FRED HUTCHINSON CANCER CENTER

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Title of Protocol:
ACT on Vaping: Development of a Digital Therapeutic for Young Adult Vaping Cessation

Principal Investigator must be listed first.

Investigators List:		
Jaimee Heffner, PhD	Associate Professor, FHCC	(206) 667-7314
Edit Serfozo, MPH	Project Manager, FHCC	(206) 667-2428
Medical Monitor:		
Panagis Galiatsatos, MD	Assistant Professor, Johns Hopkins School of Medicine	(410) 493-4866
Biostatistician:		
Kelsey Baker, M.S.	Cancer Center Biostatistical Shared Resource	(206) 667-6655

SPONSOR: National Institute on Drug Abuse

PROTOCOL SYNOPSIS

Protocol Title	ACT on Vaping: Digital Therapeutic for Young Adult Vaping Cessation
Protocol Number	
Protocol Sponsor	National Institute on Drug Abuse
Trial Phase	Phase 1
Trial Type	Pilot RCT 2 arm
Clinical Indication	Vaping cessation
Study Objectives	Develop the ACT on Vaping smartphone app and evaluate its acceptability and preliminary impact on cessation-related targets. a. Gather input from users and subject matter experts (YAs who vape, team members with expertise in YA vaping) to develop vaping-focused content for the novel program. b. Conduct a pilot RCT (n=60) to evaluate acceptability and preliminary efficacy of ACT on Vaping relative to an incentivized text message control condition. Trial go/no-go criteria for proceeding to a subsequent Phase II trial are: (1) satisfaction with ACT on Vaping averaging at least 3.5 out of 5; and, (2) relative to control, evidence of better outcomes on at least 1 of 3 efficacy endpoints: change in readiness to quit (mean difference in Contemplation Ladder change scores ≥ 1), 24-hour quit attempts (≥ 5% difference), and cotinine-confirmed 30-day point prevalence abstinence from all nicotine/tobacco products at 3 months (≥ 5% difference).
Study Design	2-arm randomized controlled pilot trial with 1:1 parallel assignment
Population	Young adult e-cigarette users
Primary Endpoints	Treatment acceptability: • Satisfaction with the assigned intervention on a 5- point Likert-type scale at 3-months post-randomization Cessation • Change in Contemplation Ladder scores from baseline: Change in readiness to quit using e-cigarettes at 3-months post-randomization • Self-reported 24-hour quit attempt: Proportion of participants making a quit attempt lasting at least 24 hours between baseline and 3-months post-randomization • Cotinine-confirmed 30-day point prevalence abstinence from all nicotine and tobacco (excluding FDA-approved pharmacotherapies) 3-months post-randomization
Secondary Endpoints	
Type of control	Incentivized text messages assessing vaping status
Treatment Groups	2 arm; ACT on Vaping app vs incentivized text message control
Treatment Schedule	The treatment period is 3 months participants will be encouraged to use their online program as desired during that time.
Number of trial subjects	n=60
Estimated duration of trial	6 months
Duration of Participation	3 months

ABBREVIATIONS

ACT	Acceptance and Commitment Therapy
NRT	Nicotine Replacement Therapy
RCT	Randomized Controlled Trial
PPA	Point Prevalence Abstinence
USCPG	US Clinical Practice Guidelines
YA	Young Adult

Table of Contents

1.0 GENERAL INFORMATION

This document is a clinical research protocol for a randomized, controlled 2-arm pilot trial that will be conducted in compliance with the IRB-approved protocol, associated Federal regulations, and all applicable IRB requirements. The research plan is consistent with Stage IB of the NIDA Stage Model for Behavioral Intervention Development. We will use these pilot trial data to determine if the ACT on Vaping program meets the following go/no-go criteria for proceeding to a fully-powered RCT: (1) satisfaction with ACT on Vaping averaging at least 3.5 out of 5; and, (2) relative to control, evidence of better outcomes on at least 1 of 3 efficacy endpoints: change in readiness to quit (mean difference in Contemplation Ladder change scores ≥ 1), 24-hour quit attempts (≥ 5% difference), and cotinine-confirmed 30-day point prevalence abstinence from all nicotine/tobacco products at 3 months (≥ 5% difference).

Rationale

The prevalence of vaping among young adults (YAs) has increased substantially in recent years.
Almost one in ten YAs report current e-cigarette use, putting them at risk of developing nicotine addiction and long-term health effects of exposure to inhaled toxicants [11]. Despite the need for effective treatments to help these young users quit, very few treatments targeting any type of tobacco use among YAs have been evaluated, particularly for YA e-cigarette users, who have unique treatment needs. Innovative approaches are needed to engage YAs in treatment, as they are low users of traditional treatment. They do appear to benefit from newer, digital treatment modalities combined with theory-driven therapeutic approaches. Also needed are interventions capable of engaging YAs across the spectrum of readiness to quit, as a majority will not be motivated to quit at any given time and would benefit from encouragement to consider quitting.

We developed a digital Acceptance and Commitment Therapy (ACT) program designed for YA cigarette smokers aged 18-30 at all stages of readiness to quit. ACT's overarching focus on increasing psychological flexibility offers a new approach for YAs to motivate and support cessation, and ACT may have better efficacy than standard care approaches for tobacco cessation. The program also employs another exciting innovation: an avatar guide to make the program more engaging and effective. The original program, called Flexiquit, showed promise in motivating smoking cessation in a pilot randomized controlled trial (RCT) with YAs in Cyprus, with a 29% self-reported posttreatment quit rate for Flexiquit vs. 11% for waitlist control. Our single-arm pilot results with US sexual and gender minority YAs who smoke cigarettes were similarly promising: 93% satisfaction and a 23% biochemically confirmed quit rate at 2 months.

Overview of Study Design

In this study, we propose to evaluate the acceptability and efficacy of ACT on Vaping for young adult e- cigarette users in a 2-arm randomized controlled pilot trial (n=60 total with 1:1 allocation to the two treatment arms). The primary aim is to develop the pilot trial-ready version of the ACT on Vaping program and evaluate its acceptability and preliminary efficacy for impacting cessation-related targets. We will test the intervention using a 3-months treatment period, and, consistent with the evaluation period in our previous cessation app pilot study, our primary outcomes will be assessed at the 3-months end-of-treatment mark.

1.1 Protocol Title: ACT on Vaping: Development of a Digital Therapeutic for Young Adult Vaping Cessation

1.2 Sponsor Information: National Institutes of Health, Grant Number: 1UG3DA057032

1.3 Investigator Information:
Jaimee Heffner, Ph.D. (206) 667-7314

1.4 Contractors and Consultants for the Study (if applicable):
Megan Kelly, Ph.D. (The University of Massachusetts and Edith Nourse Rogers Memorial Veterans Hospital)

Maria Karekla, Ph.D. (University of Cyprus, UCY)
Amanda Graham, Ph.D. (Truth Initiative)
Carla Berg, Ph.D., (George Washington University)
Noreen Watson, Ph.D.
Nandini Murthy, M.S., RAC (ENEM Consulting)
Datatope LLC
Moby Inc.

2.0 INTRODUCTION TO THE PROTOCOL

2.1 Introduction

E-cigarette use has increased exponentially among YAs over time [1]. National Health Interview Survey (NHIS) data from 2019 show that 9.3% of YAs aged 18-24 reported current use of e-cigarettes, which were the most frequently-used tobacco product in this age range [2].

2.1.1 Problem and prevalence:

E-cigarettes pose numerous risks, particularly to youth and YAs. Use of nicotine- containing e-cigarettes can lead to nicotine addiction, especially given that contemporary e-cigarette devices like Juul and pod-based e-cigarettes that employ nicotine salt formulations expose users to high levels of nicotine and are more likely to lead to dependence [3]. Indeed, a majority (55-69%) of YA e-cigarette users perceive themselves to be at least somewhat addicted [4]. In addition, longitudinal studies have demonstrated increased risk of initiating and escalating cigarette smoking among adolescents and YAs who use e-cigarettes [5, 6]. Long-term health risks of e-cigarettes require more study, but it is well-documented that e-cigarette aerosols contain toxicants introduced by the heating of flavorants and other chemicals in e-liquids as well as metals in the heating element [7]. These exposures are associated with number of health risks, including lung injury and inflammation, greater risk of respiratory disease (asthma, COPD), and increased vulnerability to infection [7]. The 2016 US Surgeon General's Report on e-cigarette use among adolescents and YAs highlighted these and other risks as part of a call to action to address the growing health threat posed by vaping among young people [8].

Young adulthood is a critical time for cessation interventions, as tobacco use behaviors can become entrenched during this period, and almost all tobacco-related harms can be prevented by quitting before age 30 [9]. Unfortunately, very few treatment programs targeting any type of tobacco or nicotine product use among YAs have been developed and evaluated, particularly for YAs who are not in college. Thus, the literature on YA tobacco cessation treatment is sparse, has major methodological weaknesses, and very few studies report long-term follow-up data [10]. In a systematic review of YA cessation interventions, 4 of the 14 studies targeting YAs resulted in significant abstinence rates post-treatment and two improved cessation outcomes at 4-6 month follow-up [10]. Given the recency with which e-cigarettes were introduced into the market and quickly become the most frequently used product among YAs, the current body of research on YA vaping cessation is nascent.

2.1.2 Solution

Addressing the high prevalence of e-cigarette use by YAs requires effective and accessible treatments to support current users to quit. YAs who vape have unique treatment needs that are not well-addressed by standard tobacco cessation programs. In a recent review of the cessation treatment needs of YAs who vape [11], Drs. Berg (consultant), Graham (co-I), and co-authors outlined four focal areas for vaping cessation interventions targeting YAs. First, there is variability among YA e- cigarette users on types of products used, resulting in differing levels of nicotine exposure and not identifying with common ways of describing their use (e.g., the term "smoker" or the concept of being addicted do not resonate for some). Second, although most YAs who vape use e-cigarettes exclusively and have no history of cigarette smoking [2], a substantial minority concurrently use other nicotine/tobacco products as well as cannabis and alcohol, which may make cessation more difficult. Third, YA e-cigarette users have less extensive quit histories and low current readiness to quit. Only a small minority (6-13%)

of YAs report that they've ever tried to quit vaping completely [4]. Similarly, findings from the Population Assessment of Tobacco and Health (PATH) study suggest that, although 62.3% of e-cigarette users reported planning to quit vaping at some point, only 15.7% reported plans to quit in the next month [12]. Fourth, YAs have unique reasons for continuing to vape, such as perceiving it to be less harmful than smoking or liking the flavors. They also have unique reasons for quitting vaping, such as dissatisfaction with the taste or its perceived impact on cigarette smoking cessation. In addition to these points, there are also knowledge deficits, with YAs lacking awareness of the high nicotine content of pod devices like Juul [13]. Taken together, these findings suggest that interventions are needed that target e-cigarette users across a broad spectrum of readiness to quit, with content that resonates for a population that is treatment-naïve and that may not identify with terms like "smoker" and addiction." Additionally, such programs must recognize and address motives for using or quitting e-cigarettes that differ from other tobacco product use. Standard treatment programs do not fit this description, and new programs are needed that are specific to young e-cigarette users.

In addition to the need for vaping-focused content, innovative approaches are needed to engage YAs in treatment, as they are low users of traditional treatment [14]. They do appear to prefer, and to benefit from, newer methods of treatment delivery (i.e., digital modalities), combined with theory-driven therapeutic approaches [10]. Digital therapeutics are advantageous for a number of reasons: (1) They have high potential reach relative to other treatment modalities; (2) COVID-19 has increased demand for remotely-delivered treatments, including digital health, for a variety of purposes [15]; (3) YAs are digital natives who use technology and the internet in high numbers: 96% of YAs age 18-29 are smartphone users [16] and 98% of YAs age 18-29 use the Internet [17]. Regarding preferences for digital tobacco treatment, research conducted by Dr. Berg and colleagues [18] suggested that YA tobacco users (over 70% of whom used e-cigarettes) are highly interested in technology-delivered treatment, with the greatest preference for smartphone apps (85.9%), followed by SMS text messaging (62.1%), web-based programs (57.1%), social media–based programs (48.4%), and video counseling (41.6%). Data from Truth Initiative's This is Quitting SMS text message program confirm that high numbers of YAs will use digital interventions for e-cigarette cessation when they are well-promoted [19]. Since This is Quitting launched in January 2019, more than 386,000 young people have enrolled (145,000 teens, 241,000 YAs).

Truth Initiative's This is Quitting SMS text messaging program was the first and only digital intervention to be evaluated in a randomized controlled trial for YA vaping cessation. In that trial [19], 2588 YAs who were ready to quit in the next month were randomized to either This is Quitting or to an assessment-only control group. Self-reported 30-day point prevalence abstinence rates were compared at 7 months post-randomization under intent-to-treat analysis. Graham et al. found that 24.1% of the participants who received This is Quitting stopped vaping compared to 18.6% in the assessment-only arm (OR=1.39, 95% CI=1.15-1.68, p <.001) providing support for the effectiveness of a digital treatment approach using text messaging. The effects of the program among YAs not currently preparing to quit vaping is not yet known, however, as the sample was restricted to those who were ready to quit in the next 30 days.

