21 Part 312, other applicable government regulations and Institutional research policies and procedures.

2 Background

2.1.1 Preclinical Experience

Pharmacotherapy: Varenicline, an FDA-approved smoking cessation medication, functions as a partial agonist for the α4β2 nicotinic receptor and is the most effective monotherapy for smoking cessation.[1-3] There is also persuasive evidence from a large clinical trial that varenicline is safe in a psychiatric population and does not increase the rate of suicidality or depression.[1] The American Thoracic Society (ATS) Clinical Practice Guidelines, the most recent comprehensive tobacco treatment guideline released in July 2020, suggests that varenicline should be prescribed as first line pharmacotherapy even in smokers who are not ready to quit.[21] Currently there is minimal literature that addresses pharmacotherapy as a treatment option for vaping. This study will add to the literature on treatment options for adults who use e-cigarettes alone (mono-vapers). The participants will be given a dose titrated to 2mg daily which co aligns with the current FDA approved dose for smoking cessation.

2.1.2 Clinical Experience

We are using the same dose of the oral medication for vapers as we would for cigarette smokers. The participants will be given a dose titrated to 2mg daily which co aligns with the current FDA approved dose for smoking cessation.

Black-box warnings were removed by the FDA in recent years following the large clinical EAGLES trial showing that this is a low risk medication.[1] Additionally, meta-analyses have been conducted that show varenicline as a safe and useful medication. [17-20] Some side effects of varenicline include nausea, constipation, indigestion, abdominal pain, heartburn, increased or decreased appetite, trouble falling asleep or staying asleep, unusual dreams or nightmares, headache, lack of energy, back, joint, or muscle pain, and abnormal menstrual cycles.

2.2 Background/prevalence of research topic

The U.S. tobacco product landscape has changed dramatically within the last decade with the advent of new nicotine products, particularly electronic cigarettes (e-cigarettes).[1] While e-cigarettes were initially considered hopeful as a smoking alternative, they have shown to be less innocuous than previously believed. E-cigarettes are highly addictive, [1, 3, 44] used commonly by youth,[4,5] and are toxic to the lungs and circulatory system.[6, 7, 47] In addition, most e-cigarette users commonly continue to smoke cigarettes, thus raising concerns about their ability to reduce tobacco-related harm. [8-10, 11, 45]

Recent studies have shown that 20.7% of current combustible cigarette smokers that try e-cigarettes become dual users.[49] An increasing number of individuals are interested in quitting e-cigarette use and open to treatment for this purpose.[44-48] Nevertheless, there is minimal literature on treatment options for e-cigarette addiction. There is a gap in research that does not address proper cessation methods for individuals who are mono e-cigarette users.

Varenicline is a highly efficacious FDA-approved smoking cessation pharmacotherapy. The aim of this study is to examine the effectiveness of varenicline for e-cigarette cessation medication for mono- e-cigarette use in combination with a minimal, self-guided behavior change booklet. This booklet will include general tips for e-cigarettes cessation and information about the free web-based e-cigarette cessation program sponsored by The Truth Initiative and Mayo called “This is Quitting”. This study will have an 8-week treatment period and a 4-week follow-up

phase. Participants will be randomized to receive an 8-week supply of varenicline or matching placebo (gel capsule filled with cellulose powder) in combination with the self-change booklet. We hypothesize that participants who receive varenicline will have higher rates of e-cigarette cessation.

Electronic cigarettes, also referred to as e-cigarettes, vaping devices, or vape pens, are battery-operated devices that heat and aerosolize a liquid solution that may contain nicotine and other additives such as flavors. Introduced to the U.S. in 2007, these devices were proposed as a potential harm reduction option for people who smoke combustible cigarettes. Indeed, there is some evidence that supports e-cigarettes for smoking cessation and tobacco-related harm reduction.[9] Nevertheless, many smokers who try e-cigarettes to quit smoking are unsuccessful and become dual users of both products and among those who are successful quitting smoking, a number become dependent long-term e-cigarette users.[10] The highly addictive nature of e-cigarettes, the potential toxicity to the body, and the minimal research on the long-term health effects of e-cigarettes present much risk to individuals who use e-cigarettes for smoking cessation.[6, 7, 47] In the Tobacco Treatment Service at Smilow Cancer Hospital (for Yale) and in the Tobacco Treatment Program (at MUSC), we are now treating patients who quit smoking combustible cigarettes using e-cigarettes for their e-cigarette dependence. These patients used e-cigarettes to quit smoking but reported that they became more dependent on e-cigarettes than combustible cigarettes and expressed a desire to stop for health reasons. Data from recent reports provide support for our clinical experience and that most adults who use e-cigarettes exclusively (60%) plan to quit use of these products.[23]

In the past decade, there has been a substantial increase in e-cigarette use in all adult age groups.[17] A recent study[52] shows that over 10% of the adult population in the US has tried e-cigarettes. At the same time, young people and never smokers also started using e-cigarettes, cohorts for whom these products were not intended.[11-12] Between 2011 and 2014, e-cigarette use increased by 900% among U.S. middle and high school students and e-cigarettes have been the most commonly used tobacco product among U.S. youth since 2014.[12-13] Several factors contributed to e-cigarette initiation among young people and never smokers including the availability of flavor products that are appealing to youth (e.g., candy flavors) and new technology that made it easier to use and conceal use from others.[11] Although these new products have been created to market to youth, adults have also succumb to this enticing marketing. This new technology also improved the nicotine delivery of these products, increasing their addiction potential. Earlier e-cigarette models did not deliver high nicotine levels to users.[14] However, newer devices such as nicotine salt-based e-cigarettes (e.g., JUUL) more closely mimic combustible cigarettes by quickly delivering high levels of nicotine.[14-15] In fact, a single JUUL pod contains as much nicotine as a pack of cigarettes.

Due to this rapidly evolving e-cigarette landscape, a new generation comprising never, former, and current smokers is now highly dependent on e-cigarettes and needs help. Tobacco product regulation and tobacco control policy cannot keep pace with this technology and are insufficient to address this new public health challenge. There has been minimal research on treatment for e-cigarette dependence; the limited focus has been on adolescents and young adults.

To address this significant gap, we propose to conduct a preliminary test of a highly effective FDA-approved smoking cessation pharmacotherapy (varenicline tartrate) for the treatment of e-cigarette dependence among adult mono- e-cigarette users coupled with a brief behavioral intervention, adapted for e-cigarette dependence, and informed by evidence-based behavioral techniques for smoking cessation. A case report of varenicline for e-cigarette cessation provide evidence for its potential efficacy.[53] Moreover, a clinical trial of varenicline for e-cigarette cessation is underway in adult dual users and adolescents.[54-55] As more adults initiate vaping either for mono use or to quit smoking, e-cigarette dependence is

increasing. Yet, there is minimal scientific research on treatments for e-cigarette dependence. Our study aims to advance the science in this area.

3 Rationale/Significance

3.1 Problem Statement

As more adults initiate vaping either for mono use or to quit smoking, e-cigarette dependence is increasing. Yet, there is minimal scientific research on treatments for e-cigarette dependence. Our study aims to advance the science in this area.

3.2 Purpose of Study/Potential Impact

The purpose of this study is to understand if varenicline tartrate can help people stop or reduce vaping. Varenicline has been proven to reduce the desire to smoke cigarettes. With this study, we aim to test whether it shows a similar benefit for individuals who vape and are interested in quitting.

3.2.1 Potential Risks

The main study procedures include completion of questionnaires (minimal risk), varenicline use (use will be tracked as well as any new or recurring symptoms), and Truth Initiative texting services. This is a low-risk medication study (see text below). 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 (i.e., participants who receive placebo). We will conduct scheduled assessment throughout the intervention to review participant symptoms, mood, and wellbeing.

Breach of confidentiality: Study investigators across both sites 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.

Assessments and Rating Scales: All assessments and rating scales are non-invasive and involve minimal risk to study participants.

Varenicline is an FDA approved smoking cessation medication. Black-box warnings were removed by the FDA in recent years following the large clinical EAGLES trial showing that this is a low risk medication.[1] Additionally, meta-analyses have been conducted that show varenicline as a safe and useful medication. [17-20] Some side effects of varenicline include nausea, constipation, indigestion, abdominal pain, heartburn, increased or decreased appetite, trouble falling asleep or staying asleep, unusual dreams or nightmares, headache, lack of energy, back, joint, or muscle pain, and abnormal menstrual cycles.

