PROTOCOL TITLE: Development and Evaluation of a Brief Behavioral Activation Mobile Application for Nicotine Vaping Cessation Among Adolescent Primary Care Patients

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1.0 Objectives / Specific Aims

The goal of this Stage 1 treatment study is to develop, systematically refine, and clinically evaluate a depression-specific Brief Behavioral Activation (BA) for adolescent vaping cessation mobile app ("VapeX").

Aim 1: **Develop and refine VapeX.** Individual interviews with end-users (n=10) will inform the design of VapeX.

Aim 2: **Via a two-arm pilot randomized controlled trial (N=106, randomized 1:1), examine the feasibility and efficacy of 1) VapeX vs. 2) treatment as usual.** Subsequent iterative usability testing (n=5, or until saturation) will guide app refinements. Main outcomes, which will be assessed across 4-weeks of follow-up, include: 1) treatment feasibility, 2) treatment acceptability, 3) change in depression over time as a function of treatment, and 4) changes in vaping behavior (e-cigarette use episodes per day, days using an e-cigarette per week, number/duration of quit attempts, 7-day point prevalence abstinence at Week 4, use of other tobacco products) as a function of treatment.

2.0 Background

Nicotine Vaping is an Epidemic among Adolescents. The prevalence of vaping nicotine (i.e., e-cigarette use) has skyrocketed among adolescents in recent years[1-3], rising from near zero in 2011 to 27.8% in 2019[4]. These rapid increases in adolescent vaping led the Surgeon General in 2018 to declare adolescent e-cigarette use an epidemic[5]. High rates of vaping among adolescents are concerning because: 1) vaping carries a variety of short-term health risks[6-8], with largely unknown long-term risks, 2) nicotine is highly addictive[9], and 3) adolescents who vape are three times more likely to initiate combustible cigarette use[10-14].

Adolescents who Vape are Interested in Quitting, but Interventions are Limited. Nearly half of all adolescents who vape are seriously interested in quitting, as our group reported in *JAMA Pediatrics*[15]. Yet, vaping quit attempts are often unsuccessful: one quarter of current vapers have made a quit attempt in the past year that resulted in relapse[15]. Despite high interest in quitting, extant cessation interventions have received little empirical investigation and no NIH-funded trials have examined the efficacy of interventions for adolescent vaping cessation. FDA-approved medications for adult nicotine dependence are not approved for adolescent use[16]. Instead, clinical guidelines[17] and systematic reviews[18,19] conclude that behavioral/psychosocial counseling is the first-line treatment approach for adolescent nicotine dependence. As such, there is clear need to develop, evaluate, and disseminate evidence-based psychosocial interventions for adolescent vaping cessation.

An Appropriate Intervention Must Target Established Vaping Risk Factors. Depressive symptoms, which are common among adolescent vapers (36%)[20], have recently been identified as a predominant vaping-related risk factor. Similar to the general population of adolescents who vape, 46.8% of adolescent vapers with depressive symptoms report seriously thinking about quitting[15]. Consistent with the transdiagnostic emotional vulnerability framework[21], the relationship between depression and vaping is bidirectional such that depressive symptoms prospectively predict vaping initiation, and sustained e-cigarette use exacerbates depression[22]. This aligns with decades of research documenting depression as a robust risk factor for initiation of combustible tobacco use among adolescents[21,23,24], transition to regular smoking[25,26], difficulties quitting[27-29], and relapse[30-33].

Among cigarette smokers with depressive symptoms, tailored interventions that target both depression and tobacco use are necessary for cessation[34,35]. Thus, an ideal candidate treatment for adolescent vapers with depressive symptoms likely must also target depressed mood. Brief Behavioral Activation (BA) is a well-established, evidence-based treatment for depression[36-39] that has demonstrated promise for smoking cessation among adults[40] and adolescents[41]. Brief BA focuses on regular self-monitoring to 1) examine

already occurring activities and 2) facilitate the incorporation of new activities consistent with individualized values/goals across life areas. Completing enjoyable, important activities improves mood, making it easier to initiate and sustain cessation[40]. An adapted version of Brief BA for adolescent vaping cessation could offer a promising approach to simultaneously target depressive symptoms in the service of promoting vaping cessation.

Summary of Scientific Premise. Nicotine vaping among adolescents is an epidemic. Adolescents want to quit vaping, but available treatment approaches within primary care, where youth are likely to receive treatment, are limited both in scope and in evidence base. To maximize efficacy and reach, a product that will fill this gap must: 1) directly target established risk factors for adolescent vaping and 2) be accessible via platforms already utilized by adolescents. The goal of this Stage 1 treatment study is to develop, systematically refine, and preliminarily evaluate a depression-specific Brief BA for adolescent vaping cessation mobile app ("VapeX"). This will build upon our team's prior and ongoing research developing mobile app adaptations of Brief BA for depression and smoking cessation treatment within primary care[42-45].

3.0 Intervention to be studied

VapeX. Features identified via individual interviews will form the basis of VapeX development. VapeX will be developed for iOS and Android, will be HIPAA-compliant, and will retain all key elements of Brief BA and standard cessation treatment in Goal2Quit (our team's Brief BA for smoking cessation app), though these features will be modified based on individual interviews. *Brief BA components include*: 1) Psychoeducation highlighting the connection between mood and vaping, 2) Identification of values and activities across life areas including relationships, responsibilities, recreation, education/career, health, and being vape-free, 3) Activity planning, and 4) Tracking mood and vaping. *Standard cessation components include*: 1) Reinforcement and support for quitting, 2) Interactive questions to identify past quit attempts and contributors to relapse, 3) Setting a quit date, suggested to be no later than two weeks after treatment initiation, and 4) Identification of triggers and development of coping strategies.