Acceptance and Commitment Therapy (ACT) may be a more effective new treatment approach for tobacco use, with a novel mechanism of action: psychological flexibility. ACT [20, 21] is similar to standard US Public Health Service guidelines-based [22] cessation treatment in that it promotes awareness of the cues that trigger tobacco use, but different in that ACT teaches skills to increase psychological flexibility in response to triggers. Psychological flexibility is defined as willingness to experience the full range of emotional, physical, and cognitive experiences without trying to change them (i.e., acceptance), and to do things that are difficult in service of one's values (i.e., commitment) [23, 24]. Empirical support for ACT comes from 10 trials that enrolled over 6,000 tobacco users in total. Collectively, these studies support the feasibility and efficacy of ACT relative to pharmacotherapy-only treatments and traditional behavioral treatments. In 8 of 10 studies [25-34], quit rates for ACT were superior to control group quit rates at both short- (i.e., 3 months) and long-term (6 to 12 months) follow-up. Together, these findings suggest that ACT is at least as effective, if not more so, than standard treatment. Regarding mechanisms of action, the research to date has focused almost exclusively on one

component of psychological flexibility: acceptance, which mediated 60-80% of treatment effects in previous studies of ACT for cessation among smokers ready to quit [25, 29]. Other dimensions of psychological flexibility require evaluation as mediators of treatment effects, including changes in values-driven action.

Previous trials of ACT for smoking cessation restricted enrollment to smokers who were ready to quit, and the intervention focused on action- oriented strategies for coping with cravings. However, ACT can also be employed to motivate tobacco users at lower levels of quit readiness by placing greater emphasis on the ACT components of awareness and enactment of personal values at the outset of the treatment. This approach is consistent with evidence-based approaches like motivational interviewing for tobacco users who are not currently ready to quit [74]. Our collaborator, Dr. Karekla, developed the first ACT program designed for tobacco cessation among smokers at all stages of readiness to quit. This web- based program, Flexiquit, is also innovative in its use of gamification and avatar guides designed to represent the target user group(s) in order to motivate user interaction. These strategies are designed to increase engagement, and ultimately cessation outcomes, among smokers at all levels of quit readiness by making the experience pleasurable through novelty and interactivity, instilling hope through personal quitting narratives shared by the avatar guide who is represented as a supportive peer who was able to quit successfully, and triggering the desired behavior with reminders and motivational "sparks" delivered both in-program and via messages (from Fogg's Behavior Model for Persuasive Design [35]). To realize the benefits of an ACT-based digital therapeutic for YA e-cigarette users, we propose to develop and evaluate the ACT on Vaping program that uses this interactive, avatar-led treatment platform as its foundation.

2.1.3 Summary of significance.

This study is significant in that: (1) it focuses on a growing population of YAs who vape, (2) e-cigarette users are at risk for developing nicotine dependence and being exposed to toxicants that negatively impact health; (3) standard care tobacco interventions don't address the unique treatment needs of YAs who vape, (4) YAs would benefit from a targeted program designed to address their treatment needs and preferences--specifically their preference for a smartphone app, tailored to their needs and challenges in a readily scalable and accessible format, and (5) there is high consumer demand for vaping cessation programs among YAs, as evidenced by 241,000 YA enrollments to Truth Initiative's This is Quitting text messaging program between January 2019 and November 2021.

2.2 Preclinical Data

Not applicable

2.3 Clinical Data to Date

The project builds off of extensive preliminary work by the team of investigators, as described below.

Flexiquit: Engaging, web-based, self-guided ACT for YA tobacco users at all levels of quit readiness. Our collaborator, Dr. Karekla, developed the first ACT program designed for YAs at all stages of readiness to quit. This web-based program, Flexiquit, is also innovative in its use of interactive games and avatar guides designed to represent the target user group(s) in order to motivate user interaction. This program was evaluated among 84 university student smokers in Cyprus, aged 18-28 years (M age=22.4, SD=2.6) [37]. Participants were randomly assigned to either Flexiquit (n=49) or a wait-list control (n=35) group. Results indicated that program content was highly acceptable, even among those who had no intention to quit. Overall, 89% said the content was easy to understand, 74% found it very interesting, and 57% completed all 6 sessions (which was incentivized in this proof-of-concept trial). Qualitative comments suggested that participants were surprised by how much they learned and how much more motivated they were to consider cessation, even when they had started the program out of curiosity and had no intention to quit. The most commonly suggested changes to the program were technical and a direct result of the limited development budget for the initial pilot work: e.g., improved

graphics for the avatar guide, technical improvements to enhance usability across web browsers. The program showed great promise in motivating cessation, with a 29% self-reported post-treatment quit rate for Flexiquit vs. 11% for waitlist control (OR=3.10, 95% CI=0.92-10.41). There were also statistically significant increases between baseline and end of treatment in self-efficacy and intention to quit as well as decreases in cigarettes per day and nicotine dependence. Treatment effects were maintained through 6-month follow-up. Importantly, the majority (65%) of participants were in the precontemplation or contemplation stages of change, demonstrating the program's utility for smokers who are at lower levels of quit readiness.

Development and pilot testing of EQQUAL. In July 2018, we were awarded a 1-year pilot grant to adapt Flexiquit for sexual and gender minority (SGM) YA cigarette smokers ages 18-30 (PI: Heffner). The study team conducted user- centered design work to target the appearance and content of the intervention to address the needs and preferences of a US YA population identifying as SGM. Initial work included: (1) developing SGM-targeted content to address known challenges to quitting in this group (e.g, minority stress, mental health conditions); (2) conducting two rounds of user interviews and a week-long diary study to test both cultural (i.e., Cyprus to US YA culture) and SGM adaptations to ACT exercises and related intervention content and to evaluate preferences for the avatar guide (e.g., level of realism, appearance, backstory, voice), (3) redesigning the program structure for use on mobile devices, (4) adding closed captioning to make the content accessible, and (5) replacing post-session homework with SMS text messaging to remind participants of key content covered. We then conducted a single-arm pilot trial of EQQUAL to evaluate its acceptability (primary) and preliminary efficacy (secondary) for smoking cessation [38]. In 1 month we enrolled 22 YAs aged 18-30 who identified as sexual minority (n=22) and/or gender minority (n=7). Of these 22 participants, 12 (55%) reported vaping as well as smoking. Over one-quarter (27%) identified as racial/ethnic minority. Baseline readiness to quit smoking ranged from 0 to 10 on the Contemplation Ladder, with a mean of 6.2 (SD=2.7).

Acceptability. Among survey respondents, 93% rated EQQUAL as useful, 93% reported being satisfied with the program, and 87% said they would recommend it to a friend. Considering specific program components, 71% felt that text messages were useful and 93% reported that PDF handouts (e.g, benefits of quitting, smoking and the LGBTQ+ community) were useful. With regard to perceived targeting/tailoring, 93% said they felt like the program was made for them. All participants (100%) said the program was easy to navigate, 100% reported that they felt more clear about how they might quit as a result of using the program, and 93% said it gave them new ways of looking at quitting. On the acceptability outcome of program usage, among those with at least one log-in (n=18), mean number of log-ins was 5.5 (SD=3.6), average number of sessions completed was 3.1 (SD=2.6), and 39% (7/18) completed all 6 sessions.

Smoking abstinence and motivation to quit. Biochemically-confirmed 7-day PPA at 2 months was 22.7% (5/22) using the missing=smoking imputation and 31.3% (5/16) using the complete-case method. This represents 7-day PPA from all nicotine and tobacco, as participants who reported quitting smoking but continued use of non-cigarette tobacco could not have their cigarette abstinence verified via saliva cotinine. Self-reported, 7-day PPA was 31.8% (7/22) in missing=smoking and 41% (7/17) in complete-case analysis. Results compare favorably to several historical control interventions for SGM YAs (see Table 1). Compared to the only other targeted digital intervention for SGM YAs—a professionally moderated Facebook intervention— the self-guided EQQUAL program's biochemically-confirmed quit rate was over three times higher (23% vs. 7.1%). On the secondary outcome of self-reported 7-day PPA, EQQUAL's 31.8% quit rate also exceeds that of the SGM-targeted Facebook intervention (23.8%), a non-targeted Facebook intervention (12.3%), a non- targeted ACT intervention (18%), and Smokefree.gov (3.3%-8%). In addition to these promising quit rates, EQQUAL participants also showed an overall increase in motivation to quit, averaging a 2.1-point increase (SD=3.0) on the 10-point Contemplation Ladder. Of the 12 EQQUAL participants who used either e-cigarettes (n=11) or other non-cigarette products (n=1) at least weekly in addition to smoking cigarettes, 3 (25%) had cotinine-confirmed, 7-day PPA from all nicotine-containing products. This suggests that this treatment approach can be effective at promoting abstinence from multiple forms of nicotine and tobacco use.

Table 1. **Studies of digital cessation interventions with quit rates available for SGM YAs**

Study/Intervention name	Intervention type, # assigned	Quit rate, verified**	Quit rate, self-report***
EQQUAL pilot [38]	Targeted, self-guided ACT (n=22)	22.7%	31.8%
Put It Out Project [39]	Targeted, moderated social media (n=84)	7.1%	23.8%
Put It Out Project [39]	Non-targeted, moderated social media (n=75)	3.7%	12.3%
Put It Out Project [39]	Non-targeted, self-guided standard care (Smokefree.gov) (n=60)	1.7%	3.3%
WebQuit [28, 40]*	Non-targeted, self-guided ACT (n=45)	N/A	18%
WebQuit [28, 40]*	Non-targeted, self-guided standard care (Smokefree.gov) (n=48)	N/A	8%
* Unpublished subgroup analysis; ** Biochemically confirmed quit rate at end of treatment, missing=smoking; *** Self-reported quit rate at end of treatment, missing=smoking			

Psychological flexibility. Exploration of changes in psychological flexibility showed descriptive increases in values-based action on the Valuing Questionnaire (VQ) [41]) and acceptance on the Avoidance and Inflexibility Scale (AIS) [30], all in the hypothesized direction.

Perceptions of the avatar. Because of the novelty of the use of avatars within a cessation treatment program and the lack of guidance on how to effectively design avatars for this purpose, we included numerous quantitative and qualitative assessments of participant reactions to the avatar, "Jen." On qualitative responses, Jen was described as human-like, supportive, and non-judgmental. For example: "She encouraged me when I thought I couldn't quit smoking," "She made it feel like a real person was there," "[I liked] her approachable, non-judgmental tone." One participant even reported of Jen, "I'm in love with her." When asked what they would change about Jen, two dominant themes emerged: (1) making the body movements more natural (e.g., "She just kinda moved a little awkwardly") and (2) the need for the participant to be able to see themselves in the avatar's appearance (e.g., "She should be a person of color so I can relate to her more."). On the Agent Persona Inventory [42], all subscale scores suggested very positive overall impressions of the avatar.

Design and evaluation of other digital cessation interventions. Dr. Heffner and colleagues developed the first web- and mobile-delivered ACT interventions for smoking cessation and evaluated them in randomized controlled trials. Specifically, aside from EQQUAL, the PI has led or collaborated on development and evaluation of six mobile apps (SmartQuit 1.0, SmartQuit 2.0, iCanQuit, Actify, Quit2Heal, GEMS) [27, 32, 33, 43, 44] and two websites (WebQuit, WebQuit Plus) [28, 45] for smoking cessation. Of these 8 programs, 6 are ACT-based and 7 are designed for those motivated to quit.

2.4 Study Agent

Control condition: Incentivized text message check-ins. The control condition will be incentivized text message check-ins, similar to the design of Graham et al.'s [19] seminal study of a text messaging program (i.e., *This is Quitting*) for vaping cessation. Text message check-ins will occur at 2 weeks, 1 month, and 2 months post-randomization. At 2 weeks, participants will receive the following message: "Checking in: Have you cut down how much you vape nicotine in the past 2 weeks? Respond w/ letter: A=I still use the same amount, B=I use less, C=I don't use at all anymore. Make sure to respond in the next 24 hrs to get your $5 incentive!" At 1 and 2 months, they will receive the following message: "How's it going? When was the last time you vaped nicotine, even a puff of someone else's? Respond w/ letter: A- in the past 7 days, B- 8-30 days ago, C- More than 30 days ago. Make sure to respond in the next 24 hrs to get your $5 incentive!" Participants will be compensated $5 for each message that they respond to, for a maximum of $15 for responding to all 3 messages. In the Graham et al. [19] study, these text message check-ins were perceived as engaging and had placebo-like effects—e.g.,

participants assigned to the control condition, on average, expressed agreement with the following statements about these messages: “They helped me feel more confident about quitting,” “I liked being able to interact with the text messages,” and “They made me feel less alone in quitting.” Because their perceived value in support of quitting, use of the incentivized text messages as a control condition allows for an estimate of the efficacy of the experimental ACT on Vaping intervention above and beyond any behavior changes caused by attention and expectancy effects alone. They are also designed to minimize attrition among participants assigned to the control arm. All participants assigned to the control condition will be given access to the ACT on Vaping program when they have completed their participation in the study. Participant responses to text message check-ins will not be analyzed as a study outcome.

ACT on Vaping. Consistent with the foundational Flexiquit/EQQUAL program, ACT on Vaping will contain 6 sessions to be completed in order with at least 3 days between sessions to allow for post-session practice, with automated pacing and prompting from the program. Each session takes 10-20 minutes to complete. After completing all sessions, users are emailed a copy of session handouts. Content is ACT-based [23, 24]. Later sessions include prompts to reduce vaping and set a quit date for stopping all (non-therapeutic) nicotine and tobacco use. Text messages will be used to (a) prompt completion of the next session, and (b) push select intervention content to users. Messages will be tailored to the user’s level of quit readiness, with those who are not ready to quit in the next 30 days receiving values-focused, motivational messages and those who are ready to quit in the next 30 days receiving action-oriented messages (e.g., identifying and responding to triggers). Content of the six ACT on Vaping sessions will be as follows:

Session 1 introduces the avatar guide, who provides an overview of the program and shares their own story of quitting vaping. Users complete an interactive game to identify personal values guiding quitting and review quit stories from other YAs. Session 2 focuses on trigger awareness through interactive questions, graphs, pictures, and experiential exercises and metaphors, and it introduces the ACT concept of creative hopelessness—recognizing that efforts to control thoughts, feelings, or sensations related to vaping (e.g., urges to vape) can be counterproductive. Session 3 completes the topic of creative hopelessness and introduces cognitive defusion—i.e., psychological distancing from thoughts—as an alternative to thought control as a strategy for coping with triggers. Session 4 completes the topic of cognitive defusion, encourages setting a quit date in the next week, and prompts users to practice defusing from thoughts that they won’t be able to quit as part of quit planning. Session 5 starts with a reflection on recent successes and difficulties, introduces the acceptance strategy of willingness as a means of handling triggers, and covers relapse prevention via self-compassion and re-commitment to quitting. Session 6 also starts with a reflection on recent successes and difficulties, reviews content from previous sessions, and ends with a video emphasizing the importance letting go of the need to control feelings, sensations, and thoughts in order to follow one’s valued life direction.