Other contraindications for varenicline include suicidal ideation.[21] Suicidality will be assessed at prior to randomization and during the follow-up assessments. If an individual endorses suicidality during the pre-randomization screening, they will be marked as ineligible for the study. This will be assessed using the PHQ9 toolkit for suicide ideation (refer to assessments section). An alert is programmed into the REDCap system that if an individual indicates an active plan to either physically harm or kill themselves, an alert will be sent to the study team. They will then be contacted by our clinical team to complete a risk assessment over via phone. A member of the clinical team will query the participant for details regarding the suicidal ideation, including a likelihood of harming oneself imminently and a plan for committing suicide. If the participant reports an imminent likelihood of harming him/herself or a plan for committing suicide, the clinical team member will call emergency services and will remain on the phone with the participant until emergency services arrive. In the event that the participant expresses an imminent likelihood of harming him/herself, and

the connection is lost, emergency services will be contacted to provide emergency services with the participant's contact information, including address. If the participant is not in imminent danger, the clinical staff will provide referrals for local mental health resources and/or instruction to go to the ED or call 911 should suicidal ideation worsen. The clinical team member will suggest that the participant seek treatment and then will follow-up with the participant via phone one week later.

In the event that a participant endorses suicidal ideation but is not responsive to clinical staff's phone call within 48 hours, the participant will be emailed a list of local mental health resources and will suggest that the participant seek additional treatment. The email will also ask that the participant respond to the clinical staff either via phone or e-mail within 24 hours to confirm receipt of the treatment referrals. Should the participant not respond to the clinical staff's email within an additional 48 hours (4 days from completion of the assessment) and endorse "Several days", "More than half the days" or "nearly everyday" to "Thoughts that you would be better off dead or of hurting yourself in some way" on the PHQ9 suicidality toolkit at study screening, emergency services will be contacted and will be provided with the participant's name and address.

We will utilize the PHQ9 assessment to track depression and suicidal ideation during the baseline assessments. If suicidal ideation is endorsed, an automated "red flag" will be processed through our REDCap database. This red flag will indicate either a a) clinically significant increase in total PHQ scoring with an overall score of at least 15 (>5 point increase from baseline and resulting score >15), OR b) any value >0 for item 9/suicidal ideation). The red flag indicators will be monitored daily by our clinical team and will be met with the appropriate measures. These measures are based on prior MUSC-IRB approved protocols of varenicline (i.e., the STARS Pro00098479).

3.2.2 Potential Benefits

The treatment the participant receives may prove to be more effective than other available treatments. In addition, participant participation will aid researchers in evaluating new methods of how varenicline, a medication approved for combustible smoking, affects e-cigarette use behavior. Participants will also be compensated for their time.

4 Study Objectives

4.1 Hypothesis

We hypothesize that participants who receive varenicline will have higher rates of e-cigarette cessation

4.2 Primary Objective

The primary objective of this study is to determine whether varenicline increases cessation in e-cigarette users.

5 Study Design

5.1 General Design Description

For this preliminary, proof-of-concept study, we require smartphone ownership or email access to allow for receipt of weekly surveys (via text or email) during the sampling period, as well as weekly assessments (methods described below). According to the latest Pew survey, 77% of Americans own a smartphone; >73% among those under age 65. Requirement for smartphone ownership will not affect internal validity, but it could reduce external validity.[2]

This is a randomized, placebo-controlled, double blind pilot study. This study aims to enroll 20 adults who report daily mono- e-cigarette use at MUSC and 20 adults who report daily mono- e-cigarette use at Yale (N=40 total). This is a 12-week study with 8 weeks of study drug use (either varenicline or placebo) provided to the enrolled participants. Inclusion/exclusion criteria will be determined via initial online screening and then confirmed with tele-video/phone call final screening. Non-pregnancy verification will be ascertained via remote pregnancy test. If any of these exclusions are endorsed, then the potential participant will not be enrolled into the study. Once screening and informed consent are complete, eligible participants will be randomized to 1 of the following 2 groups:

1) VRN + Self-Change Pamphlet
2) Placebo + Self-Change Pamphlet

All participants will be asked to provide assessments (as described below) throughout the sampling process to assess vaping & smoking behavior (if the participant initiates smoking after enrolling in the trial), craving, varenicline/placebo use, use of web-based program, etc.

Randomization: 20 participants per site (MUSC and Yale) will be stratified status of former or never smoker. Former smoker is defined as an individual who has smoked at least 100 cigarettes in their lifetime but have not smoked in the past 6 months or longer.

Study Details

Guided Self-Change Booklet: This 3-page pamphlet includes information on how to reduce and quit e-cigarettes on their own (on Page 1), how to prevent relapse to combustible cigarettes (for mono vapers who quit combustible cigarettes by vaping; on Page 2), and how to enroll in the online This is Quitting services (described above; on Page 3).

All groups will receive this pamphlet as a brief behavioral component of the intervention. This 2-page pamphlet will include information on how to reduce and quit e-cigarettes on their own on one page, how to prevent relapse to combustible cigarettes (for mono vapers who quit combustible cigarettes by vaping) on the second page, and the third page will contain information about how to enroll in the Truth Initiative/Mayo “This is Quitting" online self-guided e-cigarette treatment program (described below).

Truth Initiative/Mayo “This is Quitting” Program: All participants will be given information about how to enroll in treatment with the This is Quitting Program, which is a free online program that was created by the Truth Initiative in conjunction with Mayo Clinic as a tobacco cessation treatment tool. This program offers online and texting services that assist individuals with their quit attempts for general tobacco use, but they also have specific content/support for vaping. Upon enrolling in the program, the participant is prompted to select a quit date and give their contact

information (i.e., email and phone number). The participant is then granted access to the platform that gives them links with cessation tips such as how to deal with cravings, building a support system, dealing with relapse, using medication to help with cessation, etc. The This is Quitting Program also incorporates a text message option. This text message will send the participant 3-4 tobacco cessation related messages per day. If the participant texts “ECIG,” a new text thread will be created that will send vaping related messages directly to the participant.

Pharmacotherapy: Twenty participants will be randomized to receive active varenicline. Prior to randomization, the study physician, Dr. Baldassarri or nurse practitioners from the Tobacco Treatment Service/PI Dr. Lisa Fucito will conduct a pre-randomization medical review to ensure that they qualify for varenicline based on study eligibility criteria collected during primary (e.g., smoking history, age, medical history, and comorbidities) and secondary screening (psychiatric history, suicidal history, pregnancy status). A summary report that we create within our REDCap screening database, will be delivered electronically to study physician/nurse practitioners/PI Dr. Lisa Fucito. They will review each participant’s information and will determine whether to 1) accept the individual into the study, 2) reject the individual into the study (i.e., not eligible for varenicline), or 3) ascertain more information from the individual before either the decision to accept/reject the participant. The study physician/nurse practitioners may contact the individual to engage in further clinical interviewing of the potential participant. The disposition of each participant will be tracked within this screening database, allowing us to complete all CONSORT steps to study flow. The individual will not proceed to randomization and intake until we have signed, explicit documentation from the study physician/nurse practitioners/ PI Dr. Lisa Fucito to do so. Thus, these procedures ensure that we retain physician/APRN oversight and approval of varenicline disbursement at the study outset. Dr.Baldassarri/APRNs from the Tobacco Treatment Service retains their role in evaluation of adverse events as noted elsewhere within this application.

Other contraindications for varenicline include suicidal ideation.[21] Suicidality will be assessed at prior to randomization and during the follow-up assessments. If an individual endorses suicidality during the pre-randomization screening, they will be marked as ineligible for the study. This will be assessed using the PHQ9 toolkit for suicide ideation (refer to assessments section). An alert is programmed into the REDCap system that if an individual indicates an active plan to either physically harm or kill themselves, an alert will be sent to the study team. They will then be contacted by our clinical team to complete a risk assessment over via phone. A member of the clinical team will query the participant for details regarding the suicidal ideation, including a likelihood of harming oneself imminently and a plan for committing suicide. If the participant reports an imminent likelihood of harming him/herself or a plan for committing suicide, the clinical team member will call emergency services and will remain on the phone with the participant until emergency services arrive. In the event that the participant expresses an imminent likelihood of harming him/herself, and the connection is lost, emergency services will be contacted to provide emergency services with the participant’s contact information, including address. If the participant is not in imminent danger, the clinical staff will provide referrals for local mental health resources and/or instruction to go to the ED or call 911 should suicidal ideation worsen. The clinical team member will suggest that the participant seek treatment and then will follow-up with the participant via phone one week later.