TAU. TAU is designed to mimic existing vaping cessation standard treatment. Participants in both conditions will be provided educational material about depression and vaping available via the National Cancer Institute's Smokefree Teen website with a suggestion to discuss questions with their PCP. Across conditions, participants will not be precluded from obtaining additional treatment, which will be tracked as an outcome.

4.0 Study Endpoints (if applicable)

Primary outcome variables include:

Depression. The PHQ-8 will be used for preliminary screening and the PHQ-9 will be administered at final screening. Across all timepoints depressive symptoms will also be assessed via the Beck Depression Inventory-II (BDI-II). The BDI-II is a validated assessment of depressive symptoms among adolescents and is our primary depression outcome. Self-report and Electronic Health Record (EHR) data will be used to categorize concurrent depression treatment (therapy, medications) at baseline and across the trial.

Vaping. Nicotine vaping and quit outcomes will be assessed at each follow-up using a Timeline Followback for the last 6-months at baseline and since prior follow-up for each subsequent assessment. Frequency of vaping will be assessed in multiple ways including number of vaping episodes per day and number of days per week vaping. Use of other tobacco products and frequency of use will also be assessed. Cessation outcomes include: 1) number of quit attempts since last assessment, 2) duration of each quit attempt, 3) point-prevalence abstinence, and 4) continuous abstinence. E-cigarette dependence

will be assessed at baseline via the 10-item Penn State Electronic Cigarette Dependence Index (ECDI). Participants will report motivation to quit and confidence in quitting using a modified Contemplation Ladder.

Treatment Utilization. VapeX utilization will be tracked via analytics data. Specifically, we will examine 1) number of app sessions, 2) average time per session, and 3) total time using the app. Additionally, we will assess engagement with each individual component of the app. Analytics will be examined within each week and across the entire trial duration.

VapeX Feasibility and Acceptability. VapeX participants will self-report feasibility and acceptability at all follow-ups. As in our prior trials, participants will report: 1) ease of app use, 2) continued desire to use the app, 3) perceived benefits of using the app, and 4) suggested improvements.

Assessment Grid

	Screening	Baseline	Week 1	Week 2	Week 3	Week 4
Screening Questionnaire	x					
PHQ-8	x					
Demographics		x				
PHQ-9		x				
BDI-II		x	x	x	x	x
Current use of Psych Meds		x	x	x	x	x
TLFB		x	x	x	x	x
Cessation outcomes		x	x	x	x	x
ECDI		x	x	x	x	x
Contemplation Ladder		x	x	x	x	x
Tech Comfort		x				
Feasibility/Acceptability			x	x	x	x
VapeX Usability Scale			x	x	x	x
VapeX Utilization			x	x	x	x

5.0 Inclusion and Exclusion Criteria/ Study Population

Inclusion criteria:

a) age 16-20
b) vaped nicotine on ≥20 days out of the last 30[46]
c) elevated depressive symptoms, defined as a score of ≥10 on Patient Health Questionnaire-8 (PHQ-8) during preliminary screening and the Patient Health Questionnaire-9 (PHQ-9)[47] at final eligibility during baseline
d) currently own an iOS or Android smartphone
e) report willingness to utilize an app for quitting vaping nicotine (response of "yes" on yes/no item)
f) have a valid e-mail address that is checked regularly or regular access to text messages (for follow-up assessments)
g) has been seen (in person or remotely) by a primary care physician within the last year

Exclusion criteria:

a) smoked cigarettes or used other tobacco products on ≥9 days out of the last 30[48-50]
b) severe visual impairment
c) currently receiving treatment for vaping or tobacco use
d) current suicidal ideation, defined as a response ≥2 on item 9 of the BDI-II at baseline (See Protection of Human Subjects for comprehensive plans to address suicidality and clinical deterioration)
e) household member currently enrolled in the study
f) inability to read the consent form

6.0 Number of Subjects

We will recruit up to 10 participants for individual interviews and 106 for the RCT, the first 5 of the RCT will be for usability testing.

7.0 Setting

Study participants will be recruited from primary care/family medicine practices affiliated with MUSC's Primary Care Integrated Center of Clinical Excellence (ICCE). Participants may also be recruited remotely via advertisements (e.g., online ads).

8.0 Recruitment Methods

Recruitment will occur proactively and remotely leveraging data available within the EHR. As part of routine clinical care, adolescents are screened at each visit for nicotine/tobacco use, including e-cigarette use, and for depressive symptoms via the Patient Health Questionnaire-2 (PHQ-2). To recruit our targeted population, we will utilize cold contact methods by submitting a Research Data Request to obtain a EHR recruitment report created for all patients treated within the Primary Care ICCE during the past 12 months who: 1) are age 16-20, 2) vape, and 3) had depressive symptoms during their last visit. Depressive symptoms will be defined as *either*: 1) a score of ≥3 on their last PHQ-2 (the optimal cut-point to identify those symptomatic), 2) depression on their problem list, *or* 3) a depression-related billing code. The study team will not cold-contact any patients who have chosen to opt-out of receiving contact about research or who have met the maximum number of contact attempts at the time of recruitment.