New vaping-targeted treatment content will include short, animated videos embedded into the ACT- focused content that provide brief advice to quit and education about the risks of vaping, benefits of quitting, and evidence-based guidance on how to quit that follows US Clinical Practice Guidelines for tobacco dependence treatment (e.g., information about cessation medications, setting a quit date, seeking support, etc.) [22]. In addition to this content, other areas in which the program will be targeted to address vaping cessation include (1) the persona and narrative of the avatar guide, which will be presented as a former e-cigarette user who has successfully quit, (2) the narratives of other program users who share quit stories, (3) examples provided for implementing ACT strategies to reduce or quit vaping, and (4) the intervention content of the text messages that accompany the program. To address the issue of co-occurring alcohol and marijuana use and other tobacco use as impediments to quitting, ACT on Vaping will highlight applicability of ACT skills to other substance use in both didactic (e.g., explaining how the ACT strategy of acceptance could also be applied to situations that trigger alcohol use or cigarette smoking) and personal narrative format (e.g., sharing stories of other YAs who quit vaping both nicotine and marijuana, connecting personal values to decisions about substance use more broadly).

Participants assigned to the ACT on Vaping arm will receive the same incentivized text messages as the control arm, at the same time intervals: 2 weeks, 1 month, and 2 months post-randomization. Providing these messages in both arms will ensure that the incentives for responding to the text messages have a similar impact on engagement across arms, preventing differential attrition.

Study agent assignment: Following the completion of the baseline and contact information survey the participant will receive a text message with a link. Once this link is clicked an automated algorithm will randomize participants 1:1 to either the ACT on Vaping or the incentivized text message control arm, and the study team will send an email indicating that they are enrolled in the study. This email will inform them of the randomly assigned condition and, if assigned to the ACT on Vaping arm, with login credentials to access the app. If in 3 days the participant has not opened the app, they will receive a text message reminder. If in 3 more days the participant has still not opened the app, study staff will reach out by phone and offer technical assistance.

2.5 Risks/Benefits

Potential Risks: Participants will be told that the study may involve the following risks and/or discomforts:

Therapeutic risks. Therapeutic risks include the physical and psychological consequences of nicotine and tobacco abstinence, such as nicotine withdrawal symptoms. Participants will be informed of the discomfort associated with nicotine withdrawal, including common withdrawal symptoms. Participants will also be informed of the possibility that the intervention provided as part of the study may not be effective in helping them to quit using tobacco products.

Research risks. Participants will be informed of the following research-related risks: (1) the possibility that answering some questions may be emotionally upsetting, and (2) the possibility of breach of confidentiality. It is possible that some of the questions asked of participants may cause some emotional discomfort. There is also a small risk of breach of confidentiality if participant data were to be accessed by an unauthorized person.

Potential Benefits of the Proposed Research to the Subjects and Others
Participants will be provided with information regarding potential benefits of participation in the study, including:
1) the possibility that the study intervention might help them to quit using nicotine and tobacco, and
2) access to a smartphone app to learn about their interest in quitting vaping and methods of quitting at no cost.

Importance of the Knowledge to be Gained
This study involves development and testing of an intervention that, if found to be effective, could have an enduring, positive impact on the high prevalence of e-cigarette use among young adults. As such, the minimal risks associated with participation in the proposed study are exceeded by the potential benefits of completing this research.

3.0 PRE-TRIAL INTERVENTION CONTENT DEVELOPMENT AND USABILITY TESTING

1.1 Objectives:
Add vaping related content to *ACT on Vaping* program by conducting one on one interviews with young adults (n~6-12), and conduct a heuristic evaluation, conducted by expert reviewers, to evaluate usability

3.1.1 Study Population
For the ACT on Vaping content development phase, we will recruit ~6-12 young adults, ages 18-30, who meet basic eligibility criteria for the trials described below.

Participants will be recruited nationally via one or more recruitment strategies used successfully in our previous studies (e.g, social media, targeted Craigslist ads).

3.1.2 Study Design

The investigators will adapt the content of the EQQUAL intervention following the user-centered design process employed by Dr. Heffner's team. To create vaping content, we will: 1) conduct one on one interviews with young adults, including e-cigarette users (n~6-12), 2) utilize the existing literature on barriers to, and facilitators of, vaping cessation in young adults and youth, and 3) utilize the clinical and research expertise of the investigative team in smoking cessation, ACT, and treating young adults and vulnerable populations of e-cigarette users. Expected outcomes of this formative research include common barriers to quitting experienced by youth, in their own words; composite narratives of their experiences with overcoming the challenges of quitting ("Quit Stories")—an effective health communication tool (12) which can be relayed by the virtual coaches; and desirable characteristics of virtual coaches. Content updates and design changes to the app will be made on the basis of this formative work.

1:1 Interviews will proceed in 1-2 rounds of ~6 participants each, with recruitment continuing until thematic saturation is achieved within each round (i.e., no new themes emerge from interviews). If major changes are required after the first round of interviews, another group of ~6 participants will be recruited to provide feedback on the new designs, with recruitment continuing until thematic saturation is achieved. The total estimated sample size needed for 1:1 interviews is therefore ~6-12 participants.

When a programmed version of the *ACT on Vaping* program is ready, we will conduct a heuristic evaluation of its usability using expert reviewers. Usability is the extent to which a digital intervention can be easily navigated and understood by the user [52]. Usability is a critical outcome of the intervention development process, as low usability can undermine engagement with the intervention as well as its potential efficacy for tobacco cessation [53].

3.1.3 Primary Objective:

Completed development of the *ACT on Vaping* smartphone application for tobacco cessation based on ACT. The ACT on Vaping app will be easily navigated and understood by the user and free from any technical difficulties.

3.2 Usability Testing

A Heuristic evaluation with students (n=10) of the Human Centered Design Center at the University of Washington will be conducting by a UX Researcher to uncover any usability issues. A heuristic evaluation is an effective and fast method for uncovering any usability issues.

3.10 Completion of the Intervention Development Phase

The data gleaned from the heuristic evaluation will inform any needed changes to *ACT on Vaping* app's content and structure as well as to address any technical difficulties experienced. Based on prior work, the types of changes needed at this stage of development are typically smaller adjustments such as changes to increase readability of text on different devices (e.g., font size, color), changes to the wording of specific messages, or de-bugging new features (e.g., inactive buttons). The Moby Inc. programming team will then make changes needed to improve the usability and/or content of the app. The final version of *ACT on Vaping app*, that will be developed after the heuristic evaluation, and will be used in the pilot RCT.

4.0 OVERVIEW OF CLINICAL TRIAL

4.1 Study Objectives

In this study, we will evaluate the acceptability and efficacy of *ACT on Vaping* for young adult e-cigarette users in a 2-arm randomized controlled pilot trial (n=60 total with 1:1 allocation to the two arms). The primary aim is to develop the pilot trial-ready version of the *ACT on Vaping* program and evaluate its acceptability and preliminary efficacy for impacting cessation-related targets.

4.1.1 Primary Endpoints

- Treatment acceptability as indicated by overall treatment satisfaction rating
- Treatment efficacy:
  - Change in Contemplation Ladder scores from baseline to 3-months post-randomization
  - Self-reported 24-hour quit attempt at 3-months post-randomization
  - Cotinine-confirmed 30-day point prevalence abstinence from all nicotine and tobacco at 3-months post-randomization

Trial go/no-go criteria for proceeding to a subsequent Phase II trial are: (1) satisfaction with ACT on Vaping averaging at least 3.5 out of 5; and, (2) relative to control, evidence of better outcomes on at least 1 of 3 efficacy endpoints: change in readiness to quit (mean difference in Contemplation Ladder change scores ≥ 1), 24-hour quit attempts (≥ 5% difference), and cotinine-confirmed 30-day point prevalence abstinence from all nicotine/tobacco products at 3 months (≥ 5% difference).

Efficacy benchmarks were based on clinically meaningful differences in Contemplation Ladder (ie., at least one-step change in average ladder score) or behavior change outcomes (5% difference in 24-hour quit attempts, 30-day PPA rates).

4.2 Study Population

We will include n=60 participants in the pilot trial. Participants will be YA e-cigarette users who are interested in using a digital intervention designed to motivate and support vaping cessation. The 60 participants will be recruited over the course of approximately 1 month, based on previous trials which used a similar national recruitment strategy (e.g., targeted Facebook and social media ads, UW Classified ads, Twitter and Craigslist posts, and study flyers).

Inclusion of Women & Minorities

We will actively seek participants who are diverse in their gender identity, including people who identify as cisgender men and women and those who identify transgender and gender expansive. We will also make every effort to ensure that members of diverse racial/ethnic groups are adequately represented in the study by targeting our online recruitment efforts based on location (e.g. Craigslist ads in cities with a high proportion of racial/ethnic minority residents) and use of the Facebook advertising platform to target on user interests and affiliations. In previous studies we have achieved at least 25% minority participation in trials using these methods. In the most recent large trial of a web-delivered intervention [28], the sample was 27% racial minority and 8% Hispanic/Latino. In our EQQUAL pilot study, 27% identified as racial/ethnic minority. We will program the recruitment website to ensure that 25% identify as racial/ethnic minority.

4.3 Study Design

This is a pilot, randomized controlled trial (n=60 with 1:1 allocation to the two treatment arms) to test the primary outcome of treatment acceptability and efficacy for the ACT on Vaping vs. the control program. We will test the interventions using a 3-month treatment period, and, consistent with the evaluation period in our previous cessation app pilot study, our primary outcomes will be assessed at the 3-month end-of-treatment mark.

4.3.1 Primary Objectives

- Develop the pilot trial-ready version of the *ACT on Vaping* program and evaluate its acceptability and preliminary efficacy for impacting cessation-related targets

4.3.2 Primary Endpoints

- Treatment acceptability as indicated by overall treatment satisfaction rating
- Treatment efficacy:
  - Change in Contemplation Ladder scores from baseline to 3-months post-randomization
  - Self-reported 24-hour quit attempt at 3-months post-randomization
  - Cotinine-confirmed 30-day point prevalence abstinence from all nicotine and tobacco at 3-months post-randomization

4.4 Estimated Accrual:
1 month

4.5 Name of Sponsor/Funding Source: National Institutes of Health

5.0 SUBJECT ELIGIBLITY

5.1 Inclusion Criteria

- age 18-30
- current weekly user of e-cigarette product(s) for the last 30 days
- has a smartphone either an Android (running version 10.1 or higher) or iPhone (running iOS version 13 or higher)
- experience downloading and using one or more apps on their smartphone
- have a mobile data plan and/or access to WiFi to support the use of the ACT on Vaping app
- has access to text messaging
- has an email address
- US resident, with a US mailing address
- willing to complete all study procedures
- comfortable reading and writing in English

5.2 Exclusion Criteria

- currently using other tobacco cessation treatments at the time of screening, including pharmacotherapy or behavioral support (note: use of these treatment is allowable during trial participation)
- member of the same household as another research participant
- currently in prison
- Google voice number as sole phone number, due to its association with fraudulent study entry attempts
- is ineligible per fraud prevention protocol
- employees/family of investigator or study center

6.0 SUBJECT REGISTRATION

Recruitment materials will direct potential participants to a secure recruitment website, which provides basic information about the study and a portal to the screening survey.

For participants who screen eligible on the recruitment website and provide their email address, we will instantly send them an email (and two reminders over a 7-day period) inviting them to provide informed consent and complete the baseline assessment.

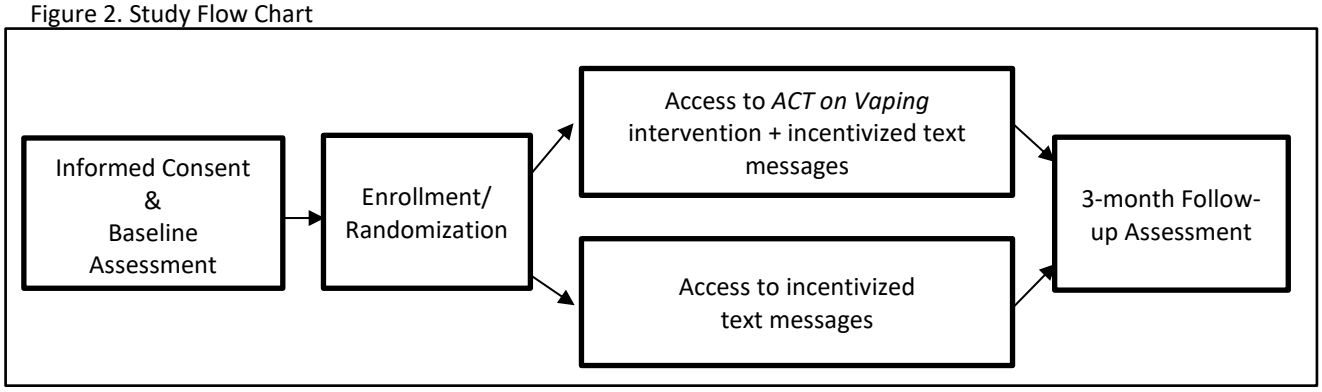
To prevent fraudulent study enrollment, we will use a multi-stage evaluation and exclusion of potential participants based on the following: IP address check for non-US addresses, proxy IP addresses, and IP addresses reported to have engaged in fraud; check for duplicate email addresses within-study; check for completing too many survey pages too fast, too many missing responses in the baseline survey (90% or more missing), inconsistent responses between screening and baseline; a final check for duplicate contact info provided based on name, phone number, or email address, or IP address; and a test SMS text message to check for virtual numbers.
Research staff will contact potentially eligible participants by telephone if any aspect of automated data collection revealed suspicious activity (e.g., very brief survey completion times or unusual patterns in email addresses). To further deter fraudulent attempts to enter the study, no compensation will be provided for completion of the screening and baseline surveys.