In the event that a participant endorses suicidal ideation but is not responsive to clinical staff’s phone call within 48 hours, the participant will be emailed a list of local

mental health resources and will suggest that the participant seek additional treatment. The email will also ask that the participant respond to the clinical staff either via phone or e-mail within 24 hours to confirm receipt of the treatment referrals. Should the participant not respond to the clinical staff's email within an additional 48 hours (4 days from completion of the assessment)

We will utilize the PHQ9 assessment to track depression and suicidal ideation during the baseline assessments. If suicidal ideation is endorsed, an automated "red flag" will be processed through our REDCap database. This red flag will indicate either a a) clinically significant increase in total PHQ scoring with an overall score of at least 15 (>5 point increase from baseline and resulting score >15), OR b) any value >0 for item 9/suicidal ideation). The red flag indicators will be monitored daily by our clinical team and will be met with the appropriate measures. These measures are based on prior MUSC-IRB approved protocols of varenicline (i.e., the STARS Pro00098479).

We will work with the Investigational Drug Service (IDS) pharmacy (MUSC) and Yale-New Haven Pharmacy (Yale) to package and label varenicline. Both packaging and labelling will be done within the YNNH pharmacy, following all applicable laws. Under no circumstances will non-credentialed study staff package or label the medication. The IDS pharmacy (MUSC) and Yale-New Haven Pharmacy (Yale) will package and label the varenicline under our prescriber's order.

Upon receipt of medication, the participant will receive a call from our team. This will be a brief orientation call during which they will have an overview of the medication. All participants will be encouraged to start their medication as soon as they receive it and to set a quit date 1-2 weeks from medication initiation. The varenicline prescription will follow the standard induction period: varenicline 0.5 mg once per day for Days 1-3, varenicline 0.5 mg twice per day for Days 4-7, then varenicline 1 mg twice per day (when varenicline reaches peak efficacy for tobacco cessation). Participants will remain on varenicline for 8 weeks total. Dose adjustments (e.g., reduction to 0.5 mg twice per day if 1 mg is not well tolerated) will be allowed at the discretion of the clinical pharmacist/APRN/physician. An 8-week supply of varenicline will be shipped.

A novel alert system will be built into the Adverse Event surveys REDCap database such that any severe adverse events (e.g., severe nausea, severe sleep disturbances, severe changes in mood) that are endorsed along with self-report of cessation of pharmacotherapy use will be monitored by research staff, who will consult with the study physician/APRN from the Tobacco Treatment Service/PI Dr. Lisa Fucito when indicated for clinical assessment and management. We believe this alert system will improve varenicline medication adherence if the pharmacist/APRN/physician can quickly follow-up on any side effects that may be associated with pharmacotherapy use and call the patient with any recommended dose adjustments. All dose adjustments will be recorded in our REDCap database.

Guided Self-Change Pamphlet: All groups will receive this pamphlet as a brief behavioral component of the intervention. This 3-page pamphlet includes information on how to reduce and quit e-cigarettes on their own (on Page1), how to prevent relapse to combustible cigarettes (for mono vapers who quit combustible cigarettes by vaping; on Page 2), and how to enroll in the online This is Quitting services (described above; on Page 3).

5.1.1 Study Date Range and Duration

The duration of this study is 12 weeks.

5.1.2 Number of Study Sites

This is a dual site study that will be carried out at Yale and Medical University of South Carolina. The study will use remote/telehealth procedures, as much as possible, as detailed below

5.2 Outcome Variables

5.2.1 Primary Outcome Variables

The primary outcome will be abstinence from vaping at week 8. Abstinence is defined as no vaping, not even a puff, every day for the last 7 days via self-report (i.e., 7 day point prevalent abstinence).

5.2.2 Secondary Outcome Variables (if applicable)

5.2.3 The secondary outcome will be abstinence from vaping at week 12. Abstinence is defined as no vaping, not even a puff, every day for the last 7 days via self-report (i.e., 7 day point prevalent abstinence).

5.2.4 Exploratory Outcome Variables (if applicable)

N/a

5.3 Study Population

Participants: This study will use various media outlets to recruit adults who report current e-cigarette use in South Carolina (for MUSC) and in Connecticut (for Yale). Advertising will target e-cigarette users who have a desire to quit and are willing to undergo treatment, set a quit date, and attempt to maintain e-cigarette abstinence. Mono-vapers will click the link in our Craigslist and social media ads which will open a screening survey through REDCap on their mobile devices. If the individual meets pre-screening eligibility, the research staff will call the participant to schedule an intake to confirm final eligibility for the study.

5.3.1 Number of Participants

We plan to enroll 40 participants across two sites. As with previous studies, we will make every effort to maximize participant retention via a thorough informed consent process, careful screening, and other practices.

5.3.2 Eligibility Criteria/Vulnerable Populations

Prospective participants will be screened on initial eligibility criteria.
Following completion of the screener, research staff will inform potential patients of their initial eligibility status. Those who meet initial criteria will be invited to attend an intake (via HIPPA compliant telehealth platform since this study is fully remote) to provide written informed consent and complete final screening for inclusion/exclusion criteria. Eligible individuals will be randomized to their condition to begin immediately after intake.

Inclusion criteria:

1. age 18+;
2. daily use of an e-cigarette containing nicotine (defined as use for at least 25 days out of the past month);
3. use of an e-cigarette containing nicotine> 6 months;
4. have desire to quit e-cigarettes, are willing to set a quit date and maintain e-cigarette abstinence;
5. have daily access to a smartphone or have regular (daily) access/use of email; and

6. and live in South Carolina or Connecticut.
7. No use of combustible tobacco in the past 30 days (including cigarettes, cigarillos, etc).
    a. In the 2 months prior to the past 30 days, patients must not use combustible tobacco for >1 time per week.
8. No use of non-combustible nicotine products (ie pouches, smokeless tobacco, etc.) in the past 30 days.
    a. In the 2 months prior to the past 30 days, patients must not use non-combustible nicotine products (ie pouches, smokeless tobacco, etc.) for >1 time per week.

Exclusion criteria:

1. Vulnerable Populations: We will not be enrolling vulnerable populations, specifically pregnant women, children, prisoners, or institutionalized individuals.
2. We also will not enroll participants incapable of providing their own consent. 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.
3. We will exclude individuals with medical contraindications for varenicline use (i.e., severe renal impairment)
4. We will exclude anyone currently using smoking cessation medications.
5. Individuals will also be excluded if another household member is currently enrolled in the study.
6. Individuals will be excluded if not proficient in English.
7. Verification of Non-Pregnancy: Females ages $\leq$55 will be mailed a commercially available pregnancy test to verify non-pregnancy. Written confirmation of negative pregnancy test via REDCap will be required prior to enrollment in the trial. Participants are also informed that they should let us know if they become pregnant during the trial. Medications will not be sent until this verification is in place. These procedures are based on the MUSC IRB approved STARS protocol (MUSC IRB Pro00098479).

6 Methods

6.1 Treatment

6.1.1 Identity of Investigational Product

Varenicline tartrate (sometimes called Chantix, Apo-Varenicline, or Par-Varenicline), is a prescription medication for smoking cessation. The oral supply we will use is approved by the US Food and Drug Administration (FDA), Par-varenicline. Many studies show that varenicline can help people who smoke quit smoking. Varenicline is a prescription medication, which usually means that you must see your doctor to get it. Varenicline is used to treat tobacco use dependence. It helps reduce cravings for tobacco use and decreases the pleasurable effects of cigarettes and other tobacco products.

6.1.2 We will be receiving the medication from the YNNH Investigational Drug Service. They will be the ones storing the medication. They will also do the encapsulation of the active drug and placebo. Written instructions will be attached to the medication from the pharmacy and the research staff will distribute the medication to the participant.