Identified patients will be sent an electronic communication (e-mail or message via the EHR patient portal, based on patient preferences) from a member of the study team inviting them to participate in a study. This electronic communication will include a link to complete study screening via REDCap. Within South Carolina, the legal age to consent to medical treatment is 16. At age 16, all MUSC patients can receive their own patient portal account and parents/guardians can be appointed as proxies. If participants do not respond to this invitation within 72-hours, we will contact them via phone, e-mail, and/or text-message (based on preferences within the EHR) to ensure they received the message. If interested, participants will complete an eligibility screening via MyChart/REDCap. This eligibility screening will assess: age, sex, e-mail access, English fluency, smartphone ownership, nicotine vaping status, willingness to use a mobile app for nicotine vaping cessation, and depressive symptoms via the PHQ-8. This eligibility screening will be used solely for screening purposes, not for research purposes. Within our informed consent documents, if a participant provides informed consent to participate in the study, they will agree that their screening information can be used for research purposes. After completing determination of eligibility, a member of the research team will complete remote electronic informed consent with the participant (see details below).

Recruitment may also occur in the following ways:

1) In Clinic: Participants may be recruited in clinic after being identified as a nicotine vaper by research personnel listed on this application.
2) Via advertisements (e.g., flyers) and online postings such as Craigslist.
3) Snowball recruitment: Enrolled participants can refer others to the study. If they refer someone that enrolls, they will receive additional compensation.
4) Recruiting parents with children who vape directly using IRB approved advertisements on online platforms.

9.0 Consent Process

Signed informed consent will be obtained from study participants. The consent process will take place via one of the following modalities: 1) Remote or in person electronic consent (e-consent) via REDCap (if remote, e-consent will be facilitated with a discussion over the phone or via video), 2) Remote consent via doxy.me facilitated with either a discussion over the phone or video connection via doxy.me, 3) Mailed

(paper) consent facilitated with a discussion over the phone, or 4) in person consent (e.g., in clinic, in the investigator's lab space).

All participants will be provided with a hard copy and/or an electronic copy of the consent form. Participants will be informed that participation in this research is strictly voluntary. Informed consent will include a detailed description of the purpose and the procedure of the study emphasizing our policy regarding privacy and confidentiality and an opportunity for the individual to ask any questions or voice concerns. Signatures on the consent form may be obtained with paper and pen OR electronically via REDCap/doxy.me. Participants who do not have access to the required technology to complete consent remotely via REDCap or doxy.me will be given the option to complete consent via mail facilitated with a discussion over the phone.

Parents/guardians of participants under 18 years old will be required to attend the informed consent/assent procedure. Participants 18 years and older will be able to provide their own informed consent. Particular caution will be exercised in obtaining informed adolescent assent separately and independently from parental consent to limit potential for coercion. To this end, an initial step in participant recruitment involves obtaining parental/legal guardian permission for participation by the adolescent. Once parental consent is secured, youth will be asked separately and independently for informed consent (i.e., parental consent will not be used to persuade teens to participate). This approach is considered very effective in minimizing coercion to participate. In the case of adolescents in South Carolina Department of Social Services custody, state guidelines regarding consent for clinical research participation will be followed.

10.0 Study Design / Methods

Aim 1: Develop and Refine VapeX.

VapeX Development Testing

VapeX development will take place in three steps: 1) semi-structured individual interviews with end-users (n=10) and 2) software development. Individual interviews will follow standard procedures[51]. Individual interviews (1hr each, $40 compensation in electronic gift card codes (e.g., Amazon) emailed to participants) will be divided into four parts: 1) discussion of apps for positive health behavior change and participants' experiences with such apps, 2) narrowed focus on mobile apps for quitting vaping and managing low mood, 3) even narrower focus on an initial version of the VapeX app, which will be previewed for the participant during the interview, and 4) discussion of features that participants would like included in VapeX that are not currently included This discussion will begin with facilitators presenting participants with a list of features that have been included in other mobile app interventions for adolescent substance use treatment (***Table 1***)[52,53]. Individual interviews may occur either remotely using an MUSC-approved HIPAA compliant video conferencing platform (e.g., Microsoft Teams) or in person, depending on the status of the COVID-19 pandemic.

Table 1: App Features to Consider for VapeX

Domain	Specific Potential Features
Gamification	Rewards earned for continued app use or decreased vaping; Competitions within the app
Social Interaction	In-app communication with peers; Ability to help others quit vaping/provide peer support
Family Involvement	Resources for discussing depressed mood and/or substance use with parents
Dual Use	Psychoeducation about dual use and strategies to quit smoking while quitting vaping

Features identified via individual interviews will form the basis of VapeX development. VapeX will be developed for iOS and Android, will be HIPAA-compliant, and will retain all key elements of Brief BA and standard cessation treatment in Goal2Quit, though these features will be modified based on individual interviews. Brief BA components include: 1) Psychoeducation highlighting the connection between mood and vaping, 2) Identification of values and activities across life areas including relationships, responsibilities, recreation, education/career, health, and being vape-free, 3) Activity planning, and 4) Tracking mood and vaping. Standard cessation components include: 1) Reinforcement and support for

quitting, 2) Interactive questions to identify past quit attempts and contributors to relapse, 3) Setting a quit date, suggested to be no later than two weeks after treatment initiation, and 4) Identification of triggers and development of coping strategies. As in prior projects, to develop VapeX, we will follow an agile software development approach[54]. Key phases of development will include whiteboard design, wireframing of user stories, graphic design, programming, and deployment. Development will be led by MoutainPass Technology LLC, with iterative testing completed by the PI and co-Is.

HIPAA Compliance

Regarding user privacy while using VapeX, users will create a username and password in order to login to their account without storing their true identity. In VapeX, we will store a one-way hashed version of the patient's email address to support password reset and unique identification, but that identification will not be traceable back to the user's true identity. We will not store any personally identifiable information (e.g., first name, last name, email address, phone number) of users in our app database. VapeX will be HIPAA compliant. We will use a HIPAA-compliant server protected by industry-standard safeguards to prevent unauthorized access. Since we are not associating patient health information with personally identifiable information there will not be a risk of unauthorized release of patient medical data in the event of a security breach. User personal information will be contained behind secured networks and will only be accessible by the investigators, who will have special access rights to such systems. In addition, all sensitive information users supply will be encrypted via Secure Socket Layer (SSL) technology. We will not sell, trade, or otherwise transfer personally identifiable information to outside parties. Our privacy policy will be available within the app for users to view at any time. This plan is consistent with that used by our partnering app development company, MountainPass Technology LLC, in several other previous products with similar protection requirements. Mr. Kustanowitz from MountainPass Technology has expertise in HIPAA-compliant software development and will oversee all aspects of HIPAA compliance within this project.