Participants completing this process will be enrolled in the study. This information will be stored in a secure research database behind FHCC firewall. See section 7.2 Enrollment Procedures and Appendix C for more details.

7.0 TREATMENT PLAN

7.1 Treatment Plan Overview

Figure 2. Study Flow Chart



7.2 Description of the interventions

Control condition: Incentivized text message check-ins. The control condition will be incentivized text message check-ins, similar to the design of Graham et al.'s [19] seminal study of a text messaging program (i.e., *This is Quitting*) for vaping cessation. Text message check-ins will occur at 2 weeks, 1 month, and 2 months post-randomization. At 2 weeks, participants will receive the following message: "Checking in: Have you cut down how much you vape nicotine in the past 2 weeks? Respond w/ letter: A=I still use the same amount, B=I use less, C=I don't use at all anymore. Make sure to respond in the next 24 hrs to get your $5 incentive!" At 1 and 2 months, they will receive the following message: "How's it going? When was the last time you vaped nicotine, even a puff of someone else's? Respond w/ letter: A- in the past 7 days, B- 8-30 days ago, C- More than 30 days ago. Make sure to respond in the next 24 hrs to get your $5 incentive!" Participants will be compensated $5 for each message that they respond to, for a maximum of $15 for responding to all 3 messages. In the Graham et al. [19] study, these text message check-ins were perceived as engaging and had placebo-like effects—e.g., participants assigned to the control condition, on average, expressed agreement with the following statements

about these messages: “They helped me feel more confident about quitting,” “I liked being able to interact with the text messages,” and “They made me feel less alone in quitting.” Because their perceived value in support of quitting, use of the incentivized text messages as a control condition allows for an estimate of the efficacy of the experimental ACT on Vaping intervention above and beyond any behavior changes caused by attention and expectancy effects alone. They are also designed to minimize attrition among participants assigned to the control arm. All participants assigned to the control condition will be given access to the ACT on Vaping program when they have completed their participation in the study. Participant responses to text message check-ins will not be analyzed as a study outcome.

Experimental condition: ACT on Vaping: The ACT on Vaping app will contain 6 sessions to be completed in order with at least 3 days between sessions to allow for post-session practice, with automated pacing and prompting from the program. Each session takes 10-20 minutes to complete. Content is ACT-based [23, 24]. Later sessions include prompts to reduce vaping and set a quit date for stopping all (non-therapeutic) nicotine and tobacco use. Text messages will be used to (a) prompt completion of the next session, and (b) push select intervention content to users. Only the notifications will be tailored to the user’s level of quit readiness, with those who are not ready to quit in the next 30 days receiving values-focused, motivational messages and those who are ready to quit in the next 30 days receiving action-oriented messages (e.g., identifying and responding to triggers). Content of the six ACT on Vaping sessions will be consistent for all participants at all stages of readiness and is as follows:

Session 1 introduces the avatar guide, who provides an overview of the program and shares their own story of quitting vaping. Users complete an interactive game to identify personal values guiding quitting and review quit stories from other YAs. Session 2 focuses on trigger awareness through interactive questions, graphs, pictures, and experiential exercises and metaphors, and it introduces the ACT concept of creative hopelessness—recognizing that efforts to control thoughts, feelings, or sensations related to vaping (e.g., urges to vape) can be counterproductive. Session 3 completes the topic of creative hopelessness and introduces cognitive defusion—i.e., psychological distancing from thoughts—as an alternative to thought control as a strategy for coping with triggers. Session 4 completes the topic of cognitive defusion, encourages setting a quit date in the next week, and prompts users to practice defusing from thoughts that they won’t be able to quit as part of quit planning. Session 5 starts with a reflection on recent successes and difficulties, introduces the acceptance strategy of willingness as a means of handling triggers, and covers relapse prevention via self-compassion and re-commitment to quitting. Session 6 also starts with a reflection on recent successes and difficulties, reviews content from previous sessions, and ends with a video emphasizing the importance letting go of the need to control feelings, sensations, and thoughts in order to follow one’s valued life direction.

New vaping-targeted treatment content will include short animated videos embedded into the ACT- focused content that provide brief advice to quit and education about the risks of vaping, benefits of quitting, and evidence-based guidance on how to quit that follows US Clinical Practice Guidelines for tobacco dependence treatment (e.g., information about cessation medications, setting a quit date, seeking support, etc.) [22]. In addition to this content, other areas in which the program will be targeted to address vaping cessation include (1) the persona and narrative of the avatar guide, which will be presented as a former e-cigarette user who has successfully quit, (2) the narratives of other program users who share quit stories, (3) examples provided for implementing ACT strategies to reduce or quit vaping, and (4) the intervention content of the notifications that accompany the program. To address the issue of co-occurring alcohol and marijuana use and other tobacco use as impediments to quitting, ACT on Vaping will highlight applicability of ACT skills to other substance use in both didactic (e.g., explaining how the ACT strategy of acceptance could also be applied to situations that trigger alcohol use or cigarette smoking) and personal narrative format (e.g., sharing stories of other YAs who quit vaping both nicotine and marijuana, connecting personal values to decisions about substance use more broadly).

Participants assigned to the ACT on Vaping arm will receive the same incentivized text messages as the control arm, at the same time intervals: 2 weeks, 1 month, and 2 months post-randomization. Providing these messages in both arms will ensure that the incentives for responding to the text messages have a similar impact on engagement across arms, preventing differential attrition.

Comparison of ACT on Vaping and the Control Condition		
Type	**Name**	**Description**
Behavioral (e.g., Psychotherapy, Lifestyle Counseling)	Smartphone app + incentivized text message check-ins	Smartphone app intervention plus incentivized check-ins about changes in vaping via text message
Behavioral (e.g., Psychotherapy, Lifestyle Counseling)	Incentivized text message check-ins	Incentivized check-ins assessing changes in vaping via text message

Study agent assignment: Following the completion of the baseline and the contact information survey, the participant will receive a text message with a link. Once this link is clicked an automated algorithm will randomize participants 1:1 to either the ACT on Vaping or the control arm, and the study team will send an email and/or text message indicating that they are enrolled in the study.

If assigned to the ACT on Vaping arm, the email will include login credentials to the app. If in 3 days the participant has not opened the app, they will receive a text message reminder. If in 3 more days the participant has still not opened the app, study staff will reach out by phone and offer technical assistance.

7.3 Data collection protocol

Most study data will be collected electronically. Participants who do not respond to the electronic follow-up survey invitation will have the opportunity to complete the follow-up survey either by telephone or by mail.

Baseline data: For participants who screen eligible on the recruitment website and provide their email address, we will instantly send them an email (and two reminders over a 7-day period) inviting them to complete a secured online survey to provide informed consent and complete the baseline assessments (see Table 2 below). At baseline, we will also collect email, phone number, and mailing address.

3-month follow-up data: The follow-up data collection protocol is as follows: Assessment Day -14: Mailed reminder of upcoming survey, with $2 pre-incentive included; Day 0: First email and/or text invitation with link to online survey; Day 5: Second email and/or text invitation with link to online survey; Day 9: Third email and/or text invitation with link to online survey; Days 10 to 18: Eight attempts to complete telephone version of survey (one call per day); Day 18: Send mailed version of survey. Participants will receive an incentive of $50 for the follow-up survey completed and an additional $25 for returning cotinine results if asked. In addition, an extra incentive of $10 will be provided to participants who respond to the first invitation and complete the survey online within 24 hours. Based on previous trials using these same procedures [19, 28], we expect that 80% of participants will complete assessments via web-based survey, ~2% by phone, and ~3-4% by mailed survey.

7.4 The schedule of assessments is provided in Table 2 below. Participant compensation

Participants will receive up to $102 for participating in this study. Specifically, participants will receive compensation based on the following structure:

- $5 for responding to each of three text message assessments of e-cigarette use, for a total of up to $15
- $2 in a pre-incentive letter for the 3-month follow-up
- $50 for the 3-month follow-up survey completed in any modality
- $10 bonus for completing the 3-month follow-survey within 24 hours of the initial email invitation

- $25 for returning cotinine results (if asked)

8.0 SUBJECT EVALUATION

8.1 Data Collection Overview

Table 2. Schedule of assessments

Measure	# items	Screening Survey	Baseline Survey	3-mo. Follow-up Survey	Primary Purpose
Eligibility criteria	11	X			Eligibility
Demographics	10		X		Sample description
e-FTCD (severity of dependence)	6		X	X	Sample description
Tobacco/nicotine use history	9		X		Sample description
Contemplation Ladder (readiness to quit)	1		X	X	Primary outcome
Recent tobacco/nicotine use	3		X	X	Primary outcome
Saliva cotinine	n/a			X	Primary outcome
Outside tobacco treatment	2		X	X	Concomitant treatment
Treatment satisfaction	8			X	Primary outcome
Treatment adherence (tracked automatically)	n/a			X	Primary outcome
Abstinence self-efficacy	1		X	X	Exploratory
AIS cravings subscale (psychological flexibility)	9		X	X	Exploratory
Valuing Questionnaire (psychological flexibility)	10		X	X	Exploratory
Past 30-day alcohol and cannabis use	2		X	X	Exploratory
Agent Persona Instrument (avatar perceptions)	25			X	Exploratory
Adverse events				X	Safety monitoring
Total number of items		*11*	*62*	*73*	
Estimated duration (mins)		*5-10*	*30-35*	*35-40*	

8.2 Enrollment Procedures

The study recruitment website provides basic information about the study, FAQ, information about the study team and Fred Hutchinson Cancer Center (FHCC), and a portal to online screening survey.

Individuals who do not meet eligibility criteria will be sent an email notifying them that they were not enrolled and provide both the link to Smokefree.gov and the 800-QUIT-NOW phone number for cessation support.

We will use the identical enrollment method proven successful in our previous, remotely-conducted RCTs. Specifically, for participants who screen eligible on the recruitment website and provide their email address, we will instantly send them an email (and two reminders over a 7-day period) inviting them to provide informed consent and complete the baseline assessment.
To address potential fraudulent responses to web-based screening surveys, we will use the same methods used in our previous studies: CAPTCHA verification, ineligibility if the IP address was previously used or suspicious, and telephone contact by research staff if any aspect of automated data collection revealed suspicious activity (e.g., very brief survey completion times or unusual patterns in email addresses). To further deter fraudulent attempts to enter the study, no compensation will be provided for completion of the brief (< 10 min) screening and baseline surveys.

Informed Consent. Participants will be asked to review and provide consent to participate in this study before completing the baseline assessment. The informed consent will encourage individuals to contact either Dr. Heffner or the project manager (Edit Serfozo) with questions about the study (contact information will be provided). The informed consent will be collected and stored in the secure database behind FHCC firewall (see DSMP for additional details). Participants who complete the enrollment process will receive a copy of the informed consent via email for future reference.

Baseline Assessment. The baseline survey assesses demographics, tobacco/nicotine use history and current vaping behaviors, and use of electronic cigarettes. More details below in section 9.3. The baseline survey data will be collected and stored in a research database behind FHCC firewall (see DSMP for additional details).

Following the completion of the baseline survey and contact information form the participant will receive a text message. Once this link is clicked an email and/or a text message will be sent indicating that they are enrolled in the study.

Participants will be randomized to either the ACT on Vaping app arm or the incentivized text message control arm. The randomization algorithm will use a permuted-block design with random block sizes, with stratification by high (>5) vs. low (5 or less) readiness to quit on the Contemplation Ladder.

If applicable, the email and/or text message will provide participants with a link to the login credentials of the ACT on Vaping program. If in 3 days the participant has not logged onto the app, they will receive a text message reminder. If in 3 more days the participant has still not logged onto the app, study staff will reach out by phone to check in.

8.3 Assessments/On-Study Clinical Evaluations

A complete schedule of assessments is provided in Table 2 above. Measures collected at baseline will also be collected at the 3-month follow-up timepoint except for questions related to demographics, severity of dependence and tobacco/nicotine use history, as answers to these questions will be used to describe our study population.

All data from these assessments will be collected via web- based, telephone, or mailed surveys.

8.3.1 Eligibility and sample description

Demographics assessed at baseline will include age, assigned sex at birth, gender identity, sexual orientation, education, employment, income, number of dependents, and relationship status. The 6-item E-cigarette Fagerström Test for Cigarette Dependence (e- FTCD) [57, 58] and the 1-item Contemplation Ladder [56] will be used to assess e-cigarette dependence and readiness to quit using e-cigarettes, respectively. Nicotine and tobacco use history will be assessed using items derived from major epidemiologic surveys (e.g., BRFSS, PATH).

8.3.2 Treatment acceptability

Overall satisfaction will be assessed with a 5-point Likert-type item on the 3-month survey. The ACT on Vaping benchmark average of 3.5 falls between ratings of “somewhat satisfied” (3) and “mostly satisfied” (4).

8.3.3 Efficacy for cessation

Efficacy will be assessed via: (1) self-reported 24-hour quit attempt, (2) change in readiness to quit, and (3) cotinine-confirmed 30-day point prevalence abstinence.

Self-reported 24-hour quit attempt

Making a 24-hour quit attempt between baseline and 3-month follow-up will be assessed via self-report at the 3-month follow-up.

