Website Smoking Cessation Intervention for the Promotion of Smoking Cessation in Low-Income Veterans
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Title of Protocol:
A Scalable e-Health Smoking Cessation Intervention for Socioeconomically Disadvantaged Veterans

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PROTOCOL SYNOPSIS

Protocol Title	A Scalable e-Health Smoking Cessation Intervention for Socioeconomically Disadvantaged Veterans
Protocol Number	RG-1007109
Protocol Sponsor	National Cancer Institute
Trial Phase	Phase 1
Trial Type	Randomized pilot trial
Clinical Indication	Socioeconomically Disadvantaged Veteran Smokers
Study Objectives	Aim 1. Compare the relative acceptability of Vet Flexiquit vs. SmokefreeVET among socioeconomically disadvantaged US Veterans, as indicated by treatment satisfaction and objective measures of web site utilization. Aim 2. Preliminarily evaluate effects of Vet Flexiquit vs. SmokefreeVET on quit attempts and abstinence rates as well as readiness to quit and acceptance of smoking triggers—ACT's theory-based mechanism of change.
Study Design	Randomized pilot trial
Population	Low income US Veteran smokers
Primary Endpoints	1. Acceptability of the intervention: a. Treatment satisfaction b. Website utilization (number of log ins, number of days used from first to last day)
Secondary Endpoints	1. Number of quit attempts 2. Changes in readiness to quit from baseline to 3-months 3. Changes in acceptance of smoking triggers as measured by the AIS from baseline to 3-month follow-up 4. Cotinine-confirmed, self- reported abstinence from smoking
Type of control	Standard care: SmokefreeVet.gov
Trial Blinding	Eligible participants will be randomized via a web-based system at the baseline visit using an automated algorithm
Treatment Groups	2 arms; Vet Flexiquit or SmokefreeVET
Treatment Schedule	Vet Flexiquit contains 6 sessions designed to be completed in order, spaced out over a minimum of 3 days between sessions, with automated pacing and prompting from the program. Each session takes approximately 25 minutes to complete. The control intervention will be SmokefreeVET. This web site was designed to promote smoking cessation among Veterans by providing educational materials about cessation treatments, tools to cope with urges and relapse, how to stay motivated, and brief tips for Veterans with depression and anxiety, substance use disorders, HIV, and other physical and mental health problems. Content is consistent with US Clinical Practice Guidelines for tobacco treatment, which include heterogeneous techniques most closely aligned with cognitive behavioral therapy.
Number of trial subjects	n=50
Estimated duration of trial	9 months
Duration of Participation	3 months

ABBREVIATIONS

ACT	Acceptance and Commitment Therapy

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1.0 GENERAL INFORMATION

This document is a clinical research protocol for a two-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 Behavioral Therapies Development Model [33]. Specifically, we will conduct a pilot feasibility trial of Vet Flexiquit (n=25) vs. a standard care comparison web site (n=25).

Rationale: Although cigarette smoking rates have declined in the US over the past 50 years, there has been an upturn in smoking among military personnel in the last several decades. With over 8 million Veteran enrollees, the Veterans Health Administration serves 75% of low-income and disabled Veterans. Less than 5% of Veterans receiving care through VHA access intensive treatment for smoking cessation, and these services employ a standard approach to cessation counseling that is most relevant for smokers who are ready to quit. To optimize acceptability, reach, and effectiveness, cessation treatments for Veteran smokers should be appropriate for all levels of readiness to quit. In this study, we propose pilot testing Vet Flexiquit, a program designed for US Veteran cigarette smokers at all stages of readiness to quit. Specifically, we propose a pilot feasibility trial (n=50) comparing Vet Flexiquit to a standard care comparison web site (SmokefreeVET.gov). The primary goals of the pilot study are to compare Vet Flexiquit to SmokefreeVET on acceptability (i.e., user satisfaction and website utilization) and efficacy for impacting theory-based change processes and promoting smoking cessation. This pilot project is significant and innovative in four key respects: (1) it addresses the top cause of cancer and other preventable diseases among socioeconomically disadvantaged US Veterans served by VHA, (2) it applies a novel treatment approach and advances the science of ACT for smoking cessation by testing its effectiveness for smokers at all stages of readiness to quit rather than only among smokers who are ready to quit, (3) web-based delivery has high potential reach, cost-effectiveness, and scalability within VHA, a health care setting where tobacco cessation is under-resourced; and (4) gamification and inclusion of virtual coaches as engagement strategies are substantially different than standard web-based tobacco treatments, including SmokefreeVET. If found to be effective in a larger trial, Vet Flexiquit would be well-positioned for VHA-wide scale-up due to its low maintenance cost and high potential reach, and the core program could be built upon in innovative ways (e.g., capability for virtual coaches to understand and respond to natural language) to further improve engagement and outcomes.

Objectives:
Aim 1. Compare the relative acceptability of Vet Flexiquit vs. SmokefreeVET among socioeconomically disadvantaged US Veterans, as indicated by treatment satisfaction and objective measures of web site utilization.

Aim 2. Preliminarily evaluate effects of Vet Flexiquit vs. SmokefreeVET on quit attempts and abstinence rates as well as readiness to quit and acceptance of smoking triggers—ACT's theory-based mechanism of change.