Aim 2: Pilot Feasibility RCT (N=106) of VapeX vs. TAU.

Procedures

After completing determination of eligibility and consent, usability testing will commence. Recruitment will continue until we reach data saturation (planned n=5)[56]. The first 5 participants enrolled will be assigned to the VapeX group to assess to capture any app refinements necessary at the start of the trial. All other procedures while remain the same across participants. The remaining participants (n=98) will be randomized via REDCap 1:1 to VapeX or TAU. Participants will be randomized via a mixed block design stratified by age, baseline depressive symptoms, and concurrent depression treatment. All participants will complete baseline assessments remotely and if randomized to VapeX, study staff will remotely provide participants with app download codes and will ensure successful downloads. Study staff will then give participants brief overviews regarding app utilization and will provide the participants 10 minutes to use the app and ask questions.

Assessments

Participants will be text messaged or emailed a REDCap link to complete follow-up assessments **weekly for 4 weeks**. Assessments are estimated at 20 minutes each. Participants will be compensated in electronic gift card codes (e.g., Amazon) emailed to participants in the amount of $20 for completion of each assessment with a $50 bonus if all are completed. If a participant does not meet final eligibility at baseline, they will be compensated $20 for the visit but will not be enrolled. Enrolled participants may also refer others to this study. If they refer someone that is eligible and enrolls they will receive an additional $40 (Total possible compensation = $190). If fraud is detected within the surveys, the Principal Investigator may decide to withdraw a participant from the study. Fraud may include 1) a research assessment being completed in an unusually short period of time, 2) straightlining (i.e., responding with the same answer to

all items on a survey), 3) inaccurate responses to a validity check question. If fraud is suspected, the study team may request additional verification of identity such as a photo ID prior to trial enrollment.

Vaping. Nicotine vaping and quit outcomes will be assessed at each follow-up using a Timeline Followback for the last 6-months at baseline and since prior follow-up for each subsequent assessment[59]. Frequency of vaping will be assessed in multiple ways including number of vaping episodes per day and number of days per week vaping. Use of other tobacco products and frequency of use will also be assessed. Cessation outcomes include: 1) number of quit attempts since last assessment, 2) duration of each quit attempt, 3) point-prevalence abstinence, and 4) continuous abstinence. E-cigarette dependence will be assessed at baseline via the 10-item Penn State Electronic Cigarette Dependence Index (ECDI)[60,61]. Participants will report motivation to quit and confidence in quitting using a modified Contemplation Ladder[62]. Depression. The clinic-administered PHQ-2[63] will be used for preliminary her screening and the PHQ-8 will be completed during initial screening. As the PHQ-8 does not assess suicidality, the full PHQ-9[47] will be administered at final screening. Across all timepoints depressive symptoms will also be assessed via the Beck Depression Inventory-II (BDI-II)[64,65]. The BDI-II is a validated assessment of depressive symptoms among adolescents[65] and is our primary depression outcome. Self-report EHR data will be used to categorize concurrent depression treatment (therapy, medications) at baseline and across the trial. Treatment Utilization. VapeX utilization will be tracked via analytics data. Specifically, we will examine 1) number of app sessions, 2) average time per session, and 3) total time using the app. Additionally, we will assess engagement with each individual component of the app. Components will be finalized based on feedback from individual interviews but are likely to include identification of activities, scheduling of activities, mood tracking, monitoring frequency of vaping, and standard vaping cessation treatment content (e.g., setting a quit date, education about the benefits of quitting vaping). Participants will be asked to use the app at least once per day for at least 5-10 minutes at a time. Analytics will be examined within each week and across the entire trial duration. VapeX Feasibility and Acceptability. VapeX participants will self-report feasibility and acceptability at all follow-ups. As in our prior trials, participants will report: 1) ease of app use, 2) continued desire to use the app, 3) perceived benefits of using the app, and 4) suggested improvements.

11.0 Data Analysis and Data Management

Data Analytic Plan for Aim 1 Qualitative Data

Qualitative data from interviews, quantitative data from questionnaires, and video and audio recordings will be incorporated for mixed methods data analysis[66]. This approach was chosen because, while quantitative data can identify usability errors and areas of dissatisfaction, qualitative data provides guidance on the root of errors and methods for optimization. Qualitative data will be analyzed using NVivo software[67] and a deductive/inductive template analysis approach[68,69] using iterative codes to identify core concepts[70]. From these core concepts, we will determine the needs, concerns, and impressions of our prototypes. Two coders will independently review and code data using an iterative, team-based process with discrepancies resolved by the study team. Qualitative themes will be supplemented by patterns identified in quantitative results. After completing qualitative and quantitative data analysis independently, data from each source will be synthesized using graphical matrix configurations for data triangulation[71]. This analytic approach was selected due to the expectation that participants will raise unanticipated needs. Mean ratings of VapeX components from the After-Scenario Questionnaires (ASQs) will be calculated and components with lowest satisfaction will be flagged for refinement. Video and audio recordings be coded for navigation errors (difficulty locating a function), content errors (difficulty due to information labeling), and usage errors (improper tool use). Problems will be grouped according to severity (critical/serious/minor).