Change in readiness to quit
The single-item Contemplation Ladder will be used to evaluate readiness to quit. Change between baseline and 3-month follow-up will be evaluated as in indicator of efficacy.

Cotinine-confirmed 30-day point prevalence abstinence from all nicotine and tobacco
We will assess 30-day point prevalence abstinence (PPA) from all nicotine and tobacco use (excluding FDA-approved pharmacotherapies) at 3-months post-randomization, biochemically confirmed via saliva cotinine. For comparability with the only previous trial of a digital intervention for YA vaping cessation (i.e., This is Quitting trial [19]), 30-day PPA from vaping will be assessed using the following item: ("In the past 30 days, did you vape at all, even a puff of someone else's?"), and item instructions will encourage participants to focus on all nicotine-containing vaping devices when answering. Items assessing 30-day PPA from cigarette smoking and other tobacco use will be worded similarly. We will biochemically confirm self-reported abstinence from vaping and all other non- therapeutic nicotine and tobacco products at follow-up among those who report 30-day PPA. Saliva cotinine tests (Alere iScreen) will be sent to participants via mail and they will upload photos of the test results via a secure online study portal.

Participants who report using nicotine replacement therapy (NRT) for tobacco cessation within 7 days of the scheduled date of cotinine testing will be considered abstinent without testing, since cotinine cannot distinguish e-cigarette and other tobacco use from NRT use and only method that can potentially make this distinction--urinary analysis of minor tobacco alkaloids (e.g., anatabine/anabasine) [63]—isn't feasible in a remote trial design with national recruitment.

8.3.4 Other assessments
Use of non-study cessation treatments will be assessed at the 3-month follow-up. Comparative impact of the interventions on alcohol and cannabis co-use (e.g, number of days of use in the past month) will be explored using web-based Timeline Followback [65] to assess alcohol and cannabis use over the 30 days prior to the assessment. Acceptance of vaping triggers will be assessed using an e-cigarette version of the Avoidance and Inflexibility Scale (AIS), with a subscale measuring acceptance of bodily sensations (cravings) [30]. The AIS subscale is highly correlated [25], so to limit respondent burden, we will administer only the 9-item cravings of bodily sensations subscale, which has the strongest relationship with abstinence in previous work [25]. Values-guided action will be assessed using the 10-item Valuing Questionnaire [41], which has two subscales: Values Progress (5 items) and Values Obstruction (5 items). Change in abstinence self-efficacy will be assessed via a single-item rating of confidence in one's ability to quit vaping, measured at baseline and 3 months. The Agent Persona Instrument (API) [42] will be administered as a treatment process measure only in the ACT on Vaping arm to assess how participants perceive the avatar. This 25-item scale has four subscales: (1) credible, (2) facilitating learning, (3) engaging, and (4) human-like. This scale is most often used in studies of online learning to assess the effectiveness of a pedagogical agent.
Adverse events will be collected by a web-based survey (on Day 21, 42, 63, and at the 3-month follow-up time point).

9.0 SUBJECT DISCONTINUATION OF ACTIVE TREATMENT

Participants can choose to discontinue their participation in this study at any time for any reason.

10.0 CONCOMITANT MEDICATIONS

Use of non-study cessation treatments will be assessed at the 3-month follow-up.

11.0 ADVERSE EVENTS

11.1 Adverse Events

This is a low-risk study testing the feasibility and preliminary efficacy of a behavioral intervention. Because this is a vaping cessation intervention, some participants may quit using nicotine and may experience the physical and psychological consequences of nicotine abstinence, such as nicotine withdrawal symptoms. As part of the informed consent procedures, participants will be informed about potential nicotine withdrawal symptoms and effects of abstinence. The intervention provides strategies designed to cope more effectively with symptoms of nicotine withdrawal. Finally, participants will be given information on pharmacotherapy for tobacco cessation (e.g., nicotine patch) and how to obtain these medications.

11.2 Collection and reporting of AEs and SAEs

Participants will be asked to report changes in their physical and mental health, especially if treatment was required. An email will be sent to participants asking about changes in their health on Day 21, 42 and 63. Adverse event reports will not be monitored in real time. The project manager will review the submitted responses weekly and will contact the participant by telephone to ask additional questions, if needed. Emergency and crisis resources will be provided to all study participants in the study consent, and at each adverse event collection time point.

Any adverse events detected during this study will be recorded in the Adverse Event Summary Form and reported as follows.

Monitoring.
Throughout the study, the project coordinator and outcome assessors will monitor participants' progress and responses to surveys for adverse events and protocol compliance. The study coordinator will complete quarterly reports on participant progress and status, any adverse events, and any protocol deviations.

Reporting.
All study staff working on the trial will be trained and required to report all unexpected and adverse events to the project coordinator and the Principal Investigator. A form will be available for this purpose. Adverse events beyond what would be expected in the course of vaping cessation will be reported to the Fred Hutch's IRB in accordance with Fred Hutch policy.

> **Reporting SAEs**. For AEs meeting the criteria for an SAE, regardless of attribution, the study coordinator will inform the Fred Hutch IRB per their reporting guidelines and will complete and submit a NIH SAE report form within 72 hours of the reported event. Should additional information become available after the initial report, a revised report will be submitted as soon as possible**.**
>
> **Reporting AEs that do not meet the criteria for SAE.** All reported AEs will be collected and reported via the study's electronic database. AEs that are expected will be summarized at the time of continuation review.
>
> **Reporting UEs that do not meet the criteria for AEs.** The study team will report any UEs to the Fred Hutch IRB per their reporting guidelines. Fred Hutch will report the UE to the sponsor in accordance with the protocol.

Definitions
In general, unexpected events (UEs) include any event, adverse or otherwise, that was not described as part of the study risks. For this trial, an example of an unexpected event that is not adverse is a participant who has become very unhappy with trial procedures. Adverse events (AEs) are any untoward occurrence with a trial participant whether or not it can be considered to be related to their vaping cessation intervention. Examples of

adverse events in this trial could include development or worsening of depression symptoms. Serious adverse events (SAEs) include any AE that results in death, a real risk of dying, inpatient hospitalization, persistent or significant disability/incapacity, or AEs that require intervention to prevent permanent impairment or damage. In this trial, an example of a serious adverse event would be a suicide attempt.

Management of SAEs or other study risks
UEs, AEs, and SAEs will be reported to the Principal Investigator as soon as staff members are aware of them. If there is any doubt as to whether an event qualifies as a UE, AE, or SAE, staff members will be trained and encouraged to err on the side of caution – and to bring the event to the Principal Investigator's attention for review. The PI will be responsible for managing UEs, AEs, and SAEs.

Attribution
The independent medical monitor will decide if a UE should be classified as an AE. If an event is classified as an AE, further attribution will be determined, as follows:

- Related – AEs that are definitely, probably, or possibly related to the intervention.
- Not Related – AEs that are doubtfully related or clearly not related to the intervention.

12.0 DATA AND SAFETY MONITORING PLAN

This study is a low-risk, single-site, randomized 2-arm pilot trial of a behavioral intervention for vaping cessation. Monitoring of participant safety and data quality will be overseen by an independent medical monitor, who will conduct quarterly reviews of study progress, including recruitment and retention, adverse events, and protocol adherence. A detailed DSMP in included in Appendix A.

13.0 DATA MANAGEMENT/CONFIDENTIALITY

The investigator will ensure that data collected conform to all established guidelines. Each participant is assigned a unique number to protect participant confidentiality. Only Fred Hutch IRB-approved project staff will have access to study data. All data will be maintained on a secure-access drive in permission-restricted folders only accessible to project staff. All workstations and servers are physically secured in locked offices, reside behind the Fred Hutch firewall, and fully participate in Windows NT security. The data study folder will be further safe-guarded against unauthorized access by network user login authentication controls.

In no case will participant identifiers or data be provided to any person or entity outside the IRB-approved project team. Protected health information will not be disclosed, copied, transmitted by email, or transmitted in total or in part to anyone not connected with the approved protocol and not approved by the Fred Hutch IRB. We will limit our acquisition of identifiable information to the minimum amount of information necessary to link participant data, obtain contact information for recruitment of subjects, and collect pertinent data necessary to complete the study aims.

Any data included in manuscripts or publications stemming from this study will be presented as aggregate data only, and in a way that no individual could be identified. At the end of the study, after all manuscripts are published, all identifiable files and crosswalks will be destroyed in accordance with Fred Hutch IRB policy (7 years after the end of the study). Electronic media used to store all data will be cleaned or destroyed so the data is not retrievable. As a result of these measures, we do not expect any invasion of privacy or breach of confidentiality.

When any study personnel are no longer a part of the research team, the PI will remove that person's access to all study data and notify the Fred Hutch Information Security Officer of such action.

Online Surveys. The study database will be designed and maintained by Datatope, kept behind FHCC firewall. Only key study staff will have access to the study database system. All staff have received Human Subject

Research and HIPAA training. All data will be stored in a secure password protected computer folder, which only authorized research staff will have access to.

Mailed Surveys. Numerous safeguards will keep hard copy data secure. All hard copy data will be kept in a locked file cabinet accessible only by authorized research staff. Each participant will be assigned a code number and no personally identifiable information will be sent via mail. Should any non-study personnel gain access to the data, they will not know to whom they belong.

ACT on Vaping App. The ACT on Vaping app will be hosted internally by Fred Hutch, and utilization data will be recorded for all participants. Study IDs in the database will be unrelated to any identifying information. Data will be checked for inconsistencies, omissions, and errors. Outcome assessors will receive training in data management and confidentiality procedures and will be responsible for data entry and management.

Text Message Notifications. Participants in the ACT on Vaping arm will receive SMS text messages for 90 days. Text messages will be used to (a) prompt completion of the next session, and (b) push select intervention content to users. Notifications will be tailored to the user's level of quit readiness, with those who are not ready to quit in the next 30 days receiving values-focused, motivational messages and those who are ready to quit in the next 30 days receiving action-oriented messages (e.g., identifying and responding to triggers).
All study participants will receive incentivized text message check-ins at 2 weeks, 1 month, and 2 months post-randomization.
All communication with study participants will occur over Secure Sockets Layer (SSL) and no information or phone number will be shared by anyone other than IRB approved study staff.

14.0 STATISTICAL CONSIDERATIONS

14.1 Study Design

Randomized controlled 2-arm pilot trial

14.2 Primary/Secondary Endpoints/Hypotheses and Analytical Methods

We will calculate descriptive statistics (e.g., means, proportions) for the ACT on Vaping treatment group to assess treatment satisfaction (i.e., mean level of overall satisfaction with ACT on Vaping, with 3.5 on a 5-point scale being the "go" criterion). For the three cessation related-outcomes, we will evaluate differences descriptively to determine whether ACT on Vaping showed evidence of better outcomes on at least 1 of 3 efficacy endpoints as the final "go" criterion: change in readiness to quit (mean difference in Contemplation Ladder change scores ≥ 1), 24-hour quit attempts (≥ 5% difference), and cotinine-confirmed 30-day point prevalence abstinence from all nicotine/tobacco products at 3 months (≥ 5% difference). Given that pilot and feasibility trials are not appropriate designs for testing hypotheses regarding the efficacy of interventions [66, 67], we will focus on descriptive differences as an alternative to hypothesis testing. Similarly, since a single effect size derived from a small sample is an inherently unreliable estimate of the true intervention effect size [67], we aimed to reduce the likelihood of early abandonment of a potentially promising treatment by requiring evidence of a clinically meaningful effect on one of three cessation-related outcomes as the "go" criterion for efficacy.

14.3 Sample Size and Power

We plan to accrue 60 participants in the pilot trial. A sample size of 30 per arm is consistent with the NIDA Stage Model of behavioral treatment development, which suggests that pilot trials should include approximately 15-30 participants per arm for preliminary evaluation of the intervention [36].

14.4 Randomization

Following the completion of the baseline and contact information survey the participant will receive a text message with a link. Once this link is clicked an automated algorithm will randomize participants 1:1 to either the ACT on Vaping or the assessment-only control arm. The randomization algorithm will use a permuted-block

design with random block sizes, with stratification by high (>5) vs. low (5 or less) readiness to quit on the Contemplation Ladder [56]. Only the unblinded study biostatistician will have access to treatment assignment. Although we project, based on our previous work [28], that the majority of outcome assessments will be completed via web-based survey, any outcome evaluator who has direct contact with participants will remain blinded to treatment group assignment until the final set of questions regarding acceptability of the ACT on Vaping intervention.

14.5 Missing Data

Participants with missing tobacco use data will be considered non-abstinent [73] in the primary analysis. We will also report the results of sensitivity analyses using complete case analysis of those providing follow-up data. If there is a substantially differential rate of missing data (either self-report or cotinine analytic results) across arms, we will use complete case analysis in the primary outcome analysis instead of missing=tobacco use.

14.6 Ethnic and Gender Distribution Chart

Projected Target Accrual
ETHNIC AND GENDER DISTRIBUTION CHART

TARGETED / PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex / Gender		
	Females	Males	Total
Hispanic or Latino	3	2	5
Not Hispanic or Latino	28	27	55
Ethnic Category Total of All Subjects*	31	29	60
Racial Categories			
American Indian / Alaska Native	1	1	2
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	1	3
White	25	24	49
More Than One Race	2	2	4
Racial Categories: Total of All Subjects*	31	29	60

15.0 INVESTIGATOR OBLIGATIONS

The PI is responsible for the conduct of the clinical trial at the site and is responsible for personally overseeing the treatment of all study participants. The PI must assure that all study site personnel, including sub-Investigators and other study staff members, adhere to the study protocol and to all applicable regulations and guidelines regarding clinical trials both during and after study completion.

All participants are informed of the nature of the program, its possible hazards, and their right to withdraw at any time, and each participant signs a form indicating their consent to participate prior to receiving any study-related procedures.