NOTE: The Bedford VA will be the study performance site and will manage all elements of the trial involving direct interaction with participants (i.e., recruitment, enrollment, data collection, etc). Fred Hutch will be responsible only for hosting and maintaining the intervention sites and conducting data analysis at the conclusion of the trial.

1.1 Protocol Title: A Scalable e-Health Smoking Cessation Intervention for Socioeconomically Disadvantaged Veterans

1.2 Sponsor Information: National Cancer Institute

1.3 Investigator Information:
Principal Investigator: Jaimee Heffner, PhD, (206) 667-7314
Principal Investigator: Megan Marie Kelly, PhD, (781) 687-3317, Edith Nourse Rogers Memorial VA Medical Center/University of Massachusetts

1.4 Contractors and Consultants for the Study (if applicable)
Consultant: Maria Karekla, PhD (University of Cyprus)

2.0 INTRODUCTION TO THE PROTOCOL

2.1 Introduction

2.1.1. Significance and Innovation. Smoking remains the leading preventable cause of death and morbidity among US Veterans. Cigarette smoking is responsible for over 440,000 deaths annually and causes 32% of all cancer deaths [1, 2]. In addition, smoking adds $193 billion in health care expenditures and productivity losses each year in the US [3]. The Veterans Health Administration (VHA), which has over 1 million smokers among its 8.4 million enrollees [4], spends $2.7 billion per year treating smoking-related health problems [5]. Although smoking rates have declined in the US over the past 50 years, there has been an upturn in smoking among military personnel in the last two decades [6], and the prevalence of current smoking among Veterans is higher than among non-Veterans [6, 7]. Elevated prevalence of smoking is most substantial among male Veterans, who comprise the vast majority (94%) of those Veterans served by VHA [4]: smoking prevalence among Veteran vs. non-Veteran men is 50% vs. 35% for ages 18-25, 46% vs. 36% for ages 26-34, and 32% vs. 26% for ages 35-49 [7].

2.1.2 Veterans who smoke, particularly those receiving care through VHA, are a socioeconomically disadvantaged population. As stated in the FOA under which this application is being submitted (i.e., PAR-18-250, "Improving Smoking Cessation in Socioeconomically Disadvantaged Populations via Scalable Interventions"), Veterans represent an important subgroup of socioeconomically disadvantaged smokers. VHA serves an estimated 75% of all low-income and disabled Veterans [6]. Although VHA has always served as a safety-net health care provider in the US, the Affordable Care Act and health care reform have increased the proportion of VHA users who are low-SES [8-10]. Only 40% of Veterans served by VHA are in the labor force, and the median household income is just $35,999 [4]. Consistent with larger US population trends, within VHA, current smoking is associated with the lowest levels of income, educational attainment, and employment [11].

2.1.3. Novel interventions are needed to help Veterans quit smoking. There are a number of limitations to the smoking cessation treatment approaches currently available to socioeconomically disadvantaged Veterans receiving care through VHA, which include local options for group and individual counseling as well as centrally managed population health programs like the VA quitline, text messaging program, Stay Quit Coach app, and SmokefreeVET web site. Two major limitations are: (1) mismatch on readiness to quit: they rely on standard treatment approaches that are designed to meet the needs of smokers who are planning to quit in the near future (e.g., next 30 days), which is only approximately 20% of current smokers [12], and (2) low accessibility and/or engagement: traditional cessation programs like group or individual counseling are under-resourced to assist even those Veterans who are highly motivated to quit [6, 13] and they have limited reach, with only 0.9%of Veteran smokers served by the VHA receiving the US Public Health Service recommendation [14] of four or more sessions of intensive (≥10 min) cessation support [13]. Digital cessation interventions are more accessible, particularly where tobacco cessation is under-resourced, but maintaining engagement with electronic health (e-Health) interventions is a challenge [15] that requires innovative design solutions. These limitations of current treatment options are problematic not just for Veterans but for socioeconomically disadvantaged smokers more broadly, as they are less likely to be planning to quit in the near future, less likely to make a quit attempt, and, when they do attempt to quit, less likely to engage with traditional treatments and instead make unaided quit attempts relative to smokers who are not socioeconomically disadvantaged [16, 17].

2.1.4. ACT is an effective new treatment option for smokers ready to quit. Acceptance and Commitment Therapy (ACT) [18, 19] is similar to standard smoking cessation treatment in that it promotes awareness of the cues that trigger smoking behavior, but different in that ACT teaches skills to promote acceptance of triggers

(e.g., mindfulness) rather than trigger avoidance. Empirical support for ACT comes from six trials that enrolled over 3,600 smokers. Collectively, these studies support the feasibility and efficacy of ACT in comparison with pharmacotherapy-only treatments and traditional behavioral treatments. In 5 of 6 studies, 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, and in the most recent study conducted by Dr. Heffner and colleagues (R01CA166646: PI: J. Bricker), both ACT and the comparison treatment produced similarly high quit rates at 1-year post-randomization (24% vs. 26%, p=.334) [20]. Importantly, ACT is acceptable and shows evidence of efficacy for smokers with mental health conditions [21-24], which are highly prevalent among Veterans [13] and among low SES smokers more broadly [25], may interfere with quitting [26], and are not addressed in standard cessation treatments. Taken together, these findings suggest that ACT is at least as effective, if not more effective, than standard treatment approaches and that it uniquely addresses some of the challenges to cessation among low SES smokers.