6.1.3 Dosage, Administration, Schedule

Dose and schedule: We are using the same dose of the oral medication for vapers as we would for cigarette smokers. The participants will be given a dose titrated to 2mg daily which co aligns with the current FDA approved dose for smoking cessation. The varenicline prescription will follow the standard induction period: varenicline 0.5 mg once per day for Days 1-3, varenicline 0.5 mg twice per day for Days 4-7, then varenicline 1 mg twice per day (when varenicline reaches peak efficacy for tobacco cessation). Participants will remain on varenicline for 8 weeks total. Dose adjustments (e.g., reduction to 0.5 mg twice per day if 1 mg is not well tolerated) will be allowed at the discretion of the clinical pharmacist/APRN/physician. The entire 8-week supply of varenicline will be shipped at week 1 according to the Pharmacy's workflow..

Medication Schedule: Both groups will follow the same medication schedule (listed below).

- Days 1-3: 0.5mg (or matching placebo) study pill once per day
- Days 4-7: 0.5mg (or matching placebo) study pill twice per day
- Weeks 2-8: 1mg or matching placebo) study pill twice per day

Adverse Events: Other contraindications for varenicline include suicidal ideation.[21] Suicidality will be assessed at prior to randomization and during the follow-up assessments. If an individual endorses suicidality during the pre-randomization screening, they will be marked as ineligible for the study. This will be assessed using the PHQ9 toolkit for suicide ideation (refer to assessments section). An alert is programmed into the REDCap system that if an individual indicates an active plan to either physically harm or kill themselves, an alert will be sent to the study team. They will then be contacted by our clinical team to complete a risk assessment over via phone. A member of the clinical team will query the participant for details regarding the suicidal ideation, including a likelihood of harming oneself imminently and a plan for committing suicide. If the participant reports an imminent likelihood of harming him/herself or a plan for committing suicide, the clinical team member will call emergency services and will remain on the phone with the participant until emergency services arrive. In the event that the participant expresses an imminent likelihood of harming him/herself, and the connection is lost, emergency services will be contacted to provide emergency services with the participant's contact information, including address. If the participant is not in imminent danger, the clinical staff will provide referrals for local mental health resources and/or instruction to go to the ED or call 911 should suicidal ideation worsen. The clinical

team member will suggest that the participant seek treatment and then will follow-up with the participant via phone one week later.

In the event that a participant endorses suicidal ideation but is not responsive to clinical staff's phone call within 48 hours, the participant will be emailed a list of local mental health resources and will suggest that the participant seek additional treatment. The email will also ask that the participant respond to the clinical staff either via phone or e-mail within 24 hours to confirm receipt of the treatment referrals. Should the participant not respond to the clinical staff's email within an additional 48 hours (4 days from completion of the assessment) and endorse "several days" "More than half the days" or "nearly everyday" to "Thoughts that you would be better off dead or of hurting yourself in some way" on the PHQ9 suicidality toolkit at study screening, emergency services will be contacted and will be provided with the participant's name and address.

We will utilize the PHQ9 assessment to track depression and suicidal ideation during the baseline assessments. If suicidal ideation is endorsed, an automated "red flag" will be processed through our REDCap database. This red flag will indicate either a a) clinically significant increase in total PHQ scoring with an overall score of at least 15 (>5 point increase from baseline and resulting score >15), OR b) any value >0 for item 9/suicidal ideation). The red flag indicators will be monitored daily by our clinical team and will be met with the appropriate measures. These measures are based on prior MUSC-IRB approved protocols of varenicline (i.e., the STARS Pro00098479).

Compliance: The weekly assessments will have questions built in ascertaining information about their medication adherence. We will prompt them through text if the assessments show that they are not compliant.

This study is under review for and Investigational New Drug Application exemption.

6.1.4 Method of Assignment/Randomization

Randomization: 20 participants per site (MUSC and Yale) will be stratified by stratified by status of former or never smoker. Former smoker is defined as an individual who has smoked at least 100 cigarettes in their lifetime but have not smoked in the past 6 months or longer.

6.1.5 Blinding and Procedures for Unblinding

Neither the participant nor research staff will know what medication condition to which the participant has been assigned. Only the study pharmacists who prepares and mails the participant's medication will know their medication condition assignment. The study physician/APRNs will request a medication order for either Group A or B. They will not know the condition the participant is assigned since the designation of study group is only known by study statistician and pharmacist.

6.1.6 Packaging/Labelling

We will work with the Investigational Drug Service (IDS) pharmacy (MUSC) and Yale-New Haven Pharmacy (Yale) to package and label varenicline. Both packaging and labelling will be done within the IDS pharmacy, following all applicable laws. Under no circumstances will non-credentialed study staff package or label the medication. The IDS pharmacy (MUSC) and Yale-New Haven Pharmacy (YALE) will package and label the varenicline under our prescriber's order. Once a participant is enrolled into the study, the medication, in original packaging, will be mailed or directly delivered distributed to the participant by research staff.

This study is under review for an Investigational New Drug Application exemption.

6.1.7 Storage Conditions

We will use the YNHH Investigational Drug Service to prepare the study medication and store it...

6.1.8 Concomitant therapy

N/a

6.1.9 Restrictions

No restrictions

6.2 Assessments

6.2.1 Efficacy

Study Assessments

The following tools will be used for the assessments conducted at baseline (week 0) and end of follow-up (Week 0, 8 & 12).

Demographics (Week 0): This questionnaire will collect basic demographic information for each subject including gender, ethnicity/race, employment status, etc.

Smoking/Tobacco Use History (Week 0): This will collect basic info about smoking and smoking cessation history, prior varenicline use, e-cigarette history, tobacco and nicotine product flavor preference, etc.

Modified Questionnaire on Smoking Urges (QSU) (Week 0, 8 & 12): This 3-item assessment is used to examine smoking related urges such as desire to smoke, anticipation of immediate positive outcome, etc.[31]E-cigarette Dependence (Week 0 & 8): The NIH Patient-Reported Outcomes Measurement Information System (PROMIS) measure for daily smokers has also been adapted to measure for use of other tobacco products.[30, 40] This is a 4-item e-cigarette dependence questionnaire that measures withdrawal and craving.

E-cigarette Dependence Index (Week 0 & 8): This is a 10-item e-cigarette dependence questionnaire that measures difficulty quitting, withdrawal and cravings. [57]

Subjective Effects Cigarettes and E-cigarettes (Week 0, Week 4): Participants will report on subjective evaluation about cigarettes and e-cigarettes. Subjective evaluation includes items derived from the Modified E-Cigarette Evaluation Questionnaire (meCEQ)[58] that have also been adapted for alternate tobacco products. It measures the degree to which participants experience reinforcing effects from smoking and e-cigarettes. The scale yields five clusters or domains: Smoking Satisfaction, Psychological Reward, Aversion, Enjoyment of Respiratory Tract Sensations, and Craving Reduction.[56]

Patient Health Questionnaire-9 (PHQ9) (Week 0 and Bi-Weekly): which assesses for depression and includes an item on suicidal ideation.[50]

Wisconsin Withdrawal Scale Brief (WSWS2-B): This 6-item scale assesses current symptoms of nicotine withdrawal including cravings and irritability.[59]

Weekly Electronic Assessments: Participants will be asked to complete a brief compensated assessment to assess e-cigarette use, use of other tobacco products including cigarettes, and daily medication adherence. These Assessments be completed weekly throughout the entirety of the study. Assessments will assess vaping sessions/puffs per day, use of other tobacco products, medications/products used, purposes of that use (to reduce/quit), next-

day e-cigarette use/other tobacco use/quit intentions, and mood/affect. The assessment will also assess e-cigarette brand, concentration, and habits surrounding e-cigarette use (i.e., location, type of device, and flavor choice). Weekly abstinence will be assessed in three different ways: “Have you quit today?”, “Have you used an e-cigarette in the past three days?”, and “Have you used an e-cigarette in the past 7 days?” To track medication adherence, the assessment will also ask how many varenicline pills that participant took per day. This will not replace traditional adverse event assessment (below) but complement (and enrich) them. We have established procedures to auto-send an email or SMS text (their choice) on a set schedule. SMS text messaging is possible via Twilio, embedded within our REDCap system, which allows participants to complete a survey directly from their phone, without having to access a webpage. Note that assessments are not completed via texting, just prompted via text with link to REDCap. Participants can choose to receive their assessment invitations via email if they wish, again with a link to a secure REDCap survey. Thus, per eligibility criteria above, we require participants to have smartphone or other device that has internet capacity. Assessments consist of a brief (<2 minutes) survey, directly enter an online protected database (REDCap) through secure encryption; all PHI is protected. Participants will be compensated for compliance based on % assessments completed (described below).