16.0 POST-TRIAL USABILITY STUDY

Objectives:
Conduct a diary study with young adults (n=10) to assess user satisfaction with the app and its components as well as program utilization (n=10) and additional modifications needed to continue with the ACT on Vaping app development in preparation for the future UH3 phase of this study.

16.1.1 Study Population

We will recruit 10 YA e-cigarette users, ages 18-30, who meet basic eligibility criteria for the trial described below.

Participants will be recruited nationally via one or more recruitment strategies used successfully in our previous studies (e.g, social media, targeted Craigslist ads).

16.1.2 Study Design

Following the completion of the clinical trial, we will conduct a diary study as a field-based evaluation of its usability. Usability is the extent to which a digital intervention can be easily navigated and understood by the user [52]. Usability is a critical outcome of the intervention development process, as low usability can undermine engagement with the intervention as well as its potential efficacy for tobacco cessation [53].

16.1.3 Primary Objective:

Continued development of the *ACT on Vaping* smartphone application for tobacco cessation based on ACT. The ACT on Vaping app will be easily navigated and understood by the user and free from any technical difficulties.

16.2 Estimated Accrual:

We estimate that our recruitment efforts will lead to:

- 120 screened, 40 eligible and 10 enrolled.

We estimate recruitment to take 2-3 weeks

16.3 Eligibility:

16.3.1 Inclusion Criteria

- age 18-30
- current weekly user of e-cigarette product(s)
- owns an Android phone or iPhone
- has an email address
- US resident, with a US mailing address
- willing to complete all study procedures
- comfortable reading and writing in English

16.3.2 Exclusion Criteria

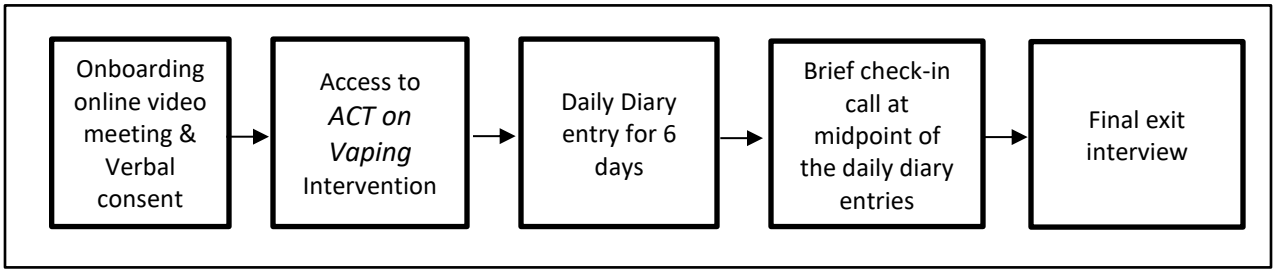
- currently using other tobacco cessation treatments at the time of screening, including pharmacotherapy or behavioral support
- previous participation in a Fred Hutch vaping or smoking cessation study
- currently in prison
- member of the same household as another research participant
- Google voice number as sole phone number, due to its association with fraudulent study entry attempts

16.4 Registration

Potential participants will be recruited via social media (e.g. Facebook, Twitter). Initial screening for participation will be conducted via web-based survey. Individuals deemed eligible will be contacted by phone to ensure eligibility and discuss study procedures; individuals remaining eligible and interested will be invited to attend an online, video-based visit.

16.5 Diary Testing Overview

Figure 1. Usability Testing Study Flow Chart



During the online, video-based onboarding visit, participants will be provided with information about the study and provide verbal informed consent to participate. During that visit, study staff will assist enrolled participants in downloading ACT on Vaping to their personal phone (Android or iPhone). Participants will be instructed to use the program for 6 days and to keep a daily diary to report on their usage of and satisfaction with the program. Daily diaries will follow a semi-structured format, including assessments of when they used the app, what prompted them to open it, what features they accessed, and what their overall experience was like. They will also be asked about any technical difficulties encountered and about ease of navigation. Following completion of the diary entries, they will be asked to attend a final debriefing session which will include a semi- structured exit interview to assess (a) usage and satisfaction with the app, and (b) the impact of *ACT on Vaping* on their e-cigarette use.

These procedures are consistent with best practices and usability testing of government-funded cessation programs [52] and have been successfully implemented previously in our treatment development work. After the diary study, the UX Researcher will work with the team of investigators to use data gleaned from the diary study to inform any needed changes to ACT on Vaping's content and structure as well as to address any technical difficulties experienced by the users. The software development team will then make changes needed to improve the usability and/or content of the app in preparation for the UH3 phase of the trial.

16.6 Participant Compensation

Diary study participants will be compensated up to $140 for completion all activities. Compensation will be pro-rated and dispersed as follows:

- $10 for the baseline visit.
- $10 for mid-point check in.
- $40 for the final debriefing visit.
- $10 for each daily diary entry, up to $60 (for 6 days).
- $20 bonus for completing all 6 diary entries.

16.7 Enrollment Procedures

Participants will be recruited nationally through online services (e.g., Facebook, Twitter advertisements). Recruitment materials will direct potential participants to a web-based screening survey. The survey provides

basic information about the study to allow individuals to choose whether or not to proceed, then assess basic eligibility criteria. Individuals who do not meet eligibility criteria will be provided with the following cessation resources via e-mail; the Smokefree.gov and the 800-QUIT-NOW phone number to reach their state's quitline.

Phone screening & informed consent:
Study staff will call individuals who are deemed potentially eligible based on the initial online screening. During this call, the purpose and procedures of the study will be explained in further detail and key eligibility criteria will be re-assessed to ensure consistency of answers. Those who remain eligible and interested will be invited and scheduled for the online onboarding meeting. Study staff will email the study information sheet to the individual to review before the online meeting.

Diary Study onboarding video meeting. We will email participants the information needed to access the online meeting, which will be conducted and recorded via video conference. The onboarding meeting will be conducted by the UX researcher and will last approximately 30 minutes. The study consent will be reviewed and discussed first, and participants will be asked to provide verbal consent before proceeding. During the onboarding meeting, participants will be given password-protected access to the *ACT on Vaping* app and will receive assistance with downloading the app. During this meeting, participants will also be asked about their motivation to quit vaping. The brief (10-15 minutes) mid-study session call and the final exit interview will also be scheduled. After the onboarding meeting, study staff will email participants their log-in credentials for the *ACT on Vaping* app as well as the date and time of their mid-study feedback call and their final exit interview.

16.8 Assessments/Evaluations

Onboarding video call (Day 1): Vaping level, motivation (importance and confidence) to change vaping habits and cost of vaping will be assessed.

Daily diary entry (Days 2-7): Participants will be instructed to use *ACT on Vaping* app for 6 days and to submit a daily diary to report on their usage of and satisfaction with the program. Daily diaries will follow a structured format, including assessments of when they used the app, what prompted them to open it, what features they accessed, and what their overall experience was like. They will also be asked about the specific device and operating system they used to access the app, any technical difficulties encountered and about ease of navigation.

Mid-study check in call (Day 3-4): the UX Researcher will connect briefly with each participant for a 10–15-minute check in about their experience and engagement with the *ACT on Vaping* app. Qualitative research notes will be taken during this call.

Final exit interview (Day 8): Following completion of the diary study, participants will be asked to attend an online video meeting for a final debriefing session which will include a semi-structured exit interview to assess (a) usage and satisfaction with the app, and (b) the impact of *ACT on Vaping* on their e-cigarette use and engagement with the app. Participants will also be asked to report any technical difficulties they may have experienced.

16.9 Analytical methods

Qualitative data from diary entries and exit interviews will be coded and analyzed using rapid inductive content analysis to extract themes.

16.10 Continued Intervention Development

The data gleaned from the diary study will inform any needed changes to *ACT on Vaping* app's content and structure as well as to address any technical difficulties experienced by the users.

The Moby Inc. programming team will then make changes needed to improve the usability and/or content of the app and will complete additional modifications to the ACT on Vaping program based on participant feedback. The next version of *ACT on Vaping app*, that will be developed after the diary study, will be used in the future (UH3) phase of this study.

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18.0 APPENDICES

Appendix A: DSMP

Appendix A
Data & Safety Monitoring Plan
Version 2, 10/24/22

1 UG3 DA057032-01

"ACT on Vaping: Digital Therapeutic for Young Adult Vaping Cessation"

PI: Heffner, Jaimee L.
Medical Monitor: Panagis Galiatsatos, MD

19.0 Table of Contents

1 Summary of the protocol

1.1 Brief description of the protocol

This study will adapt a digital Acceptance and Commitment Therapy (ACT) program into an app-based digital therapeutic for young adult (YA) vaping cessation and evaluate its preliminary acceptability and efficacy relative to an incentivized text message control condition.

1.2 The primary aims are:

Aim 1 (Y1-Y2). Develop the ACT on Vaping smartphone app and evaluate its acceptability and preliminary impact on cessation-related targets.
1.a. Gather input from users and subject matter experts (YAs who vape, team members with expertise in YA vaping) to develop vaping-focused content for the novel program.
1.b. Complete Q-submission to obtain FDA feedback on the regulatory pathway for the intervention.
1.c. Conduct a pilot RCT (n=60) to evaluate acceptability and preliminary efficacy of ACT on Vaping relative to an incentivized text message control condition.

Aim 1 outcomes will be evaluated using the following go/no-go criteria to determine whether proceeding to a larger UH3-phase study is warranted: (a) Completed FDA Q-submission. (b) From the pilot trial, evidence that ACT on Vaping is acceptable (overall satisfaction averaging at least 3.5 out of 5) and produces better outcomes than the control intervention on at least 1 of 3 efficacy endpoints: change in readiness to quit (mean difference in Contemplation Ladder change scores ≥ 1), 24-hour quit attempts (≥ 5% difference), and cotinine-confirmed 30-day point prevalence abstinence from all nicotine/tobacco products at 3 months (≥ 5% difference).

1.3 Primary outcome measures

Type	Name	Time Frame	Brief Description
Primary	Overall treatment satisfaction rating	3 months post-randomization	Satisfaction with the assigned intervention on a 5- point Likert-type scale
Primary	Change in Contemplation Ladder scores from baseline	3 months post-randomization	Change in readiness to quit using e-cigarettes
Primary	Self-reported 24-hour quit attempt	3 months post-randomization	Proportion of participants making a quit attempt lasting at least 24 hours between baseline and 3- month follow-up
Primary	Cotinine-confirmed 30-day point prevalence abstinence from all nicotine and tobacco	3 months post-randomization	Biochemically confirmed 30-day abstinence from all nicotine and tobacco products at follow-up (excluding FDA-approved pharmacotherapies)

1.4 Inclusion/exclusion criteria

Inclusion Criteria

- age 18-30
- current weekly user of e-cigarette product(s) for the last 30 days
- has a smartphone either an Android (running version 10.1 or higher) or iPhone (running iOS version 13 or higher)
- experience downloading and using one or more apps on their smartphone
- have a mobile data plan and/or access to WiFi to support the use of the ACT on Vaping app
- has access to text messaging
- has an email address
- US resident, with a US mailing address
- willing to complete all study procedures
- comfortable reading and writing in English

Exclusion Criteria

- currently using other tobacco cessation treatments at the time of screening, including pharmacotherapy or behavioral support (note: use of these treatment is allowable during trial participation)
- member of the same household as another research participant
- currently in prison
- Google voice number as sole phone number, due to its association with fraudulent study entry attempts
- is ineligible per fraud prevention protocol
- employees/family of investigator or study center

1.5 Power calculation and sample size

Sample size determination. We plan to accrue 60 participants in the pilot trial. A sample size of 30 per arm is consistent with the NIDA Stage Model of behavioral treatment development, which suggests that pilot trials should include approximately 15-30 participants per arm for preliminary evaluation of the intervention [1].

1.6 Schedule of assessments

Measure	# items	Screening Survey	Baseline Survey	3-mo. Follow-up Survey	Primary Purpose
Eligibility criteria	11	X			Eligibility
Demographics	10		X		Sample description
e-FTCD (severity of dependence)	6		X	X	Sample description
Tobacco/nicotine use history	9		X		Sample description
Contemplation Ladder (readiness to quit)	1		X	X	Primary outcome
Recent tobacco/nicotine use	3		X	X	Primary outcome
Saliva cotinine	n/a			X	Primary outcome
Outside tobacco treatment	2		X	X	Concomitant treatment
Treatment satisfaction	8			X	Primary outcome
Treatment adherence (tracked automatically)	n/a			X	Primary outcome

Abstinence self-efficacy	1		X	X	Exploratory
AIS cravings subscale (psychological flexibility)	9		X	X	Exploratory
Valuing Questionnaire (psychological flexibility)	10		X	X	Exploratory
Past 30-day alcohol and cannabis use	2		X	X	Exploratory
Agent Persona Instrument (avatar perceptions)	25			X	Exploratory
Adverse events	1			X	Safety monitoring
Total number of items		*11*	*62*	*73*	
Estimated duration (mins)		*5-10*	*30-35*	*35-40*	

2 Trial Management

2.1 List of participating enrolling clinics or data collection centers

Fred Hutchinson Cancer Center, Seattle, WA

2.2 Projected timetable for the pilot RCT

Based on previous trials that used a similar national recruitment strategy (ranging from 78-862 randomized/month), we estimate enrollment of at least 120 participants/month, requiring a recruitment period of less than 1 month for the UG3 phase (n=60).

2.3 Target population distribution

We will actively seek participants who are diverse in their gender identity, including people who identify as cisgender men and women and those who identify transgender and gender expansive. We will also make every effort to ensure that members of diverse racial/ethnic groups are adequately represented in the study by targeting our online recruitment efforts based on location (e.g. Craigslist ads in cities with a high proportion of racial/ethnic minority residents) and use of the Facebook advertising platform to target on user interests and affiliations. In previous studies we have achieved at least 25% minority participation in trials using these methods. In the most recent large trial of a web-delivered intervention [7], the sample was 27% racial minority and 8% Hispanic/Latino. In our EQQUAL pilot study, 27% identified as racial/ethnic minority. Although the UG3 trial is not designed to ensure statistical power to evaluate effect moderators, we will program the recruitment website to ensure that at least 25% identify as racial/ethnic minority.