2.1.5. Flexiquit: Engaging, web-based ACT for smokers at all levels of quit readiness. 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 smokers 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. Our collaborator, Dr. Karekla, developed the first ACT program designed for smokers at all stages of readiness to quit. This web-based program, Flexiquit, is also innovative in its use of gamification and virtual coaches 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 virtual coach 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 email (from Fogg's Behavior Model for Persuasive Design [27]). Additionally, the virtual coach as the embodiment of a supportive peer fits VHA organizational values. VHA is the country's largest employer of peer support specialists, recognizing the unique importance of peer support to Veterans—particularly those with mental health conditions—who may feel isolated and unable to relate as well to non-Veterans (see letter of support from Patricia Sweeney, VISN 1 MIRECC Peer Education Director).

2.1.6. Flexiquit is packaged for scalability. A significant benefit of web-based interventions is that they have high potential reach and scalability. Currently, 76-80% of Veterans use the internet at home or on mobile devices [28, 29]. In addition, 56-76% of Veterans are interested in using web-based VHA health-related programs [28, 29]. Not only do web-based treatments have strong appeal to consumers [30], they are also highly transportable into clinical settings relative to individual or group interventions that require practitioners to be willing and able to implement a new treatment model with an acceptable level of fidelity [31]. The cost-effectiveness of web-based treatments is also 5 to 10 times greater than other models of treatment delivery such as clinic-, workplace-, and telephone-based interventions [32]. In settings that serve predominantly low-SES smokers, like VHA or Federally Qualified Health Centers, low-cost tobacco interventions effectively reduce organizational and individual financial barriers to treatment utilization and increase scalability.

2.2 Clinical Data to Date

2.2.1. Flexiquit preliminary acceptability and efficacy. Flexiquit was evaluated in 105 university student smokers, aged 18-28 years old (M age=22.50, SD=2.56; 45 females). Participants were randomly assigned in a 2:1 ratio to either Flexiquit (n=70) 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 60% completed all 6 sessions. 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 improvements 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 virtual coach and technical

improvements to improve usability across web browsers and on smartphones. Compared to a wait-list control group, quit rates for Flexiquit were significantly higher at post-treatment (51.9% vs. 14.3% in the waitlist control group, OR = 6.46, 95% CI = 1.76 – 23.71, p = .005), demonstrating a strong signal for efficacy.

2.3 Risks/Benefits

Patients will be told that the study may involve the following risks and/or discomforts. Some participants may quit smoking during this study and experience the physical and psychological consequences of smoking abstinence, such as nicotine withdrawal symptoms. Participants will be informed of the discomfort associated with nicotine withdrawal, including common withdrawal symptoms, and that nicotine withdrawal may exacerbate some psychiatric symptoms (e.g., depressive symptoms). 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 smoking. Additionally, some participants may feel emotional upset while answering some of the research questions. There is also a small risk of breach of confidentially.

Participants in this research will receive access to a web-based smoking cessation intervention at no cost. This research may help some participants quit smoking or cut back on how much they smoke, thus dramatically reducing their chances of developing tobacco-related health conditions. Findings from this research will provide knowledge about ways to better help socioeconomically disadvantaged Veterans quit smoking.

3.0 OVERVIEW OF CLINICAL TRIAL

3.1 Study Objectives

3.1.1 Primary Objectives: Compare the relative acceptability of Vet Flexiquit vs. SmokefreeVET among socioeconomically disadvantaged US Veterans, as indicated by treatment satisfaction and objective measures of web site utilization.

3.1.2 Secondary Objectives: Preliminarily evaluate effects of Vet Flexiquit vs. SmokefreeVET on quit attempts and abstinence rates as well as readiness to quit and acceptance of smoking triggers—ACT's theory-based mechanism of chang*e.*

3.2 Study Population

Participants will be 50 US Veteran cigarette smokers who are interested in using a web-based intervention designed to motivate and support smoking cessation.

Inclusion of Women & Minorities

We will actively seek both male and female participants. Consistent with the US Veteran population served by VHA, we expect that, without targeted recruitment, the sample would be predominantly (94%) male. To allow for exploration of sex differences in the acceptability or efficacy of treatment, we will oversample women to achieve 25% representation in the sample. To do so, we will advertise in Women's Health clinics and use electronic medical records to identify all potentially eligible women and contact them until the 25% target is met.

We will also make every effort to ensure that members of diverse racial/ethnic groups are adequately represented in the study. The Bedford VAMC population is about 3% Hispanic/Latino, approximately 1% Native American and 4% Black/African American. This study will aim to be representative of the national racial/ethnic diversity among Veterans and include about 19% representation of minorities, following similar methods of targeted recruitment as described above. However, given the small percentages of women and minorities represented at the Bedford VAMC, future research on Vet Flexiquit would be needed to evaluate the impacts of this intervention specifically on women and minorities.

3.3 Study Design

The research plan is consistent with Stage Ib of the NIDA Behavioral Therapies Development Model [33]. We will conduct a pilot feasibility trial in which participants are randomized to one of two websites—Vet Flexiquit (n=25) or a standard care comparison web site (SmokefreeVET) (n=25). Participants will be asked to complete follow up surveys at 1 and 3 months via telephone or VA Video Connect.