Sample Size Estimation

As a pilot, our goal is to determine VapeX feasibility/acceptability and estimate effect sizes for a larger Phase II project. We can obtain more robust estimates in the VapeX group via 1:1 randomization with the first 5 being assigned to the VapeX group for usability testing. Toward these ends, we will randomize **49 to VapeX and 49 to TAU**. To account for 20% attrition, we will enroll a maximum of 108 participants.

Data Analytic Plan for Aim 2

Feasibility and Acceptability. Within the VapeX group, retention will be defined as the proportion of participants who use the app at least once within each week following enrollment. Retention point estimates and 95% CIs will be calculated, and a one-sided, one-sample proportion test will be used to determine whether retention is at least 70% (or higher) within each group. Other metrics of feasibility/acceptability (ease of use, continued desire to use, etc.) will be summarized within group via summary statistics and 95% CIs, as appropriate.

Vaping Behavior and Vaping Cessation Outcomes. Descriptive statistics will be calculated and compared for overall group differences via Fisher's exact tests, chi-square tests, or nonparametric equivalents, as necessary, for baseline variables. Pairwise differences will be explored for categorical variables that show a significant overall group difference to see where differences may exist. Significant baseline demographic differences between groups will be included as covariates in vaping and depression outcomes analyses. Descriptive statistics (e.g., means, frequencies, percentages) will be calculated for the primary vaping-related outcomes including frequency of vaping and other tobacco product use (number of e-cigarette use episodes per day, number of days using an e-cigarette per week, number of days using other tobacco products including cigarettes) and vaping cessation outcomes (number and duration of e-cigarette quit attempts, 7-day point prevalence abstinence at Week 4) overall and by treatment group. To examine group differences adjusted for relevant covariates based on baseline differences between groups, generalized linear mixed models with logit links for binary outcomes will be used, including a random component for participant and/or clinic. These mixed models will account for any clustering effects within participant and clinics.

Depression. Similar generalized linear mixed models will be used to examine group differences (VapeX vs. TAU) in depression (BDI-II) over time along with an interaction between group and time adjusting for baseline differences and baseline depression. All models will include a random component to account for any clustering effects from the clinic from which the participant was recruited along with a random effect for repeated measures within an individual. Sex will be examined for inclusion as a covariate in all models. These generalized linear models allow for examination of overall main effects of group, time, and the interaction between group and time, while also accounting for repeated measures within participants and clustering with clinics[72,73].

Missing Data. All randomized participants will be included in primary analyses, and imputation methods will be used to accommodate missing data if missing data is >10%. Sensitivity analyses will be done using only those with complete data, with results compared to primary analyses. Attrition will be assessed to determine whether there is differential dropout by group.

Adverse Events (AEs). AEs will be defined as a clinically significant (i.e., 10-point[64]) increase in depression on the BDI-II from baseline or any incidence of suicidality (response of "I would like to kill myself" or "I would kill myself if I had the chance" on the BDI-II suicidality item). We will determine the incidence of AEs and associated 95% CIs. A chi-square test will determine if the rate of AEs is greater than 5% in any group.

Data Management

Regarding questionnaire data, data will be obtained for research purposes only. The recruitment project is stored in REDCap and only study team members will have access to the recruitment project database. The research team will only have access to the REDCap recruitment project while actively enrolling for the study. The recruitment project will be stored separately from the project containing research data. The recruitment REDCap project will potentially contain both identifiers and health information in the same project. All data will be collected, stored, and managed via REDCap, which is a secure, web-based application designed exclusively to support data capture for research studies. REDCap provides secure, web-based flexible applications, including real time validation rules with automated data type and range checks at the time of entry. The underlying database is hosted in a secure data center at MUSC, a secure environment for data systems and servers on campus, and includes redundancy, failover capability, backups and extensive security checks. The system has several layers of protection including user/group account management, "Data Access Groups" which allow data to be entered by multiple groups in one database with segmented user rights for entered data, audit trails for all changes, queries and reports, and Secure Sockets Layer (SSL) encryption. Name and relevant contact information will be obtained to provide compensation and every effort will be made to maintain subject confidentiality, in accordance with HIPAA. All data will be identified only by code numbers (participant IDs). Participant IDs will be linked to participants' names in a password-protected file that is accessible only to the PI and trained research staff.

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects (if applicable)

This section is based on the recommendations in NIDA's "Guidelines for developing a Data and Safety Monitoring Plan" as well as NCI's "Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by the National Cancer Institute".

Summary of the Protocol
This R41 application consists of a 2-Aim proposal. In Aim 1, targeted end-users, defined as adolescent (ages 16-20) regular nicotine vapers (vaped on ≥20 days out of the last 30[46]) with elevated depressive symptoms (score of ≥10 on the PHQ-9[47]) who have been seen at least once in the last year by a PCP, will be recruited for individual interviews (n=10) that will inform the development of VapeX. In Aim 2, we will conduct a two-arm pilot feasibility randomized controlled trial (N=106; 1:1 randomization) with the first 5 participants recruited for usability testing and randomized to receive the VapeX app, to examine the feasibility and acceptability of VapeX as well as treatment efficacy for depression and nicotine vaping cessation relative to TAU.

Trial Management
The study will be managed from the Addiction Sciences Division within the Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina (MUSC). Recruitment, data collection, data management, and treatment provision will be coordinated and centrally managed at our research lab at MUSC and will be implemented within local Family Medicine/Primary Care clinics that are part of MUSC's Primary Care ICCE.