3 Data management and analysis

3.1 Data acquisition and transmission

Recruitment. Participants will be recruited nationally via recruitment strategies used successfully in previous studies conducted by our group: targeted Facebook ads; Craigslist ads in cities with a high prevalence of nicotine and tobacco use or racial/ethnic minority residence; other free methods of advertising on the Internet (e.g., Reddit, Twitter); ResearchMatch.org; and earned media generated by press releases from the Fred Hutch media team. Recruitment materials will direct potential participants to a recruitment website, which provides basic information about the study and a portal to screening survey. In order to ensure that at least 25% of the sample identifies as racial/ethnic minority, we will program the website to limit recruitment of those who identify as non-Hispanic White to 75% and continue recruitment until the racial/ethnic minority recruitment goal of at least 25% is reached. This similar to recruitment capping methods used in our other trials.

Informed Consent Procedures. Recruitment materials will direct potential participants to a secure recruitment website, which provides basic information about the study and a portal to the screening survey. For participants who screen eligible on the recruitment website and provide their email address, we will instantly send them an email and/or text message (and two reminders over a 7-day period) inviting them to provide informed consent and complete the baseline assessment. Those not consenting and completing or not eligible will be sent an email notifying them that they were not enrolled and providing both the link to Smokefree.gov and the 1-800-QUIT-NOW phone number for cessation support.

Sources of materials and app utilization data
The data relevant to the proposed project will be gathered strictly for research purposes. Data collected will be in the form of structured assessment instruments, app utilization data, and saliva cotinine test results.

Assessment instruments. Structured assessment instruments will be administered by web-based forms or by trained research staff in order to: (1) evaluate study eligibility and establish baseline characteristics of the sample, (2) evaluate study outcomes.

App utilization data. At randomization, participants assigned to the ACT on Vaping arm will be given a unique log-in ID to access their assigned app, which will serve as the link to the rest of their study data.

Saliva cotinine testing. Cotinine test kits will be shipped at each follow-up to all self-reported abstainers who have not used nicotine replacement therapy in the prior 7 days to biochemically verify nicotine and tobacco use status for the purpose of cessation outcome assessment. Participants will upload a photo of their test result using a secure web-based form.

3.2 Outcome data collection

Following our data collection protocol used in previous trials, we will collect email, phone number, and mailing address. The data collection protocol is as follows: Assessment Day -14: Mailed reminder of upcoming survey, with $2 pre-incentive included; Day 0: First email and/or invitation with link to online survey; Day 5: Second email and/or text invitation with link to online survey; Day 9: Third email and/or text invitation with link to online survey; Days 10 to 18: Eight attempts to complete telephone version of survey (one call per day); Day 18: Send mailed version of survey; Participants will receive an incentive of $50 the follow-up survey completed and an additional $25 for returning cotinine results if asked. In addition, an extra incentive of $10 will be provided to participants who respond to the first email and/or text invitation and complete the survey online within 24 hours. Based on previous trials using these same procedures [19, 28], we expect that 80% of participants will complete assessments via web-based survey, ~2% by phone, ~3-4% by mailed survey.

3.3 Data entry methods

All screening, baseline, and outcome survey data will be entered either directly by study participants who complete the online surveys or study staff (for participants who complete the surveys by phone or mail) into a study database managed by Datatope, LLC.

3.4 Data security and protecting confidentiality

Numerous safeguards will keep data secure. Each subject will be assigned a code number so that, should any non-study personnel gain access to the data, they will not know to whom they belong. Any hard copy data will be kept in a locked file cabinet accessible only by authorized research staff. A secure password is required to access computers at each site, and computer networks are on secured servers that meet or exceed federal confidentiality standards. Once randomized into the ACT on Vaping arm, each participant will have access to their assigned app protected with a login. All connections will be made using the secure sockets layer (SSL).

Participant data are maintained on a server in a locked server room at Fred Hutch. Full access to the server is restricted to two staff members of the Fred Hutch Public Health Sciences Information Technology (PHS-IT) group and the two developers of the study management system.

3.5 Data analysis plan

To address Sex as a Biological Variable, we will explore whether outcomes described below are associated with sex assigned at birth. If they are, that variable will be added to the relevant models. Primary analyses will be conducted as described below:

To evaluate the go/no-go criteria for the pilot trial, we will calculate descriptive statistics (e.g., means, proportions) for the ACT on Vaping treatment group to assess treatment satisfaction (i.e., mean level of overall satisfaction with ACT on Vaping, with 3.5 on a 5-point scale being the "go" criterion). For the three cessation related-outcomes, we will evaluate differences descriptively to determine whether ACT on Vaping showed evidence of better outcomes on at least 1 of 3 efficacy endpoints as the final "go" criterion: change in readiness to quit (mean difference in Contemplation Ladder change scores ≥ 1), 24-hour quit attempts (≥ 5% difference), and cotinine-confirmed 30-day point prevalence abstinence from all nicotine/tobacco products at 3 months (≥ 5% difference). Given that pilot and feasibility trials are not appropriate designs for testing hypotheses regarding the efficacy of interventions [5, 6], we will focus on descriptive differences as an alternative to hypothesis testing. Similarly, since a single effect size derived from a small sample is an inherently unreliable estimate of the true intervention effect size [6], we aimed to reduce the likelihood of early abandonment of a potentially promising treatment by requiring evidence of a clinically meaningful effect on one of three cessation-related outcomes as the "go" criterion for efficacy.

Missing data. Participants with missing nicotine use data will be considered non-abstinent [6] in the primary analysis. We will also report the results of sensitivity analyses using complete case analysis of those providing follow-up data. If there is a substantially differential rate of missing data (either self-report or cotinine analytic results) across arms, we will use complete case analysis in the primary outcome analysis instead of missing=vaping/smoking.

4 Quality assurance plan

4.1 Procedures in place to ensure the validity and integrity of the data

To prevent fraudulent study enrollment, we will use a multi-stage evaluation and exclusion of potential participants based on the following: IP address check for non-US addresses, proxy IP addresses, and IP addresses reported to have engaged in fraud; check for duplicate email addresses within-study; check for completing too many survey pages too fast, completion of hidden responses (indicative of a bot), inconsistent responses between screening and baseline; a final check for duplicate contact info provided based on name, phone number, or email address, or IP address; and a test SMS text message to check for virtual numbers.

4.2 Procedures to guarantee the accuracy and completeness of the data

Data accuracy has two aspects in this trial: (1) accuracy of self-reported data by trial participants, and (2) accuracy of data management. The trial has procedures for both, which will be reviewed annually by the project manager and approved by the Principal Investigator.

The ACT on Vaping app will be hosted internally by Fred Hutch, and utilization data will be recorded for all participants assigned to that arm. Study IDs in the database will be unrelated to any identifying information. Data will be checked for inconsistencies, omissions, and errors.

Outcome assessors will receive training in data management and confidentiality procedures and will be responsible for data entry and management.

4.3 Procedures during data transmission

Forms used by participants and staff will be web-based forms. Data are maintained on a server in a locked server room at Fred Hutch. Full access to the server is restricted to two staff members of the Fred Hutch Public Health Sciences Information Technology (PHS-IT) group and the two developers of the study management system.

Project staff access the study database from their computers via the Study Management (SM) Web site. The SM Web site is only accessible from specific Internet Protocol (IP) addresses used by study staff. All communication with the SM Web site occurs over Secure Sockets Layer (SSL).

4.4 Procedures during data analysis

When data collection is complete, the study statistician will lock the database and conduct quality checks. Data quality will be assessed through a number of analytic methods. The study statistician will tabulate categorical variables with frequency counts, and for continuous variables we will examine descriptive statistics (mean, standard deviation, median, interquartile range, minimum, maximum), distributional characteristics (skewness, kurtosis, frequency histograms, normal probability plots), and associations (correlations, scatter plots). Any free text or numeric values will be checked for range consistency, and outlying values.

5 Regulatory issues

5.1 Reporting mechanisms of AEs/SAEs to the IRB and NIDA

Reporting SAEs

It will be the responsibility of the PI to ensure that all SAEs are recorded on the study SAE reporting form, reported to NIDA within 72 hours of their discovery, and, as needed, referrals are made for appropriate care to address the SAE. In addition, unexpected and related SAEs are reported to the IRB within that same time window. Should additional information become available after the initial report, a revised report will be submitted as soon as possible.

Reporting AEs that do not meet the criteria for SAE

All volunteered, observed, or elicited AEs on study assessments, notes, or in study-related communications with participants will be recorded in an adverse events log, which includes star and stop date, severity, relationship to study treatment, outcome, and whether the AE caused the participant to withdraw from the study. A record of AEs will be maintained and reported via the study's electronic database. AEs that are expected will be summarized quarterly for the study's Medical Monitor and annually at the time of continuation review.

Reporting UEs that do not meet the criteria for AEs

The study team will report any UEs to the Fred Hutch IRB per their reporting guidelines. Fred Hutch will report the UE to the sponsor in accordance with the protocol.

5.2 Reporting mechanisms of IRB actions to NIDA

Within one business day of IRB actions on SAE, the PI will be responsible for reporting to the NIDA Program Officer of said action.

5.3 Report of changes or amendments to the protocol

The PI will apply to the Fred Hutch IRB for a modification to request changes or amendments to the protocol. When approved, the modification will serve as the official report of the changes or amendment. Major changes to the protocol will be pre-approved by the NIDA Program Officer.

5.4 Trial stopping rules

While no formal stopping rules are proposed, the PI or NIDA staff may initiate a request for the Medical Monitor to evaluate the safety of the trial and its continued progress.

Complying with trial suspension reporting requirements

Were the IRB or Clinical Trials Office to issue a temporary or permanent suspension of the trial, the trial's Principal Investigators will immediately contact the trial's Program Officer, Jana Drgonova, PhD , National Institute on Drug Abuse, Clinical/Medical Branch, Bethesda, Maryland 20892-9551. Phone: 301-827-5933, Email: jana.drgonova@nih.gov.

5.5 Disclosure of any conflict of interest

None of the investigators have a conflict of interest. If one arises, it will immediately be reported to the Fred Hutch IRB and NIDA Program Officer. The PI will request guidance from the IRB and the NIDA Program Officer on how to proceed with the DSMP given the conflict of interest.

6 Trial safety

6.1 Potential risks of intervention and mitigation plan

Therapeutic risks. Therapeutic risks include the physical and psychological consequences of nicotine and tobacco abstinence, such as nicotine withdrawal symptoms. Participants will be informed of the discomfort associated with nicotine withdrawal, including common withdrawal symptoms. Specifically, participants will be informed that, "If you quit vaping and using other forms of nicotine, you may experience some short-term discomfort associated with nicotine withdrawal including irritability, depressed mood, restlessness, difficulty sleeping, headaches, difficulty concentrating, and cravings to smoke. These symptoms typically last a few weeks and then go away." Strategies for mitigating withdrawal-related risks will be provided (e.g., using over-the-counter medications for headaches, physical activity to help with mood and sleep, etc.). Participants will also be informed of the possibility that the interventions provided as part of the study may not be effective in helping them to quit using tobacco products.

Possibility that the study intervention may not help the participant to quit using nicotine and tobacco products. Participants will receive information about the availability of pharmacotherapy to facilitate cessation, including nicotine replacement, bupropion, or varenicline. They will also be informed of alternative behavioral support options such as counseling/support through their state quitline (1-800-QUIT-NOW).

Assignment to incentivized text message control arm. Potential study participants will be informed as part of the consent process that they have a 50-50 chance of being assigned to the incentivized text message check-in control arm. All participants assigned to the control arm will be offered access to the ACT on Vaping app at the conclusion of their participation in the study.

6.2 Risks related to research procedures and mitigation plan

Participants will be informed of the following research-related risks: (1) the possibility that answering some questions may be emotionally upsetting, and (2) the possibility of breach of confidentiality. It is possible that some of the questions asked of participants may cause some emotional discomfort. There is also a small risk of breach of confidentiality if participant data, either in electronic or hard copy form, were to be accessed by an unauthorized person.

Emotional upset. On the study assessments, participants will be reminded that they have the choice to not answer any question that makes them uncomfortable.

Breach of confidentiality. Numerous safeguards will keep electronic data secure. A secure password is required to access computers at Fred Hutch, and computer networks are on secured servers that meet or exceed federal confidentiality standards. Once randomized, each participant will have access to their assigned app protected with a login. All connections to web-based data collection forms will be made using the secure sockets layer (SSL).

A Certificate of Confidentiality from the National Institutes of Health is in place to protect participants in this study from involuntary disclosure of information collected as part of the study. Participants will be informed both verbally and in writing that the Certificate of Confidentiality does not supersede federal and/or state laws governing exceptions to confidentiality (e.g., danger to self or others, mandated reporting of child or elder abuse/neglect). Similarly, participants will be notified that agents of the Fred Hutchinson Cancer Center, the National Institutes of Health, and the FDA will be allowed to inspect sections of their study records, if requested. Otherwise, no information will be released to any individual or organization without their prior written authorization. Participants will be informed that the data from the study may be published; however, they will not be identified by name. Participants will be informed that their identity will remain confidential unless law requires such disclosure.

All study personnel will receive required training in protection of human subjects in research as well as Good Clinical Practice training. Participants will be informed of therapeutic and research related risks as well as the safeguards and/or precautions taken to reduce these risks. The following procedures will be implemented to protect against the risks outlined above.