3.4 Primary Endpoints:

- Satisfaction with assigned treatment at 3-months post-randomization
- Website utilization: number of server-recorded logins to assigned website at 3-months; duration of website use from first to last login

3.4.1 Secondary Endpoints:

- Number of quit attempts at 3-months
- Cotinine-confirmed, self-reported abstinence from smoking in the 7 days prior to the 3-month follow-up
- Cotinine-confirmed, self-reported abstinence from smoking in the 30 days prior to the 3-month follow-up
- Self-reported abstinence from all nicotine and tobacco products (except nicotine replacement therapy) in the 7 days prior to the 3-month follow-up
- Change in readiness to quit as measured by the Contemplation Ladder from baseline to 3-month follow-up
- Change in acceptance of smoking triggers as measured by the AIS from baseline to 3-month follow-up

3.5 Estimated Accrual

We estimate that the 50 subjects for the proposed study will be recruited over the course of approximately 9 months. Of the 50 participants randomized into the pilot study, we project a 15% attrition rate, resulting in an estimated sample of 42 treatment completers across the two treatment groups.

3.6 Name of Sponsor/Funding Source

National Cancer Institute - 1R21CA236980

4.0 SUBJECT ELIGIBLITY

4.1 Inclusion Criteria

4.1.1 Demographic Criteria

- Participants must be a US Veteran
- Participants must be age 18 or older
- Participants must be low-income, as defined by falling below VHA national income threshold for no-cost healthcare

4.1.2 Smoking Criteria

- Participants must be a current smoker, averaging at least 5 cigarettes/day for the last 30 days

4.1.3 Treatment accessibility Criteria

- Participants must have weekly Internet access for the next 3 months
- Participants must self-report current use of a personal email address to receive the link to their assigned web site

- Participants must self-report being willing to complete all study activities
- Participants must be willing to receive study-related text messages
- Exclusion Criteria
- Currently taking part in any other smoking cessation treatment such as the nicotine patch, nicotine gum, Zyban, in-person counseling, telephone counseling, using a web-based or app-based cessation program
- Have recent (past 30 days) substance use disorder, suicidal ideation, or psychiatric hospitalization
- Previous participation in the treatment development stage of Vet Flexiquit
- Prior use of the SmokefreeVET web site
- Member of the same household as another research participant
- Woman who is pregnant or breastfeeding, or planning to become pregnant

5.0 SUBJECT REGISTRATION

Participants will primarily be recruited from Dr. Kelly's Tobacco Cessation Program at the Bedford VAMC, but we will recruit throughout the Bedford VA.

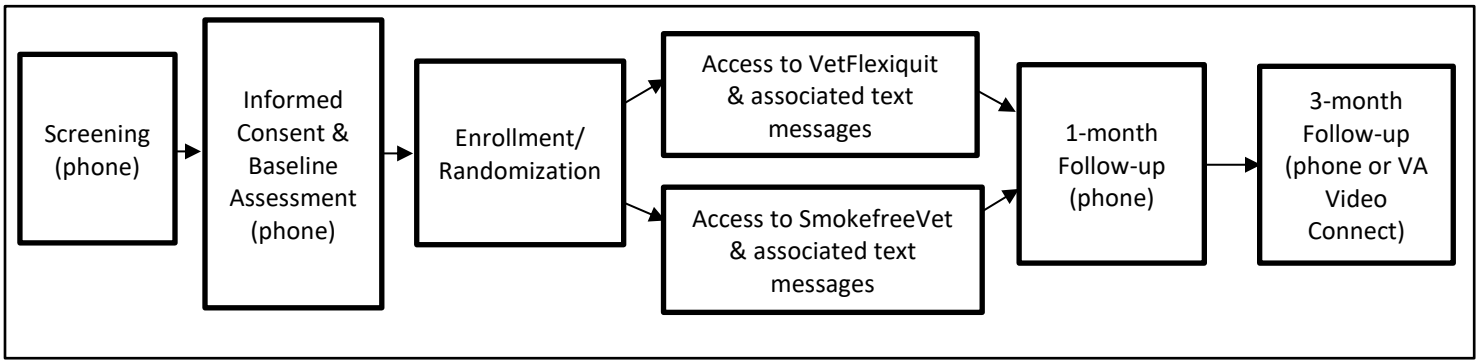
5.1 Subject Identification and Pre-Enrollment Screening:

Participants will primarily be recruited from Dr. Kelly's Tobacco Cessation Program at the Bedford VAMC. Based on the characteristics of Veterans in this clinic, 400 Veterans would meet eligibility criteria for the study during the enrollment period. We will also recruit from the Mental Health Service Line. Approximately 1840 other Veterans at the Bedford VAMC would meet study criteria. Therefore, we do not anticipate difficulty recruiting the proposed number of participants, which would be 3% of eligible Veterans. Monitoring of recruitment will be done weekly and reported and discussed during weekly conference calls. We anticipate that this granular attention to ongoing recruitment will lead to successful enrollment of participants.

Potential participants will be screened by phone to determine eligibility. These screens will be scripted and completed by trained interviewers. Eligible individuals will be invited to complete the first study visit by telephone. At the beginning of that visit, participants will be provided with detailed information about the study, and verbal consent will be obtained following the guidelines of the Bedford VAMC Institutional Review Board. Following informed consent, participants will complete remaining study procedures. Those ineligible to participate will be provided with information about other resources to help them quit smoking.