Data Management and Analysis
Participants will enter data in REDCap, a secure, web-based application designed exclusively to support data capture for research studies. REDCap provides: 1) an intuitive interface for data entry (with data validation); 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R); 4) procedures for importing data from external sources; and 5) advanced features, such as branching logic and calculated fields. These procedures are effective in minimizing data entry errors (e.g., missing or errant

data). All data from VapeX will be stored on a HIPAA-compliant server. Data analytic plans are outlined above.

Quality Assurance
Accuracy and completeness of the data collected will be ensured by weekly review. The REDCap system does not accept outliers, illogical response patterns, etc. The PI and research assistant will have weekly meetings to discuss any qualitative comments received during data collection and any problems in data collection. The PI will examine the database for potential irregularities monthly. Initial data analyses will examine distributions of variable scores and comparability of baseline characteristics across conditions (for Aim 2) in case analyses need to be adjusted for these. Confidentiality procedures are outlined above.

Regulatory Issues
This study will be registered on ClinicalTrials.gov. The study does not require an Investigational Device Exemption (IDE) from the FDA. All serious AEs will be reported to the MUSC Committee on Human Research within 48-hours. Follow-up of all unexpected and serious AEs will also be reported. All AEs will be reviewed weekly by the PI and yearly by the IRB. Any significant actions taken by the local IRB and protocol changes will be relayed to the funding agency. We estimate the significant AE rate to be very low (<5%). If monthly monitoring indicates the rate is above this, we will convene a meeting of the DSMB. Potential conflicts of interest (COI) will be reported using the rules of MUSC's COI committee.

Trial Safety
The potential risks and benefits and methods to minimize these risks are outlined in the "Risks to Subjects" section. We will determine if any AEs result in dropouts or are serious according to FDA guidelines. The PI (Dr. Dahne) will serve as the Program Manager for AEs. All unexpected AEs will be monitored while they are active to determine if treatment is needed. We anticipate that AEs will be rare given that the VapeX app is non-invasive and that all participants will be engaged with current healthcare. Nonetheless, any AEs will be coded on a weekly basis using the FDA's COSTART rules[74] and entered into a database. For each weekly study meeting, the research assistant will prepare a summary of all AEs, including their severity, whether they caused a dropout, required treatment, and presumed relation to app utilization. The PI will review this at the weekly study meeting (or before if more urgent). At the weekly meeting (or before if urgent), the research assistant will report any premonitory symptoms to suggest emergence of a serious psychiatric condition (e.g., suicidality). Dr. Diaz, a board-certified Family Medicine physician, will be available on an ad-hoc basis for on-site medical supervision for any issues that cannot be resolved by Dr. Dahne.

Study procedures will follow the FDA's Good Clinical Practice Guidelines and our research team has found Spilker's comprehensive text on conducting clinical trials to be useful[75]. We will encourage participants to notify their physicians that a) they are in a randomized controlled research study examining a treatment for depressed mood and nicotine vaping, and b) the physician should contact the PI directly if the physician has any questions.

The research assistants will be instructed not to reveal whether a person is a participant in the study and will report to the PI any outside requests for information about a participant or any breaches in confidentiality. All requests by participant's physicians and other medical providers will be referred directly to the PI.

Trial Efficacy
The Data and Safety Monitoring Board (see below) may request a blinded interim efficacy report (blinded to the PI and research team) for review while the trial is ongoing. Final (fully unblinded) efficacy analysis will occur after all participants have completed all follow-ups.

Data and Safety Monitoring Plan Administration
The PI will be responsible for monitoring the trial, with additional oversight provided by study co-Investigators. The PI will examine monthly the outcomes database for missing data, unexpected distributions or responses, and outliers. The PI will check weekly the AE database prepared by the research assistant immediately prior to the lab meeting. A DSM report will be filed with the IRB and funding agency on a yearly basis, unless greater than expected problems occur. The report will include participant characteristics, retention and disposition of study participants, quality assurance issues and reports of AEs, significant/unexpected AEs and serious AEs. We will report efficacy at the end of the trial.

Data and Safety Monitoring Board Plan
We will create a Data and Safety Monitoring Board (DSMB), comprised of 3 clinicians with expertise in adolescent depression and substance use treatment, primary care, and clinical trials, as well as a statistician. The DSMB will meet once prior to beginning Aim 2 enrollment, once during Aim 2 enrollment, and once following study completion to review any AEs related to the study, as well as review any data management related errors. The board may be called at any point if needed for unexpected, serious AEs, etc. Modification will be made in the procedures and/or the protocol if necessary based on the findings of the board.

13.0 Risks to Subjects

The potential risks in this study include those related to: a) depressive symptoms, b) clinical deterioration, c) confidentiality, d) potential data breach from the app database, and e) frustration. Risk mitigation strategies are outlined below and have previously been implemented with success in Dr. Dahne's prior trials.

a) Depressive symptoms: Depressive symptoms will be monitored via the BDI-II. All participants will complete the BDI-II weekly online via a REDCap survey that is accessible via mobile phone web browsers. All participants will own smartphones. Thus, all participants should have access to the online BDI-II assessments.

b) Clinical deterioration: Dr. Dahne and her research team will monitor participant BDI-II scores for possible clinical deterioration (i.e., increasing depressive symptoms and/or the development of suicidal ideation) throughout the course of the study as participants complete the BDI-II weekly. Clinical deterioration will be defined as an increase of 10 or more points on the BDI-II from the baseline BDI-II assessment or a response of "I would like to kill myself" or "I would kill myself if I had the chance" on the suicidal thoughts or wishes item of the BDI-II. Our team has developed real-time alerts within REDCap which alert the investigative team if a participant completes a BDI-II assessment and evidences clinical deterioration. In the event that a participant evidences clinical deterioration, Dr. Dahne will contact the participant via phone and will provide referrals for local mental health resources for depression treatment. Dr. Dahne will suggest that the participant seek treatment and then will follow-up with the participant via phone one week later. If the participant is under the age of 18, this discussion will occur both with the participant and with the parent/legal guardian. If Dr. Dahne is unavailable, Drs. Carpenter, Squeglia, and/or Diaz, all licensed clinicians, will serve as clinical back-ups.