Informed consent. At the outset of the study, participants will be provided with detailed information about the study and provided with the opportunity to ask questions about study participation. Informed consent will be obtained following the guidelines of the Fred Hutch Institutional Review Board. Participants will be reminded that they are free to withdraw from the study at any point.

6.3 Benefits for participants

Participants will be provided with information regarding potential benefits of participation in the study, including the following intervention-related benefits: 1) the possibility that study participation might help them to quit using nicotine and tobacco, and 2) access to a smartphone app to learn about their interest in quitting vaping and methods of quitting at no cost.

Benefits of research procedures

Participation in the trial's surveys will not offer any direct benefits but will advance knowledge in many important areas of young adult vaping cessation. Participants may have a positive feeling about participating in this effort by completing the trial's surveys.

Other information

Token monetary incentives are offered for completion of the study assessments. Although not the purpose of these token incentives, they may be perceived by some participants as a benefit to participation.

7 Collection and reporting of AEs and SAEs

7.1 Monitoring

Throughout the study, the project manager and outcome assessors will monitor participants' progress and responses to surveys for adverse events and for protocol compliance. Participants will be asked to report changes in their physical and mental health, especially if treatment was required. An email will be sent to participants asking about changes in their health on Day 21, 42 and 63. Adverse event reports will not be monitored in real time. The project manager will review the submitted responses weekly and will contact the participant by telephone to ask additional questions, if needed. Emergency and crisis resources will be provided to all study participants in the study consent, and at each adverse event collection time point.

Adverse event assessment ("Have you experienced any changes in your health or well-being since you started the study?") will also be completed at the 3-month follow-up survey timepoint. The project manager will complete quarterly reports on participant progress and status, any adverse events, and any protocol deviations. Protocol adherence will be monitored by the Principal Investigator.

7.2 Reporting

All study staff working on the trial will be trained and required to report all observed, volunteered, or elicited AEs, regardless of treatment group or suspected causal relationship to the study treatment, to the project manager and the Principal Investigator. A form will be available for this purpose. The PI will report these events to the study's independent medical monitor for evaluation of its causal relationship with study intervention. (See Section 5 for a description of procedures for reporting AEs and SAEs to the IRB and to NIDA).

7.3 Definitions

In general, unexpected events (UEs) include any event, adverse or otherwise, that was not described as part of the study risks. An adverse event (AE) is any unexpected medical or psychiatric occurrence in a patient or clinical investigation participant administered an intervention, which does not necessarily have a causal relationship with the treatment. This includes any clinical or laboratory change that does not commonly occur in that participant and is considered clinically significant.

FDA 21CFR312.32 defines a serious adverse event (SAE) as any adverse experience that results in any of the following outcomes: death; a life-threatening adverse drug experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability/incapacity; or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse experiences when, based on appropriate judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes in this definition. The judgment of whether a particular AE meets the above criteria for an SAE shall be determined by the study's independent medical monitor.

7.4 Management of SAEs or other study risks

UEs, AEs, and SAEs will be reported to the Principal Investigator as soon as staff members are aware of them. If there is any doubt as to whether an event qualifies as a UE, AE, or SAE, staff members will be trained and encouraged to err on the side of caution – and to bring the event to the Principal Investigator's attention for review. The PI will be responsible for managing UEs, AEs, and SAEs. Withdrawal from the study as a result of an AE or of therapeutic measures taken to treat an AE shall be at the discretion of the PI.

7.5 Attribution

The medical monitor will decide if a UE should be classified as an AE. If an event is classified as an AE, further attribution will be determined, as follows:

Related – AEs that are definitely, probably, or possibly related to the intervention.
Not Related – AEs that are doubtfully related or clearly not related to the intervention.

8 Trial efficacy

8.1 Plans for interim analysis of efficacy data

As this is a pilot study, no interim efficacy analyses will be conducted.

8.2 DSM plan administration

Responsibility for data and safety monitoring

Dr. Heffner will oversee that data and safety monitoring plan for the trial, including consultation with the independent medical monitor who will make the final determination as to whether UEs, AEs, and SAEs are related to study interventions.

Frequency of DSM reviews
Data will be reviewed in the course of the trial on a quarterly basis. A full DSM report will be generated annually.

Content of DSM report
The content of the annual DSM report will follow this structure: (1) Brief description of the trial, (2) Baseline sociodemographic characteristics, (3) Retention and disposition of study participants, (4) Q.A. issues, (5) Regulatory issues, (6) AEs, (7) SAEs, (8) Efficacy. A copy of this report will be provided to the NIDA program officer annually.

DSM Board Plan
A DSMB is not needed for this low-risk, single-site trial of two behavioral interventions for smoking cessation.

References

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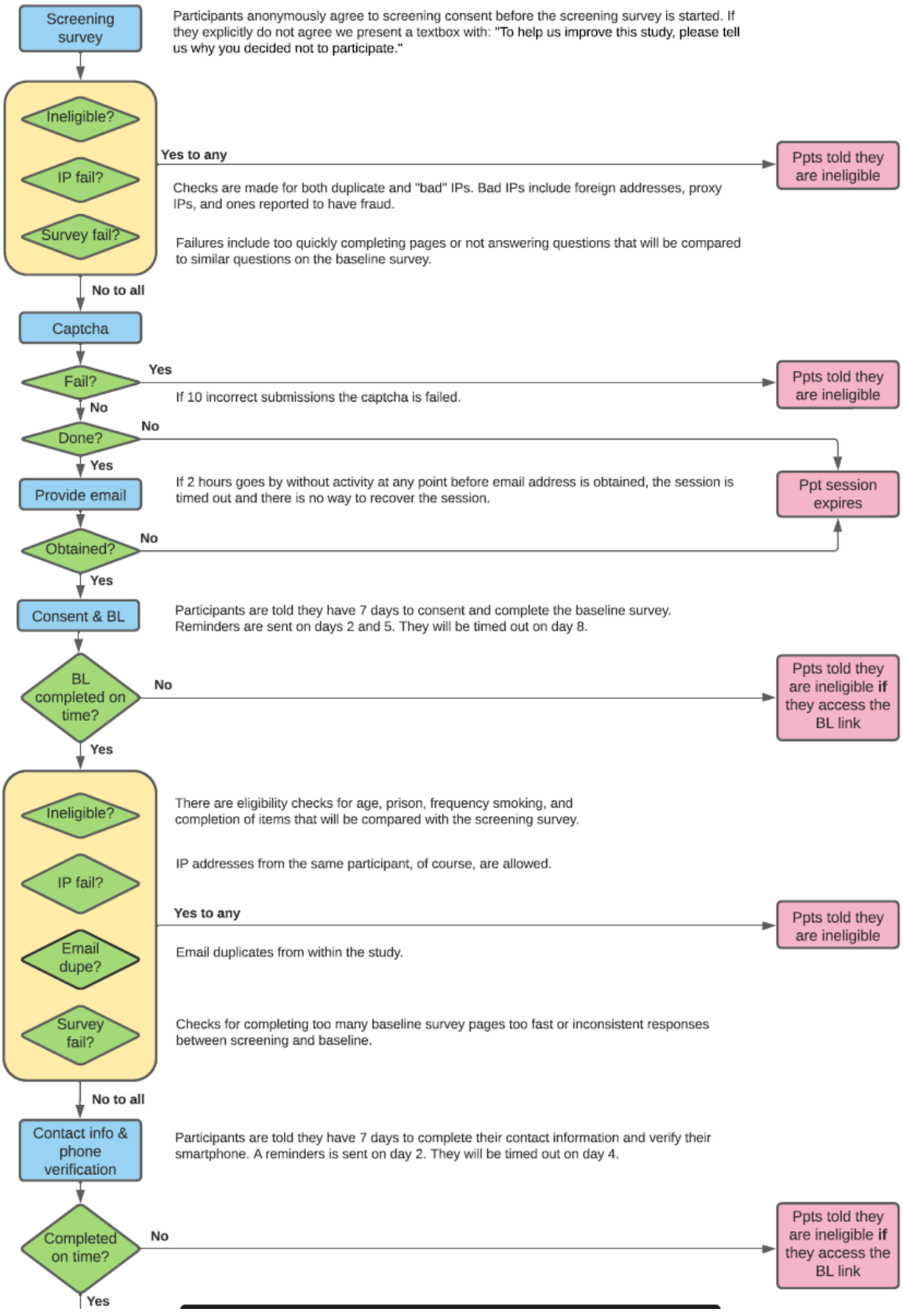
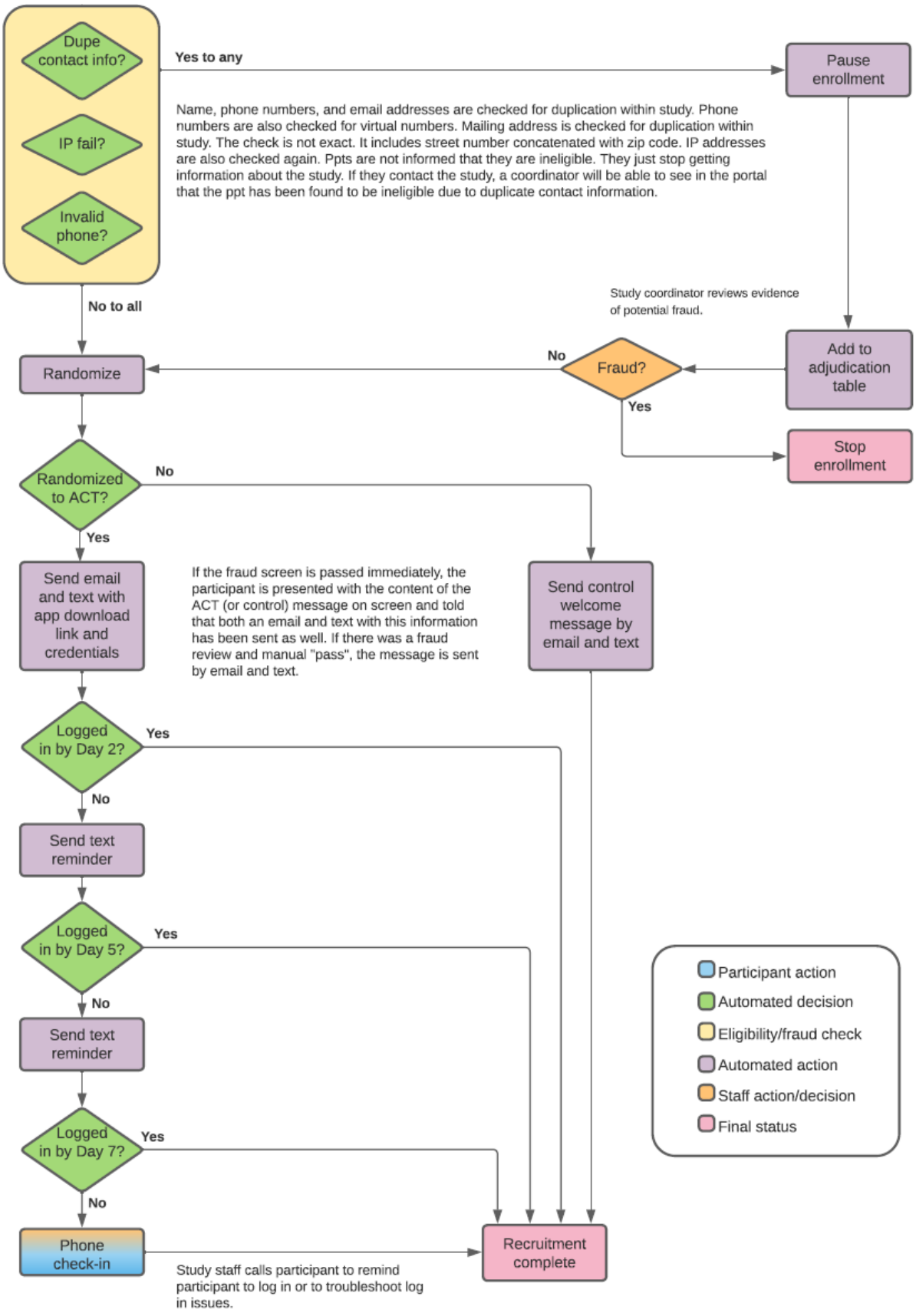
Appendix B - Sample screenshots of the ACT on Vaping intervention

Appendix C - ACT on Vaping Participant Flow: Recruitment




Dupe contact info?
IP fail?
Invalid phone?
Yes to any
Pause enrollment
Name, phone numbers, and email addresses are checked for duplication within study. Phone numbers are also checked for virtual numbers. Mailing address is checked for duplication within study. The check is not exact. It includes street number concatenated with zip code. IP addresses are also checked again. Ppts are not informed that they are ineligible. They just stop getting information about the study. If they contact the study, a coordinator will be able to see in the portal that the ppt has been found to be ineligible due to duplicate contact information.
No to all
Study coordinator reviews evidence of potential fraud.
Add to adjudication table
Fraud?
No
Yes
Randomize
Stop enrollment
Randomized to ACT?
No
Yes
Send email and text with app download link and credentials
If the fraud screen is passed immediately, the participant is presented with the content of the ACT (or control) message on screen and told that both an email and text with this information has been sent as well. If there was a fraud review and manual "pass", the message is sent by email and text.
Send control welcome message by email and text
Logged in by Day 2?
Yes
No
Send text reminder
Logged in by Day 5?
Yes
No
Send text reminder
Logged in by Day 7?
Yes
No
Phone check-in
Study staff calls participant to remind participant to log in or to troubleshoot log in issues.
Recruitment complete
Participant action
Automated decision
Eligibility/fraud check
Automated action
Staff action/decision
Final status

Notes:

1. Combined eligibility/fraud checks appear in sequence above but all issues at a particular eligibility/fraud check are performed regardless of the outcome of the other issues. Fraud issues are checked for both eligible and ineligible surveys.