6.0 TREATMENT PLAN

Figure 1. Study Flow Chart



6.1 Intervention Overview:

Both web-based interventions will be accompanied by a text messaging program that includes: (1) motivational messages, and (2) reminders to use the assigned program. The content of the motivational messages will differ based on the distinct treatment approaches employed in each arm (see Table 2 below). Both web sites (Vet Flexiquit and SmokefreVET) will cover core smoking cessation content areas [14], including coping skills, motivation, and relapse prevention. Key differences in the interventions are described below in Table 2.

Table 2

Area	Vet Flexiquit	SmokefreeVET
Overall treatment approach	Acceptance and Commitment Therapy	Heterogeneous techniques most closely aligned with cognitive-behavioral therapy
Coping skills training content	**Acceptance-based:** Coping skills focus on mindfulness and non-judgmental acceptance of uncomfortable internal states like cravings and negative affect	**Avoidance-based:** Coping skills focus on avoiding triggers, distracting attention from cravings, and behavioral substitutes for smoking
Approach to motivational enhancement	**Values:** Identification of what is most meaningful to an individual and consideration of how current behavior does or does not align with values; use of personal values to guide development of committed action plans	**Reasons:** Information about health consequences of smoking and benefits of quitting, encouragement to consider personal reasons for quitting
Approach to relapse prevention	**Responding to slips:** Metaphors and perspective-taking exercises to facilitate self-compassion and re-commitment to valued action **Handling high-risk situations:** Acceptance-based coping skills	**Responding to slips:** Analysis and problem-solving of what led to the slip and how to prevent it from happening again **Handling high-risk situations:** Avoidance-based coping skills
Structure	Structured, curriculum-based	Unstructured, informational
Directiveness	Prompting via emailed assignments to practice ACT skills, reduce smoking, and set a quit date	No specific prompting to take action
Gamification	Points/badges for completing activities, game aesthetics (virtual world)	None
Virtual Coach	Virtual coach is presented as a Veteran peer who is an ex-smoker, shares own quit story. User selects preferred coach from available options.	None

Vet Flexiquit Content. Consistent with the original Flexiquit program, Vet Flexiquit will contain 6 sessions designed to be completed in order, spaced out over a minimum of 3 days between sessions, with automated pacing and prompting from the program. Each session takes approximately 25 minutes to complete. Text messages reminders are used to prompt completion of the next session. Because Vet Flexiquit is designed for smokers at all stages of readiness to quit smoking, prompts to reduce smoking and set a quit date do not happen until later sessions. At the end of the program, users are sent an email with all session handouts.

Session 1 introduces the virtual coach, who provides an overview of the program and shares her own story of quitting. Users complete an interactive game to identify personal values guiding quitting and review quit stories from other Veterans. 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 smoking 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. 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 the past week's successes and difficulties, introduces the acceptance strategy of willingness as a means of handling smoking triggers, and covers relapse prevention via self-compassion and re-commitment to quitting. Session 6 also starts with a reflection on the past week's successes and difficulties, reviews content from previous sessions, and ends with a video emphasizing the importance of letting go of the need to control internal experiences like feelings,

sensations, and thoughts. Like SmokefreeVET, Vet Flexiquit will include links to VHA resources like the VA Quitline, local and national tobacco cessation resources, information about smoking cessation medications, and a link to the VA Crisis Line. As such, differential encouragement of non-study treatments will not be a confounding factor in evaluating the novel content of Vet Flexiquit.

SmokefreeVET Content. The control intervention will be SmokefreeVET. This web site was designed to promote smoking cessation among Veterans by providing educational materials about cessation treatments, tools to cope with urges and relapse, how to stay motivated, and brief tips for Veterans with depression and anxiety, substance use disorders, HIV, and other physical and mental health problems. Content is consistent with US Clinical Practice Guidelines [14] for tobacco treatment, which include heterogeneous techniques most closely aligned with cognitive behavioral therapy [46]. Because the web site is publicly available, a local copy will be permitted for study purposes in order to (1) prevent changes to the site while the study is ongoing, and (2) mask the name of the site to prevent treatment contamination or bias.

6.2 Concomitant Medication

Individuals who report using any quit smoking treatment, including FDA-approved quit smoking medications (e.g., nicotine patch, nicotine gum, Zyban), during the screening phase will not be eligible to participate in the study. At the 1-month phone check in appointment and at the 3-month follow-up assessment, participants will be asked about their use of FDA-approved quit-smoking medications. Initiating use of these medications during the study is allowed.

6.3 1- and 3-Month Follow-up Data Collection

Participants will be invited to complete follow-up assessments at 1-month and 3-months post-randomization. All assessments will be administered by telephone or VA Video Connect by trained study staff. A complete schedule of assessments can be found in section 7.0 Subject Evaluation, but will assess smoking, adverse events, and concomitant treatment.

At follow-up, we will make reminder calls 2-3 days before the scheduled appointment, which will take place by phone or VA Video Connect (VVC). Following our data collection protocol used in previous trials, we will collect email, phone number, mailing address, and contact information on at least two collateral contacts. These methods yielded an 85% follow-up rate in our other studies of digital health interventions for smoking cessation. If completion rates are substantially lower after the first 20 participants have been contacted for follow-up, we will consider adding postcards containing only the two primary outcome questions to the multimodal survey protocol, following the mailing of the full survey.

6.4 Participant compensation.

Participants will receive an incentive of a $15 gift card for completing the briefer, 1-month visit and a $25 gift card for the baseline and 3-month follow-up visit.