In the event that a participant reports suicidal ideation either during study screening or during subsequent assessments, Dr. Dahne (or back-up clinician) will 1) page the participant's attending primary care provider (if the participant is an MUSC patient) and 2) complete a risk assessment with the participant via phone. If the participant is under the age of 18, the participant's parent/legal guardian will also be part of this discussion. Dr. Dahne 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, Dr. Dahne will call emergency services and will remain on the phone with the participant until emergency services arrive. Contact information including home address will be collected during study screening and will be provided if necessary to emergency services personnel. Dr. Dahne is a licensed clinical psychologist and has more than 10 years of experience conducting suicide risk assessments. In the event that a participant evidences clinical deterioration, the participant will be allowed to continue in the trial, but we will recruit an additional participant for data collection purposes.

c) Confidentiality: Participants will be made aware of limits to confidentiality at the beginning of screening and during informed consent which includes a report of suicidal or homicidal intent or report of abuse or neglect. If the participant is under the age of 18, they will also be notified that clinical information disclosed as part of the research study (e.g., clinical deterioration including significant increases in depressive symptoms and/or suicidality, vaping status) may be shared with their parent or legal guardian. If the participant reports suicidal or homicidal intent or abuse/neglect during screening or at any point during the trial, Dr. Dahne will take appropriate action as outlined by the MUSC IRB, NIH, and the State of South Carolina, which may include paging the participant's physician, contacting the authorities and/or pursuing involuntary commitment at a mental health facility. If participants present no imminent danger but also need more extensive treatment of mental health concerns, they will be given appropriate referrals. All individual interviews will be recorded, transcribed, and destroyed within 12 months of completion of the entire study to protect confidentiality.

d) Data breach: Although health information will be collected within VapeX (e.g., daily mood ratings, activities, values, vaping), personally identifiable information will intentionally not be collected within the app (e.g., name, phone number, email address, etc.), and thus we will not collect nor will we retain protected health information (PHI). In the event of a data breach, it is important to note that health information will not be able to be tracked back to specific individual users. By refraining from collecting PHI within the mobile app, we ensure HIPPA compliance while also protecting the identities of our users. In the event of a data breach, all app users will be notified via email.

e) Frustration: Participants may become frustrated while completing questionnaires or while using VapeX. Participants will be informed that they may refuse to answer any question(s) that they do not wish to answer and that they may discontinue use of VapeX at any time.

Adequacy of Protection Against Risks

Recruitment and Informed Consent

Study participants will primarily be recruited from local primary care/family medicine clinics associated with MUSC's Primary Care Integrated Center of Clinical Excellence (ICCE). Study recruitment will occur proactively, and we will utilize cold contact procedures and available EHR data to identify ICCE patients between the ages of 16 and 20 with depressive symptoms who vape nicotine. As part of routine clinical care, all primary care patients (including adolescents between the ages of 16 and 20) complete the Patient Health Questionnaire-2 (PHQ-2) to screen for depressive symptoms during each primary care visit. Information on depression is also available via the EHR within each patient's problem list and billing codes. Adolescent patients will be identified who have been seen within an ICCE clinic in the last year with: 1) a score of ≥3 on their last PHQ-2 assessment (i.e., the optimal cut-point for identifying those who are symptomatic[63]), 2) depression listed on their problem list, *or* 3) a depression-related billing code associated with their last visit. We will further narrow this list to only those patients who reported vaping nicotine during their last visit. Patients on the recruitment report will be contacted via the patient EHR portal (MyChart) or e-mail (based on patient preferences in the EHR) by a study team member inviting them to participate in the research study. Within South Carolina, the legal age to consent to medical treatment is 16.

At age 16, all MUSC patients are eligible to receive their own patient portal account and parents/guardians can be appointed as proxies. If participants do not respond to the initial invitation within 72-hours, we will contact them via phone, e-mail, and/or text-message (also based on patient communication preferences within the EHR) to ensure they received the initial study invitation message. If interested, participants will complete an eligibility screening via REDCap to determine study eligibility. After determination of eligibility, a member of the study team will complete remote electronic informed consent (e-consent) with the participant via REDCap[76]. Participants will receive a link to an electronic consent form that they can review and sign. Parents/guardians of participants under 18 years old will participate with the adolescent in the screening, evaluation, and informed consent/assent procedure. Participants 18 years and older will be able to provide their own informed consent. Review of the consent form will be paired with a phone call with an IRB-approved member of the research team to ensure that the consent form is read in full and that all questions are answered prior to trial enrollment. All participants will electronically sign informed consent forms that have been IRB-approved once the study is explained to them in full and they have stated that they understand what is being asked of them. Participants will be given the opportunity to ask questions about their participation throughout the course of the study. Participants will be given a study phone number and e-mail address to contact for questions. Particular caution will be exercised in obtaining informed adolescent assent separately and independently from parental consent to limit potential for coercion. To this end, an initial step in participant recruitment involves obtaining parental/legal guardian permission for participation by the adolescent. Once parental consent is secured, youth will be asked separately and independently for informed consent (i.e., parental consent will not be used to persuade teens to participate). This approach is considered very effective in minimizing coercion to participate. The complex issues of informed consent and assent, and related limitations of confidentiality, as they apply to adolescents and their parents/guardians, are understood by the investigative team and will be communicated clearly during screening and consent. In the case of adolescents in South Carolina Department of Social Services custody, state guidelines regarding consent for clinical research participation will be followed.