Exit Survey: This survey, designed for the study, will be conducted for all participants. Questions to ascertain participants’ reactions to the different intervention conditions (i.e., varenicline, booklet) (e.g.,, overall satisfaction, perceived helpfulness, etc.), whether they utilized any of the external resources in the booklet (i.e., This is Quitting program) and their reactions, as well as any other use of other medications (e.g., NRT), and behavioral strategies that they used to reduce their e-cigarette use during the study (e.g., titrate e-cigarette nicotine dose, change flavors or switch to unflavored).

6.2.2 Safety and Pregnancy-related policy

Verification of Non-Pregnancy: Females ages ≤55 will be mailed a commercially available pregnancy test to verify non-pregnancy. Written confirmation of negative pregnancy test via REDCap will be required prior to enrollment in the trial. Participants are also informed that they should let us know if they become pregnant during the trial. Medications will not be sent until this verification is in place. These procedures are based on the MUSC IRB approved STARS protocol (MUSC IRB Pro00098479).

6.2.3 Adverse Events Definition and Reporting

Adverse Events:

Participants will have the phone numbers of the Co-PIs, Dr. Lisa Fucito (201-341-8865) and Dr. Benjamin Toll (203-376-6113) and will be prompted to contact them if an adverse event occurs, along with the previously mentioned adverse event procedures. 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 criteria below. Adverse events will also be tracked via weekly assessments, where they will be able to rate the incident as mild, moderate, or severe. The research staff, with the guidance of Dr. Gray (for MUSC) and Dr. Baldassarri (for Yale), will track the relatedness of the incident to study medication. The variables that we will encourage the pharmacist/APRN to assess include severe renal impairment, history of serious hypersensitivity or skin reactions to varenicline, an immediate (within 2 weeks) post myocardial infarction period, serious arrhythmias, unstable angina pectoris, or hemodynamically or electrical instability. We will determine if any adverse events result in dropouts or are serious according to FDA guidelines.

Serious adverse events, whether unanticipated or anticipated, will be reported immediately (within 24 hours) to the MUSC or Yale Institutional Review Board. The PIs 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.

Plans for reviewing and reporting non-serious anticipated or unanticipated adverse events: Any participants' experiences of anticipated and unanticipated adverse events will be reported on an annual basis to the MUSC Institutional Review Board.

Plan for grading adverse events. Serious Adverse Events (SAE). 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. 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 (i.e., 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 intervention

6.2.4 Pharmacokinetics (if applicable)

N/A

6.2.5 Biomarkers (if applicable)

N/a

6.3 Study Procedures

This is study aims to enroll 20 adults who report daily mono- e-cigarette use at MUSC and 20 adults who report daily mono- e-cigarette use at Yale (N=40 total). This is a 12-week study with 8 weeks of study drug use (either varenicline or placebo) provided to the enrolled participants. Inclusion/exclusion criteria will be determined via initial online screening and then confirmed with tele-video/phone call final screening. Non-pregnancy verification will be ascertained via remote pregnancy test. If any of these exclusions are endorsed, then the potential participant will not be enrolled into the study. Once screening and informed consent are complete, eligible participants will be randomized to 1 of the following 2 groups:

1) VRN + Self-Change Pamphlet

2) Placebo + Self-Change Pamphlet

All participants will be asked to provide assessments (as described below) throughout the sampling process to assess vaping & smoking behavior (if the participant initiates smoking after enrolling in the trial), craving, varenicline/placebo use, use of web-based program, etc.

Randomization: 20 participants per site (MUSC and Yale) will be stratified by status of former or never smoker. Former smoker is defined as an individual who has smoked at least 100 cigarettes in their lifetime but have not smoked in the past 6 months or longer.

Study Details

Guided Self-Change Booklet: This 3-page pamphlet includes information on how to reduce and quit e-cigarettes on their own (on Page 1), how to prevent relapse to combustible cigarettes (for mono vapers who quit combustible cigarettes by vaping; on Page 2), and how to enroll in the online This is Quitting services (described above; on Page 3).

All groups will receive this pamphlet as a brief behavioral component of the intervention. This 2-page pamphlet will include information on how to reduce and quit e-cigarettes on their own on one page, how to prevent relapse to combustible cigarettes (for mono vapers who quit combustible cigarettes by vaping) on the second page, and the third page will contain information about how to enroll in the Truth Initiative/Mayo “This is Quitting" online self-guided e-cigarette treatment program (described below).

Truth Initiative/Mayo “This is Quitting” Program: All participants will be given information about how to enroll in treatment with the This is Quitting Program, which is a free online program that was created by the Truth Initiative in conjunction with Mayo Clinic as a tobacco cessation treatment tool. This program offers online and texting services that assist individuals with their quit attempts for general tobacco use, but they also have specific content/support for vaping. Upon enrolling in the program, the participant is prompted to select a quit date and give their contact information (i.e., email and phone number). The participant is then granted access to the platform that gives them links with cessation tips such as how to deal with cravings, building a support system, dealing with relapse, using medication to help with cessation, etc. The This is Quitting Program also incorporates a text message option. This text message will send the participant 3-4 tobacco cessation related messages per day. If the participant texts “ECIG,” a new text thread will be created that will send vaping related messages directly to the participant.

Pharmacotherapy: Twenty participants will be randomized to receive active varenicline. Prior to randomization, the study physician/nurse practitioner/PI Dr. Lisa Fucito conduct a pre-randomization medical review to ensure that they qualify for varenicline based on study eligibility criteria collected during primary (e.g., smoking history, age, medical history, and comorbidities) and secondary screening (psychiatric history, suicidal history, pregnancy status). A summary report that we create within our REDCap screening database, will be delivered electronically to the study physician/nurse practitioners/ PI Dr. Lisa Fucito. They will review each participant’s information and will determine whether to 1) accept the individual into the study, 2) reject the individual into the study (i.e., not eligible for varenicline), or 3) ascertain more information from the individual before either the decision to accept/reject the participant. The study physician/nurse practitioners/PI Dr. Lisa Fucito may contact the individual to engage in further clinical interviewing of the potential participant. The disposition of each participant will be tracked within this

screening database, allowing us to complete all CONSORT steps to study flow. The individual will not proceed to randomization and intake until we have signed, explicit documentation from the study physician/nurse practitioners/PI Dr. Lisa Fucito to do so. Thus, these procedures ensure that we retain physician/APRN oversight and approval of varenicline disbursement at the study outset. Dr. Baldassarri/APRNs from the Tobacco Treatment Service retains their role in evaluation of adverse events as noted elsewhere within this application.

Upon receipt of medication, the participant will receive a call from our team. This will be a brief orientation call during which they will have an overview of the medication. All participants will be encouraged to start their medication as soon as they receive it and to set a quit date 1-2 weeks from medication initiation. The varenicline prescription will follow the standard induction period: varenicline 0.5 mg once per day for Days 1-3, varenicline 0.5 mg twice per day for Days 4-7, then varenicline 1 mg twice per day (when varenicline reaches peak efficacy for tobacco cessation). Participants will remain on varenicline for 8 weeks total. Dose adjustments (e.g., reduction to 0.5 mg twice per day if 1 mg is not well tolerated) will be allowed at the discretion of the clinical pharmacist/APRN/physician. The entire 8-week supply of varenicline will be shipped at week 1. .

Guided Self-Change Pamphlet: All groups will receive this pamphlet as a brief behavioral component of the intervention. This 3-page pamphlet includes information on how to reduce and quit e-cigarettes on their own (on Page1), how to prevent relapse to combustible cigarettes (for mono vapers who quit combustible cigarettes by vaping; on Page 2), and how to enroll in the online This is Quitting services (described above; on Page 3).