7.0 SUBJECT EVALUATION

7.1 Data Collection Overview

Table 1. Schedule of assessments for pilot trial

Measure	Screening (phone)	Baseline (person)	1-month follow-up (phone)	3-month follow-up (Phone or VA Video Connect)	Primary Purpose
Eligibility criteria *(~11 items)*	X				Eligibility
Demographics *(~10 items)*		X			Eligibility, sample description
FTND *(6 items)*		X			Sample description
Contemplation Ladder *(1 item)*		X	X	X	Sample description, stratification, efficacy
Outside tobacco treatment use *(~2 items)*			X	X	Acceptability, efficacy
Treatment satisfaction *(~8 items)*				X	Acceptability
Tobacco/Nicotine use *(~12 items)*		X	X	X	Efficacy
Avoidance and Inflexibility Scale *(27 items)*		X		X	Mechanism of change
Saliva Cotinine				X	Efficacy
Total number of items	*11 items*	*57 items*	*15 items*	*59 items*	
Estimated duration	*5-10 min*	*25-30 min*	*10 min*	*25-30 min*	

7.1.1 Assessments/On-Study Clinical Evaluations. A complete schedule of assessments is provided in Table 1.

Eligibility, sample description, and stratification variables: Demographics assessed at baseline will include age, gender, education, employment, income, number of dependents, and marital status. The baseline survey will also assess smoking and quitting history for purposes of sample description. The 6-item Fagerström Test for Nicotine Dependence (FTND) [40] will be used to assess degree of physical dependence on nicotine and the 1-item Contemplation Ladder [39] will be used to assess readiness to quit smoking.

Acceptability will be assessed using measures of treatment utilization and satisfaction. The primary treatment utilization outcome will be number of log-ins to the assigned web site, with a secondary outcome of time from first to last use. Consistent with our prior studies, satisfaction will be assessed with 8 items on the 3-month outcome survey, covering both overall satisfaction and satisfaction with specific program components. Specifically, the satisfaction survey contains forced-choice response items assessing overall satisfaction, whether participants would recommend the program to a friend, and satisfaction with the program's content, organization, and ease of use. Open-ended questions will inquire about what participants liked most and least about their assigned program. Acceptability measures will be administered last to prevent unblinding of intervention group assignment until the end.

Efficacy for smoking cessation will be assessed as the 7-day point prevalence abstinence at 3-months post-randomization ("Have you smoked at all, even a puff, in the last 7 days?"), biochemically confirmed by saliva cotinine < 10 ng/mL on a NicAlert test strip, Secondary efficacy endpoints include: (1) cotinine-confirmed 30-day point prevalence abstinence at 3-months post-randomization, (2) self-reported 7-day PPA from any nicotine or tobacco products other than FDA-approved cessation medications, and (3) increase in readiness to quit on the Contemplation Ladder. Use of all nicotine and tobacco products will be measured at baseline and each follow-up. For all endpoints involving biochemical verification, abstinence from smoking will limited to self-report only participants who are using other sources of nicotine (either therapeutic or non-therapeutic), as saliva cotinine testing cannot distinguish between smoked tobacco and other sources of nicotine. Saliva cotinine test strips will be sent by mail to Veterans a few days ahead of their 3-month follow-up visit via telephone or VA Video Connect (VVC). Veterans will be instructed on how to use the test strip and how to read it, and will report the results to study staff over telephone or VVC. Veterans can then throw away the test strip after it has been used.

Efficacy for impacting ACT's theory-based mechanism of change will be assessed using the 27-item Avoidance and Inflexibility Scale (AIS) [43] at baseline and 3-month follow-up to measure changes in acceptance of smoking triggers.

Other measures. Use of other behavioral and pharmacological interventions for tobacco cessation will be assessed at each follow-up point.

7.2 Enrollment Procedures.

At the beginning of the first telephone visit, participants will be provided with detailed information about the study, and verbal consent will be obtained following the guidelines of the Bedford VA Medical Center Institutional Review Board (details below). Following informed consent, participants will complete study procedures as outlined in the research plan. Potential subjects who screen ineligible to participate will be provided with information about other resources to help them quit smoking.

Our methods allow for remote study visits (phone/VA Video Connect) in light of the COVID-19 pandemic. It is not practicable to obtain written informed consent in a timely manner and asking people who may be self-quarantining to mail back a signed consent form may pose risk to the participants. Therefore, we will be implementing a verbal consent process. We will review an information sheet about the study and ask if they have any questions. We will assure the privacy of participants by asking them to use a private space, rather than

a shared office or common area, to speak with us. The information sheet will explain in simple terms the risks and benefits to the patient. The information sheet will contain a statement that the consent is freely given, that the patient is aware of the risks and benefits of entering the study, and that the patient is free to withdraw from the study at any time. Consent will be obtained after a thorough explanation of the study by the PI or other study personnel (e.g., research assistant, postdoctoral fellow), and an opportunity for the participant to ask questions about the study. This discussion will take place under conditions in which the participant has adequate time to consider the benefits and risks associated with his/her participation in the study.