Protections Against Risk

The recruitment project is stored in REDCap and only study team members will have access to the recruitment project database. The research team will only have access to the REDCap recruitment project while actively enrolling for the study. The recruitment project will be stored separately from the project containing research data. The recruitment REDCap project will potentially contain both identifiers and health information in the same project. All screening information will be kept in a password protected REDCap database. Only key study personnel will have access to the database. If an individual is not eligible to participate, his/her screener will include his/her first name and last initial and the reason for disqualification. Eligible participants' full name, telephone number and e-mail address will be recorded in the database. This is the only place where participants' names and subject identification numbers appear together. Eligible participants will be assigned a subject number, will complete informed consent (see procedures above), will be randomized (Aim 2), will complete baseline assessments, and subsequently will receive their randomized intervention (or will complete focus group Aim 1).

Upon completing eligibility screening, if study eligible, individuals will be provided with a verbal overview of the study, asked to review a consent form, and asked to provide informed consent (or assent, if under the age of 18). Participants will be informed of limitations of confidentiality (i.e., abuse or neglect, intention to harm self or someone else) both verbally and in writing during the informed consent process. The consent form will include the participant's name, but not his/her subject number. Consent forms will be provided in English. As utilization of VapeX requires that participants are able to read, participants unable to read the consent form on their own will not be included.

Regarding questionnaire data, data will be obtained for research purposes only. All data will be collected, stored, and managed via REDCap, which is a secure, web-based application designed exclusively to support

data capture for research studies. REDCap includes real time validation rules with automated data type and range checks at the time of entry. The underlying database is hosted in a secure data center at MUSC and includes redundancy, failover capability, backups and extensive security checks. The system has several layers of protection including user/group account management, "Data Access Groups" which allow data to be entered by multiple groups in one database with segmented user rights for entered data, audit trails for all changes, queries and reports, and Secure Sockets Layer (SSL) encryption. Name and relevant contact information will be obtained to provide compensation and every effort will be made to maintain subject confidentiality, in accordance with HIPAA. All data will be identified only by code numbers (participant IDs). Participant IDs will be linked to participants' names in a password-protected file that is accessible only to the PI and trained research staff.

Regarding user privacy while using VapeX, users will create a username and password in order to login to their account without storing their true identity. In VapeX, we will store a one-way hashed version of the patient's email address to support password reset and unique identification, but that identification will not be traceable back to the user's true identity. We will not store any personally identifiable information (e.g., first name, last name, email address, phone number) of users in our app database. VapeX will be HIPAA compliant, which we believe will be critical not only for protecting patient information, but also for ensuring that VapeX will be a viable commercial treatment option. We will use a HIPAA-compliant server protected by industry-standard safeguards to prevent unauthorized access. Since we are not associating patient health information with personally identifiable information there will not be a risk of unauthorized release of patient medical data in the event of a security breach. User personal information will be contained behind secured networks and will only be accessible by the investigators, who will have special access rights to such systems. In addition, all sensitive information users supply will be encrypted via Secure Socket Layer (SSL) technology. We will not sell, trade, or otherwise transfer personally identifiable information to outside parties. Our privacy policy will be available within the app for users to view at any time. This plan is consistent with that used by our partnering app development company, MountainPass Technology LLC, in several other previous products with similar protection requirements. Mr. Kustanowitz from MountainPass has expertise in HIPAA-compliant software development and will oversee all aspects of HIPAA compliance.

Protection against risk resulting from depressive symptoms includes the following: Regarding suicidal ideation and broader mental health concerns, Dr. Dahne (or back-up clinician), a licensed clinical psychologist, will take appropriate action as outlined by the MUSC IRB, NIH, and the State of South Carolina, which may include paging the participant's referring physician, disclosing information to the participant's parent/legal guardian, contacting the authorities and/or pursuing involuntary commitment at a mental health facility. If participants present no imminent danger but also need more extensive treatment of mental health concerns, they (and their parent/legal guardian, as appropriate) will be given appropriate referrals. As noted above, BDI-II data will be monitored over time in order to detect any possible clinical deterioration. BDI-II data will be monitored using only the participants' subject numbers. Should a participant evidence clinical deterioration, Dr. Dahne will then use the participant database in order to obtain contact information for the participant based on their subject number. We will also form a Data Safety and Monitoring Board (DSMB) comprised of individuals with expertise in adolescent depression and substance use treatment, primary care, and clinical trials, as well as a statistician. If the percent of serious or severe AEs related to clinical deterioration appears to be greater than 5% the DSMB will be notified to make a decision on early termination of the study.

Regarding recordings, all focus group sessions will be audio recorded and transcribed with recordings stored on an MUSC secure, password protected server. Recordings will be destroyed within one year of recording. Only IRB approved research staff will have access to recordings. Recordings will be destroyed within 12 months of completion of the entire study. Only IRB approved research staff will have access to recordings.

14.0 Potential Benefits to Subjects or Others

All participants in this trial will receive at minimum treatment as usual. There is the potential benefit to participants that the treatment they receive may prove to be more effective than other available treatments for quitting vaping, although this cannot be guaranteed. The majority of participants will also receive a mobile app developed to improve depressive symptoms in the service of quitting vaping. The major benefit to society will be whether VapeX is feasible, acceptable, and improves depression and vaping outcomes relative to TAU. Potential issues of clinical deterioration, confidentiality, data security, and frustration are a high priority and will be closely monitored throughout the study. Consequently, the risk to benefit ratio in the proposed study appears to be acceptable.

15.0 Sharing of Results with Subjects

Study outcomes will not be shared with subjects.

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