Participant compensation: Participants in this study will have the opportunity to earn up to $185 for completing their assessments. After completing the randomization and intake during enrollment, they will be paid $20. Starting on week 1, they will be asked to complete a brief, weekly assessment. Payments for the weekly assessments will increase gradually throughout the treatment phase. You will be paid $5 for the completing weekly assessments during weeks 1-4, $10 per assessment for weeks 5-8, $15 for weeks 9-10, and $25 for weekly assessment at week 12. End of treatment assessments will be completed at week 12 for a payment of $35.

	Study Week												
	0	1	2	3	4	5	6	7	8	9	10	11	12
Baseline Assessments	$20												
Weekly Assessments		$5	$5	$5	$5	$10	$10	$10	$10	$15	$15	$15	$25
End of Follow-up Assessments													$35

Week Total	$20	$5	$5	$5	$5	$10	$10	$10	$10	$15	$15	$15	$60
Maximum Total Compensation: $185													

6.3.1 Study Schedule

1. Intake Procedures (Week 0): Before joining the study, the patient will have first completed a screening visit using a telehealth platform (i.e., Doxy.me, Zoom, or other HIPAA compliant tele-video conferencing software) to obtain their consent using an electronic REDCap consent form) to confirm their eligibility. This research study will use exclusively remote/telehealth procedures as detailed below.

   Once the informed consent has been signed, the research staff will ask a few additional questions to determine final eligibility. If they are a female of the age 55 or below, we will send them a pregnancy test in the mail. They will take the at home pregnancy test and complete a secure online survey to verify their test results. After final eligibility has been confirmed, they will be asked to complete some questions about their e-cigarette use.

   Randomization (Week 0): They will be randomly assigned, like a flip of a coin, to either the (a) active varenicline medication group, or (b) the placebo group. Neither they nor research staff will know what medication condition to which they have been assigned; only the study pharmacists who prepare and mail their medication will know their medication condition assignment.

   Treatment Phase (Week 0-Week 8): They will be sent an 8-week supply of the medication or placebo, along with a guided self-change booklet with information regarding quitting vaping. The study medication will be mailed to them free of charge. Neither they nor your doctor will decide which group they are in. Upon receipt of medication, they will receive a call from our tobacco treatment specialist. This will be a brief orientation call during which the specialist will go over medication use instructions with them. All participants will be encouraged to start their medication as soon as they receive it and to set a quit date 1-2 weeks after receiving the medication.

   End of Follow up Phase (Week 12): End of treatment assessments will be completed at week 12.

6.3.2 Informed Consent

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.

Remote consent via HIPAA compliant tele-video conferencing: This essentially is video, or telephone facilitated live discussion with study staff and potential study participants. After the initial determination of study eligibility, assessed online in our secure survey, participants will be asked about their capacity for virtual procedures (i.e., Doxy.meor other HIPAA compliant tele-video conferencing software), 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 HIPAA compliant tele-video conferencing, we will offer this option and follow IRB-approved procedures as per precedent. All tele-conferencing signed consent forms will be saved as pdf files within our study records; the participant also receives an electronic copy. Research staff will then have the participant complete the baseline questionnaires.

Remote e-consent via REDCap: This is similar to the above virtual 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 virtual 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, the participants will have the research coordinators contact information for any additional support or necessary 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. REDCap consent) 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. All participants, regardless of consenting modality, will be reminded with a study overview at the beginning of the Day 0 phone call and interest in continuing study participation will be confirmed at that point. We believe these methods will maximize opportunities for study participation.

6.3.3 Screening

This study will recruit using advertisements on various media platforms including, but not limited to, Craigslist ads, social media recruitment (e.g., Facebook and Instagram), print, radio, the Hollings and Smilow tobacco treatment services, etc. Since recruitment will also occur through referrals from TTS, medical records will be reviewed for the purposes of screening/recruitment, therefore a waiver of HIPAA authorization will be utilized in this study. 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. If the research staff deems the individual eligible, our study physician/nurse practitioner from the Tobacco Treatment Service/ PI Dr. Lisa Fucito will review their medical charts and approve their use of varenicline (described in more detail below). 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.

6.3.4 Enrollment

Potential subjects will be identified through Tobacco Treatment Service at Yale New Haven Hospital as well as other clinics in Yale-New Haven Hospital. In addition, potential subjects will be identified by responses to community-based advertisements.
Individuals who contact investigators by phone or email or who respond to mobile ads will be directed to complete a 5-minute, web-based pre-screening survey.

Following completion of the pre-screener, research staff will contact potential subjects and inform them of their initial eligibility status. Those who meet initial criteria will attend an intake to provide written informed consent and complete final screening for inclusion/exclusion.

6.3.5 On Study Visits

Assessments	**Week 0**	**Week 4**	**Week 8**	**Week 12**	**Weekly**
Demographics	X				
Smoking/Tobacco Use History	X				
Modified Questionnaire on Smoking Urges (QSU)	X		X	X	
E-Cigarette Dependence	X		X		
E-Cigarette Dependence Index	X		X		
Subjective Effects Cigarettes and E-cigarettes	X	X	X		
Patient Health Questionnaire-9 (PHQ9)	X				X*
Wisconsin Withdrawal Scale Brief (WSWS2-B					
Weekly Electronic Assessments					X
Exit Survey				X	

*bi-weekly

- Baseline (Week 0):
  - Assessment
  - Randomization
- Week 1:
  - Participant sent 1 week supply of 0.5mg and 3-week supply of 1mgOrientation call about medication
  - Weekly assessments
- Week 2
  - Weekly assessments
- Week 3:
  - Weekly assessments
- Week 4:
  - Participant sent second shipment of a 4-week supply of the 1 mg dose.
  - Weekly assessments
- Week 5:
  - Weekly assessments
- Week 6
  - Weekly assessments
- Week 7
  - Weekly assessments
- Week 8
  - Weekly assessments
  - End of treatment phase
- Week 9:
  - Weekly assessments
- Week 10

- Weekly assessments
- Week 11
  - Weekly assessments
- Week 12
  - Weekly assessments
  - Exit survey

6.3.6 End of Study and Follow-up

There will be an end of treatment assessment given at 12 weeks. This survey, designed for the study, will be conducted for all participants. Questions to ascertain participants' reactions to the different intervention conditions (i.e., varenicline, booklet) (e.g.,, overall satisfaction, perceived helpfulness, etc.), whether they utilized any of the external resources in the booklet (i.e., This is Quitting program) and their reactions, as well as any other use of other medications (e.g., NRT), and behavioral strategies that they used to reduce their e-cigarette use during the study (e.g., titrate e-cigarette nicotine dose, change flavors or switch to unflavored).

6.3.7 Removal of subjects

The Investigators have the right to withdraw a participant at any time. If participants do not follow study instructions, then they may be withdrawn from the study.

This is a voluntary study, in which participants have the right to withdraw at any time. If the participant decides to withdraw at any point, they can inform the research staff. No further data will be collected, and correspondents will stop. Any data collected up to that point will remain in study.

6.4 Statistical Method

6.4.1 Statistical Design

Baseline demographic and clinical characteristics will be tabulated for the overall study cohort as well as stratified by randomized treatment assignment. Baseline characteristics will be assessed for association with the primary study abstinence outcomes using univariable logistic regression models and resulting effect sizes will be reported. The primary purpose to this pilot trial is to ascertain study efficacy and determine effect sizes of varenicline on vaping abstinence. End of treatment and study follow up 7-day point prevalence abstinence rates will be tabulated and compared between varenicline, and placebo treated participants using a modified Poisson regression approach. Proportion abstinent as well as risk ratios and associated 95% confidence intervals will be provided for the entire study time course as well as stratified by study time point (end of treatment, study follow-up). Initial models will be adjusted for baseline vaping behavior as well as strata utilized in the randomization procedure. Sensitivity analysis will be employed to compare results from available study data to those with missing study data imputed to vaping (single imputation to worst case outcome). Study results will be utilized to design and sufficiently power a follow up RCT.