Only participants capable of giving informed consent will be admitted into the study. Informed consent will be obtained by trained and highly qualified research personnel. The research staff member that conducts the informed consent process will ask each participant to verify that the information in the consent form is understood. The staff member will review understanding of the consent form, including information pertinent to study participation. During the informed consent process, we will assess whether the Veteran is competent to provide informed consent. We will determine whether the Veteran is oriented to time, place, and person. We will ask questions to understand whether the Veteran understands the basics about what the study protocol involves. We will assess whether the consequences of participating in the study are understood. We will also assess whether the Veteran is able to clearly and voluntarily express his or her preference for participating in the study. If the Veteran is not able to do these things, we will determine that the Veteran is not competent to provide informed consent and we will end the informed consent process. Only once all questions have been answered and the participant understands the purpose of the study and study procedures will the participant be asked for verbal consent.

It will be the responsibility of the site PI (Dr. Kelly) to assure that informed consent is obtained from each participant prior to the performance of any protocol procedures and in accordance with current state and federal regulations.

8.0 SUBJECT DISCONTINUATION OF ACTIVE TREATMENT

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

9.0 CONCOMITANT MEDICATIONS

Individuals who report using any other quit smoking treatment, including FDA-approved quit smoking medications (e.g., nicotine patch, nicotine gum, Zyban), during the screening phase will not be eligible to participate in the pilot study. At the 1-month telephone check in and during the 3-month follow-up assessment, participants will be asked about their use of FDA-approved quit-smoking medications. Initiating use of these medications during the study is allowed.

10.0 ADVERSE EVENTS

This is a low-risk study with no intervention agent/drug. Because this is a smoking cessation intervention, some participants may quit smoking cigarettes and may experience the physical and psychological consequences of smoking 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 smoking cessation (e.g., nicotine patch) and how to obtain these medications. Any adverse events detected during this study will be recorded in the Adverse Event Summary Form and will be reported as follows.

Participants who report feeling upset as a result of responding to study assessment items will be given the option to speak with the site PI for the pilot trial. Dr. Kelly is a clinical psychologist. The PIs will consult as needed to address any adverse events that are reported by participants.

Dr. Kelly will follow VA IRB requirements for reporting of Adverse Events.

10.1.1 Unexpected Adverse events.

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 subject 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 subject and is considered clinically significant. All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the study treatment will be recorded throughout the study and reported to the PIs. The PIs will collaboratively determine whether there is a causal relationship between the study treatment and AEs. 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 PIs.

Serious Adverse Event. 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 subject 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 at the discretion of the PIs. It will be the responsibility of the site PI to report all SAEs and/or make referrals for appropriate care.

10.2 Monitoring and Recording Adverse Events

Adverse events will be monitored during the 1-month phone check in appointment and at the 3-month follow up, in person study visit.

10.3 Grading Adverse Event Severity

All AEs will be graded in severity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the adverse event.

10.4 Adverse Event Recording Period

The PIs will be notified within 24 hours by the VA study coordinator after learning of any adverse events or of any early terminations due to an adverse event.
All adverse events will be recorded and reported to the VA IRB per the VA institutional guidelines.

10.5 Adverse Event Reporting Requirements

A summary of the investigation including all adverse events and how they were handled, enrollment, drop-outs and reason for discontinuation and any protocol modifications will be provided to the VA IRB and to the Fred Hutchinson Cancer on an annual basis.
Annual Reports will contain:

a. The number of adverse events and an explanation of how each event was handled
b. The number of complaints and how each complaint was handled
c. The number of subject withdrawals and an explanation of why the subject withdrew or was withdrawn

d. The number of protocol deviations and how each was handled

Any serious and unexpected event may prompt changes in the study protocol. Any such change will be approved by the VA IRB before implementation.

10.5.1 Reporting to Sponsor

Dr. Heffner's study team will report all SAEs to the funding agency within 72 hours of their discovery.

10.5.2 Reporting to IRB

The investigators or designee must report events to the FHCRC and to the VA IRB in accordance with the policies of the local IRB. The site PI (Dr Kelly) will be responsible for making SAE reports to the VA IRB and to Fred Hutchinson Cancer Research Center study staff.

11.0 DATA AND SAFETY MONITORING PLAN

Institutional support of trial monitoring will be in accordance with the Fred Hutch/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan.

Given that this is a low-risk, pilot trial of two behavioral interventions for smoking cessation, monitoring of participant safety and data quality will be overseen jointly by the PIs, who will have bi-monthly conference calls to discuss study progress, including recruitment and retention, adverse events, and protocol adherence.

12.0 DATA MANAGEMENT/CONFIDENTIALITY

The investigator will ensure that data collected conform to all established guidelines. Each subject is assigned a unique subject number to protect subject confidentiality. Only VA 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 VA project staff. All workstations and servers are physically secured in locked offices, reside behind the VA 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 patient identifiers or data be provided to any person or entity outside the VA 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 VA IRB. We will limit our acquisition of identifiable information to the minimum amount of information necessary to link subject 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 the VA IRB policy. 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 VA Information Security Officer of such action.

Datatope will host the intervention websites behind Fred Hutch firewall. Datatope will have access to participant first name, email address, mobile phone number for delivering the website intervention and the accompanying text messages. All of the text communication with study participants will occur over Secure Sockets Layer (SSL)

and no information or phone number will be shared by anyone other than VA IRB approved study staff. Datatope will be randomizing participants to one of two websites and will have access to stratification variables needed for the randomization.

Both Vet FlexiQuit and a copy of SmokefreeVET will be hosted internally by FHCRC so that we can collect website utilization data for all participants. Paper research files will be kept at the Bedford VAMC in a locked cabinet where data will be encoded with ID numbers and on a secure VA SharePoint site that will be used solely for this study. IDs will be unrelated to any identifying information. Data will be checked for inconsistencies, omissions, and errors. The research assistant will receive training in data management and confidentiality procedures and will be responsible for data entry and management.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design

Pilot randomized controlled trial with two intervention arms.