Secondary analysis of average reported vaping puffs per day and vaping days per week will be examined using generalized linear mixed effects models (GLMMs). Vaping puffs will be summarized weekly and differences between randomized treatment groups will be assessed during the treatment and follow up time periods. Model based means and standard errors will be used to determine pairwise comparisons and meaningful time points (weeks 8 and

12). The number vaping days per week will be assessed using GLMMs with a negative binomial specified distribution for count data. Median (inner quartile range) vaping days as well as risk ratios and associated 95% confidence intervals will be provided. Longitudinal models will include study treatment, week, and the associated interaction when appropriate.

6.4.2 Safety

Adverse events will be collected for all study emergent events throughout the treatment phase of the study. The proportion of participants reporting study emergent adverse events will be compared between groups using a Chi-Square test (Fisher's exact test when appropriate).

6.4.3 Analysis of Subject Characteristics

We will use descriptive statistics were used to summarize frequencies and percentages of sociodemographic characteristics (age, race, ethnicity, gender, college status) and clinical characteristics (medication use, e-cigarette use, etc.).

6.4.4 Interim Analysis (if applicable)

N/a

6.4.5 Health economic evaluation

N/a

6.4.6 Other

n/a

6.4.7 Subsets and Covariates

n/a

6.4.8 Handling of Missing Data

N/a

7 Trial Administration

7.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

The information we are asking to use and share is called "Protected Health Information." It is protected by a federal law called the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). In general, we cannot use or share patient's health information for research without their permission.

The specific information about them and their health that we will collect, use, and share includes:

- Research study records
- Medical and laboratory records of only those services provided in connection with this Study.
- Records about phone calls made as part of this research
- Records about their study visits
- Information obtained during this research regarding
    - Diaries and questionnaires
    - The diagnosis and treatment of a mental health condition
    - Use of illegal drugs or the study of illegal behavior
    - Records about any study drug you received

All of their responses will be held in confidence. Only the researchers involved in this study and those responsible for research oversight (such as representatives of the Yale University Human Research Protection Program, the Yale University Institutional Review Boards, and others) will have access to any information that could identify them that is provided. We will share it with others if they agree to it or when we have to do it because U.S. or State law requires it. For example, we will tell somebody if we learn that they are hurting a child or an older person.

For the purposes of recruitment, a wavier of HIPPAA will be utilized in this study.

We will use a Bank of America pre-paid debit card to provide the payment for taking part in the study. We will have to share the participant's name, address, and telephone number with Bank of America for ePayments. the participant will receive a card in the mail with the first payment. They will then need to activate the card over the phone. Each additional payment will be automatically added to the same card.

7.2 Institutional Review Board (IRB) Review

The protocol will be submitted to the IRB for review and approval. Approval of the protocol must be obtained before initiating any research activity. Any change to the protocol or study team will require an approved IRB amendment before implementation. The IRB will determine whether informed consent and HIPAA authorization are required

The IRB will conduct continuing review at intervals appropriate to the degree of risk, but not less than once per year.

A study closure report will be submitted to the IRB after all research activities have been completed.

Other study events (e.g. data breaches, protocol deviations) will be submitted per Yale's IRB's policies.

7.3 Subject Confidentiality

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.
The study monitor, representatives of the Institutional Review Board (IRB), or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.
At the end of the study, all records will continue to be kept in a secure location for 7 years. Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored on Yale redcap servers and in locked cabinets in locked office at CMHC. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used will be secured and password protected. At the end of the study, all study databases will be de-identified and archived on Yale servers and CMHC.

Identifiable information including participant's name, address, phone number, and date of birth, will be collected and used to enroll and contact participants. It will only be used for this purpose. This information will be stored in locked cabinet apart from the research records.

Research data will be collected using interviews, self-reports, wearable devices, and computer tasks. All identifiable information will be stored in a locked research cabinet. All participants will be assigned a study participant number. Subsequently, participants will be identified in the Case Report Forms (CRFs) only by that number and an encoded version of their initials (i.e., John Doe = JDO). A list of numbers and the corresponding names will be maintained by Dr. Fucito and stored in a locked research cabinet.

The data will be stored on secured server, laptop computer and desktop computer. The data will be stored in a locked room for 7 years after the final data is collected. After this point, the Data Manager and Principal Investigator, Dr. Fucito, will oversee the process in which data is destroyed or de-identified.

Several steps will be taken to safeguard the confidentiality of subjects and their data. All research data that is collected will be assigned a study participant number and that number will only identify participants in digital databases. 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 will be kept in a locked file cabinet where it can only be accessed by senior level project staff. 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 alphanumeric coding of data (in place of names) and proper storage of research records, including treatment exit interviews. Collected materials will be maintained via an alphanumeric reference system maintained by Dr. Fucito. Participants' names will appear only on the compound authorization form, and a master list maintained in a physically locked file that is separate from research data. Our data collection and management procedures are fully compliant with HIPAA. Access will be limited to personnel intimately involved in the study. A Certificate of Confidentiality will also be obtained. However, participants will also be told that if they present with suicidal or homicidal ideation and/or report any form of child/elder abuse or report plans to damage property then we will have to report this to the appropriate authorities and/or provide them with referrals for immediate treatment. Electronic data will be de-identified, and password protected. Only members of the study team will have access to the physical or electronic data.

All investigators and key personnel have taken the required Yale University HIPAA training. Right to privacy for participation in this research will be protected through coding of data and proper storage of research records. A list of numbers and the corresponding names will be maintained by the Principal Investigator in a locked research cabinet. Individually identifiable health information will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 and by additional protections of substance abuse treatment records afforded under Code of Federal Regulations (CFR) Part 2, Subpart E. All research personnel will be trained on human subjects' protection and HIPAA procedures.

We may share participant information with:
• The U.S. Department of Health and Human Services (DHHS) agencies
• Representatives from Yale University, the Yale Human Research Protection Program and the Institutional Review Board (the committee that reviews, approves, and monitors

research on human participants), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
• Those representatives at Yale who are responsible for the financial oversight of research including billings and payments
• The Principal Investigator
• The study sponsor
• Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan
• Co-Investigators and other investigators

• Study Coordinator and Members of the Research TeamOther researchers through a shared data agreement through a required policy from

NIAAA

7.4 Deviations/Unanticipated Problems

A protocol deviation is any noncompliance with the study protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.
It is the responsibility of the site investigator to identify and report deviations within 2 working days of identification of the protocol deviation. All deviations must be addressed in study source documents, reported to the study sponsor, and the reviewing Institutional Review Board (IRB) per their policies.
Unanticipated problems involving risks to participants or others include, in general, any incident, experience, or outcome that meets all of the following criteria:
Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
Related or possibly related to participation in the research (“possibly related” means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.
The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the study sponsor. The UP report will include the following information: Protocol identifying information: protocol title and number, PI's name, and the IRB project number; A detailed description of the event, incident, experience, or outcome; An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP; A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP. To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline: UPs that are serious adverse events (SAEs) will be reported to the IRB and study sponsor, if applicable immediately (if possible) followed by a written report within 5 calendar days using the appropriate forms from NIH and Yale University IRB. Any other UP will be reported to the IRB and study sponsor within 14 calendar days of the investigator becoming aware of the problem. All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 30 calendar days of the IRB's receipt of the report of the problem from the investigator.

7.5 Data Collection

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/Yale IRB, may have access to subjects' medical records containing PHI. Additionally, the funding source may have access to subjects' medical records containing PHI.

Trained research staff will administer assessments and collect measurements. They will enter data directly into a secure electronic database, which will be backed up on a secure, password protected Yale University network drive. De-identified data will be stored in the database and only accessible by research staff using a password protected login. All data with identifiable information will be stored in locked file cabinets in locked offices and will only be accessible by research staff.

7.6 Data Quality Assurance

Multiple measures are in place to ensure the validity and integrity of the data. First, all research staff receive Human Subjects Protection training, as well as training in Good Clinical Practice. Second, Dr. Fucito will supervise and train the Research Coordinator and key personnel on study procedures to ensure that all procedures are followed and are in compliance with the approved Yale University IRB protocol. Dr. Fucito will also provide training and oversight to study staff to ensure data are generated, documented, and reported according to requirements by the Yale University IRB and NIH. She will then monitor adherence to protocol procedures and use individual supervision to address any data quality concerns. Third, weekly research meetings will be held for all research staff as a forum for in-service training as well as to discuss questions regarding issues that arise in complex clinical research protocols. Fourth, all research staff will be cross-trained to 'cover' for each other; thus, review by multiple staff with oversight by the PI will facilitate early identification of errors and oversight. Fifth, Dr. Fucito will also oversee quality assurance of data. The Research Coordinator, in collaboration with Dr. Fucito, will review the study database on a monthly basis to ensure data accuracy. Any data quality issues will be addressed immediately. Last, the use of an electronic system for data capture will minimize data entry errors.

7.7 Study Records

Protocol

Consent form

weekly assessments

Subject medical records

7.8 Access to Source Documents

Source data will be maintained per Medical Records policy in a password protected, secure, Health Insurance Portability and Accountability Act (HIPAA) compliant, web-based electronic database with a built-in audit trail.
Only Institutional Review Board (IRB) approved research team members who have current HIPAA and Collaborative Institutional Training Initiative (CITI) Good Clinical Practice (GCP) and human subjects protection training will be authorized to access records.

7.9 Data or Specimen Storage/Security

Several steps will be taken to safeguard the confidentiality of subjects and their data. All research data that is collected will be assigned a study participant number and that number will only identify participants in digital databases. 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 will be kept in a locked file cabinet where it can only be accessed by senior level project staff. Any information published because of the study will be such that it will not permit identification of any participant.

Research records are maintained under the person's name, but the study number is not entered anywhere into a medical record. Right to privacy for participation in this research will be protected through coding of data and proper storage of research records. The Principal Investigators will maintain a list of IDs and the corresponding names in a locked research cabinet. 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/Yale IRB, may have access to subjects' medical records containing PHI. Additionally, the funding source may have access to subjects' medical records containing PHI.

Trained research staff will administer assessments and collect measurements. They will enter data directly into a secure electronic database, which will be backed up on a secure, password protected Yale University network drive. De-identified data will be stored in the database and only accessible by research staff using a password protected login. All data with identifiable information will be stored in locked file cabinets in locked offices and will only be accessible by research staff.

7.10 Retention of Records

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/Yale IRB, may have access to subjects' medical records containing PHI. Additionally, the funding source may have access to subjects' medical records containing PHI.

7.11 Study Monitoring

Dr. Fucito, the PI, will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency that must be conducted at a minimum of every 6 months (including when reapproval of the protocol is sought), which is appropriate for a study deemed to be of minimal risk. Dr. Fucito will review the frequency of anticipated and unanticipated adverse events overall and by study arm with key personnel. The focus of the evaluation will be to determine whether the study should continue unchanged, require modification/amendment, continue or close to enrollment. Dr. Fucito, the Yale University IRB, and the National Institutes of Health have the authority to stop or suspend the study or require modifications.
Dr. Fucito will also lead a weekly research meeting with key personnel to review the status of all enrolled participants and discuss the eligibility of potential participants. At this weekly meeting, Dr. Fucito will review study progress (i.e., recruitment goals, retention, protocol adherence). Any adverse events will be reviewed at this meeting including serious adverse events that may have been attended to outside of this weekly meeting. An annual progress report will be submitted to NIH and the Yale University IRB that lists and summarizes adverse events; documents whether adverse event rates are consistent with pre-study assumptions; summarizes recruitment and retention and reason for dropouts; and

summarizes study progress related to the stated aims.

7.12 Data Safety Monitoring Plan

Other contraindications for varenicline include suicidal ideation.[21] Suicidality will be assessed at prior to randomization and during the follow-up assessments. If an individual endorses suicidality during the pre-randomization screening, they will be marked as ineligible for the study. This will be assessed using the PH-Q toolkit for suicide ideation (refer to assessments section). An alert is programmed into the REDCap system that if an individual indicates an active plan to either physically harm or kill themselves, an alert will be sent to the study team. They will then be contacted by our clinical team to complete a risk assessment over via phone. A member of the clinical team will query the participant for details regarding the suicidal ideation, including a likelihood of harming oneself imminently and a plan for committing suicide. If the participant reports an imminent likelihood of harming him/herself or a plan for committing suicide, the clinical team member will call emergency services and will remain on the phone with the participant until emergency services arrive. In the event that the participant expresses an imminent likelihood of harming him/herself, and the connection is lost, emergency services will be contacted to provide emergency services with the participant's contact information, including address. If the participant is not in imminent danger, the clinical staff will provide referrals for local mental health resources and/or instruction to go to the ED or call 911 should suicidal ideation worsen. The clinical team member will suggest that the participant seek treatment and then will follow-up with the participant via phone one week later.

In the event that a participant endorses suicidal ideation but is not responsive to clinical staff's phone call within 48 hours, the participant will be emailed a list of local mental health resources and will suggest that the participant seek additional treatment. The email will also ask that the participant respond to the clinical staff either via phone or e-mail within 24 hours to confirm receipt of the treatment referrals. Should the participant not respond to the clinical staff's email within an additional 48 hours (4 days from completion of the assessment) and endorse ""Several days", More than half the days" or "nearly everyday" to "Thoughts that you would be better off dead or of hurting yourself in some way" on the PH-Q suicidality toolkit at study screening, emergency services will be contacted and will be provided with the participant's name and address.

We will utilize the PHQ9 assessment to track depression and suicidal ideation during the baseline assessments. If suicidal ideation is endorsed, an automated "red flag" will be processed through our REDCap database. This red flag will indicate either a a) clinically significant increase in total PHQ scoring with an overall score of at least 15 (>5 point increase from baseline and resulting score >15), OR b) any value >0 for item 9/suicidal ideation). The red flag indicators will be monitored daily by our clinical team and will be met with the appropriate measures. These measures are based on prior MUSC-IRB approved protocols of varenicline (i.e., the STARS Pro00098479).

7.13 Study Modification

Study modifications will be undertaken in response to ongoing study monitoring. Any potential modifications that could have a major impact on the study objectives will be discussed before submission to the IRB. More minor
modifications that do not impact study objectives but help with study recruitment and implementation or allow for additional assessment of important questions will be submitted to the IRB for approval.

7.14 Study Discontinuation

If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

Determination of unexpected, significant, or unacceptable risk to participants

Demonstration of efficacy that would warrant stopping

Insufficient compliance to protocol requirements

Data that are not sufficiently complete and/or evaluable

Determination that the primary endpoint has been met

Determination of futility

7.15 Study Completion

Intended to complete in two years. The IRB will be notified in writing upon study completion and the study will be archived with the IRB when all final analyses have been conducted on identifiable information.

7.16 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the appropriate conflict of interest review committee has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

All investigators will follow the applicable conflict of interest policies.

7.17 Funding Source

This research will be funded by Dr. Fucito's department internal use funds.

7.18 Publication Plan

Study results will be made available via articles written for professional and layperson publications; presentations at scientific and professional conferences; special lectures/talks in academic and professional settings; collaborating agencies/research sites, and interest groups. No identifiable information will be disclosed. Data will be presented and published in aggregate. Dr. Fucito, as PI, has primary responsibility for publishing the study results. Once all of the data have been cleaned and validated, and main findings have been published, the data will be made available to the scientific community. Datasets will be made available to any qualified individual who makes a direct request to the PI and indicates the data will be used for the purposes of research (as defined in CFR Title 45 Part 46). Data will be provided to HIPPA-compliant, de-identified files. The following plan

specifies the following conditions that need to be met before data are shared in the form of a data sharing agreement.

- A formal research question is specified a priori;
- Names, affiliations, and roles of any other individuals who will access the shared
- data;
- The deliverable(s)—e.g., manuscript, conference presentation—are specified a priori;
- Proper acknowledgement of the source of the data;
- A statement indicating an understanding that the data cannot be further shared with
- any additional individual(s) or parties without the PI's permission;
- IRB approval for use of the data (or documentation that the data are exempt);
- Agreement to maintain the data in a physically and electronically secure location.
- Data will be shared in electronic format and accessible to the software used by the Investigators; upon completion of the analyses, the requestor will be instructed to destroy all copies of the data.

The agreement to share data will be revisited annually to determine whether the current policy should be modified based upon our prior experiences in sharing the data with other investigators.

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8 Appendices

Appendix #	Title	Section	Topic

9 List of Tables