13.2 Primary/Secondary Endpoints/Hypotheses and Analytical Methods

Although we do not expect to find statistically significant differences between treatments due to the underpowered feasibility trial design, we will nonetheless conduct inferential analyses in addition to determining effect size estimates as part of our efforts to characterize the signal for acceptability and efficacy of Vet Flexiquit. To evaluate Sex as a Biological Variable, we will descriptively examine results broken down by sex to determine potential relationships between sex and outcomes that could be explored in future work.

Analyses will be conducted as follows:

Aim 1. Compare the relative acceptability of Vet Flexiquit vs. SmokefreeVET among socioeconomically disadvantaged US Veterans, as indicated by treatment satisfaction and objective measures of web site utilization. Satisfaction ratings with Flexiquit components of virtual coaches, gamification, and interactive ACT exercises will be presented descriptively. Treatment satisfaction items are reported on a Likert-type scale, with response choices ranging from "not at all satisfied" to "very satisfied". We will dichotomize values at a threshold of "somewhat satisfied" or higher. We will test for differences between arms using a logistic regression model with adjustment for the stratification variable, baseline readiness to quit (high vs. low) (see Section 13.4), as well as adjustment for any baseline variables that differ between study arms and are associated with the outcome (i.e., potential confounders). To compare treatment effects on the count outcome number of logins, we will use negative binomial regression with adjustment for the stratification variable, baseline readiness to quit (high vs. low), as well as adjustment for any baseline variables that differ between study arms and are associated with the outcome (i.e., potential confounders). We will use the same method to compare treatment groups on the secondary acceptability outcome of duration of site usage (number of days elapsed from first to last use). Adjustment of analysis models for the stratification variable ensures that the data analysis is aligned with the study design.

Aim 2. Preliminarily evaluate the effects of Vet Flexiquit vs. SmokefreeVET on quit attempts and abstinence rates as well as readiness to quit and acceptance of smoking triggers—ACT's theory-based mechanism of change. Binary endpoints of abstinence include: (1) both cotinine-confirmed and self-reported abstinence from smoking in the 7 days prior to the 3-month follow-up, (2) both cotinine-confirmed and self-reported abstinence from smoking in the 30 days prior to the 3-month follow-up, and (3) self-reported abstinence from all nicotine and tobacco products (except nicotine replacement therapy) in the 7 days prior to the 3-month follow-up. To compare each of these binary endpoints of smoking abstinence between arms, we will use a logistic regression model with adjustment for the stratification variable, baseline readiness to quit (high vs. low), as well as adjustment for any baseline variables that differ between study arms and are associated with the outcome (i.e., potential confounders). To compare the count outcome number of quit attempts between arms, we will use a

negative binomial model with adjustment for the stratification variable, baseline readiness to quit (high vs. low), as well as adjustment for any baseline variables that differ between study arms and are associated with the outcome (i.e., potential confounders). Change score endpoints include change in AIS scores and change in Contemplation Ladders scores. To compare each of these endpoints between study arms, we will calculate change score as follow-up minus baseline score and use a linear regression model with adjustment for the baseline value of the measure of interest and for the stratification variable, baseline readiness to quit (high vs. low), as well as adjustment for any baseline variables that differ between study arms and are associated with the outcome (i.e., potential confounders).

Missing data: Consistent with the Russell standard for smoking cessation trials, participants with missing smoking data will be considered non-abstinent [48] in the primary analysis. As a sensitivity analysis, we will also report abstinence rates using multiple imputation and complete case analyses. Treatment acceptability and mechanism of change (i.e., AIS scores) will be analyzed using complete case analysis, as there is no reasonable method of imputing these data.

13.3 Sample Size and Power

Sample Size: We plan to accrue a total of 50 participants in the pilot trial for a balanced design. A sample size of 25 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 in order to test intervention feasibility [33

Power: As a pilot treatment development project, this study is not designed for power to detect statistically significant differences by treatment group. However, we plan to compare the outcomes of the two interventions to obtain a preliminary estimate of effect size. We will use these pilot data to optimize the treatment and study design and prepare for a rigorous test of the efficacy of Vet Flexiquit in a subsequent R01. We plan to accrue a total of 50 patients in the pilot trial for a balanced design.

13.4 Randomization

Eligible participants will be randomized via a web-based system at the baseline visit using an automated algorithm. A permuted block design with random blocks of size 2 and 4 will be used to balance randomization on the stratification variable: high (>5) or low (5 or less) readiness to quit on the Contemplation Ladder [39]. Participants will receive an email with a link to their assigned web site. Investigators and participants will be blinded to both allocation sequence and random intervention assignment. This same procedure has been used in 3 prior Fred Hutch studies of technology-delivered interventions for smoking cessation.

13.5 Ethnic and Gender Distribution Chart

Projected Target Accrual
ETHNIC AND GENDER DISTRIBUTION CHART

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	1	0	0	0	1
Asian	0	3	0	0	3
Native Hawaiian or Other Pacific Islander	1	0	0	0	1

Black or African American	3	3	1	0	7
White	5	29	1	2	37
More than One Race	1	0	0	0	1
Total	11	35	2	2	50

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

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APPENDICES