CLINICAL STUDY PROTOCOL

Tech and Telephone Smoking Cessation Treatment for Young Veterans with PTSD

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Confidentiality Statement:

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Synopsis

Primary Objective

Aim 1: To iteratively adapt the evidence-based IC treatment manual into a technology- and telephone-facilitated smoking cessation treatment for veterans with PTSD, informed by stakeholder (CAP) and veteran (focus groups) feedback; and to examine the *feasibility* and *acceptability* of this intervention in young adult veteran smokers with PTSD.

Aim 2: To assess the impact of the adapted intervention on *treatment retention* compared to the standard of care (referral to VA Telephone Quitline).

Secondary Objectives (if applicable)

Exploratory Aims: We will examine the effect of the technology- and telephone-facilitated intervention on daily cigarette, e-cigarette, and smokeless tobacco use; nicotine dependence (Fagerström Test of Nicotine Dependence[16] [FTND]), and PTSD symptom levels (PTSD Checklist-5[17] [PCL-5]) at Weeks 8, 12, and 24; and bioverified seven- and 30-day point prevalence abstinence at Weeks 12 and 24.

Primary Outcome Variables

Primary Outcome Measures are as follows:

- We will assess *feasibility* as follows: a) proportion of those eligible among those screened; b) proportion enrolled among those eligible; c) the rate of enrollment per month; d) adherence to treatment; e) study completion rate.
- We will assess *acceptability* by collecting quantitative and qualitative data about the acceptability of the overall intervention and its components (telephone sessions, SQC app, iCO Mobile Smokerlyzer monitor) at follow-up assessments. Quantitative measures will include an acceptability measure developed by our team and the Client Satisfaction Questionnaire.

Secondary and Exploratory Outcome Variables (if applicable)

Secondary Outcome Measures are as follow:

- To examine intervention efficacy, we will assess assess abstinance and dependence through
- Daily cigarette, e-cigarette, and smokeless tobacco use
- Nicotine dependence (Fagerström Test of Nicotine Dependence[16] [FTND])
- PTSD symptom levels (PTSD Checklist-5[17] [PCL-5]) at Weeks 8, 12, and 24
- Bioverified seven- and 30-day point prevalence abstinence at Weeks 12 and 24

Study Duration

PHASE 1

Visit 1:	1.5 hours
Visit 2:	1 hour
Total:	2.5 hours

PHASE 2

Screening	4 hours
Visit 1/Week 1:	20-30 minutes
Visit 2/Week 2:	20-30 minutes
Visit 3/Week 3:	20-30 minutes
Visit 4/Week 4:	20-30 minutes
Visit 5/Week 5:	20-30 minutes
Visit 6/Week 6:	20-30 minutes
Visit 7/Week 7:	20-30 minutes

Visit 8/Week 8:	20-30 min session / 1-2 hr assessment
Visit 9/Week 12:	1-2 hours
Visit 12/Week 24:	1-2 hours
TOTAL:	10-15 hours

Study Design

Study Design: We propose a three year, two phase study comprised of (1) a nine-month Community Advisory Panel (CAP) plus Focus Group phase, in which we iteratively adapt the IC protocol to be delivered over the telephone and to incorporate technology components and gather feedback through focus groups with up to 10 veteran current or past smokers; and (2) a two-year Pilot RCT in which we examine the **feasibility and acceptability of the intervention** and assess its **efficacy in improving treatment retention in young adult veteran smokers with PTSD.** We will also preliminarily examine its impact on use of cigarette, e-cigarette, and smokeless tobacco use; PTSD symptom severity; and seven and 30-day point prevalence abstinence rates at three and six months post-randomization.

For the PHASE 1 **Community Advisory Panel (CAP)**, we will assemble a group of stakeholders (professional leaders in the areas of veteran behavioral health and/or smoking cessation) to adapt the manual to be delivered over the telephone and incorporate SQC app and iCO Mobile Smokerlyzer. For the PHASE 1 **Focus Groups**, we will recruit a group of 7-10 veterans, ages 18-50, who are current or former smokers to provide qualitative feedback on the revised treatment protocol.

For PHASE 2, we will conduct a pilot randomized controlled trial (RCT) in which we will randomize 80 veterans with posttraumatic stress disorder (PTSD), ages 18-39, to receive either (1) the telephone- and technology-facilitated PTSD-informed treatment (intervention condition, *n*=40) or (2) a VA Telephone Quitline control condition (*n*=40) over 8 weeks. Assessments will occur at Weeks 0, 8, 12, and 24.

Study Population

- Phase I: 7-10 veterans, between the ages of 18-50, who are current or past smokers.
- Phase II: 80 veterans, between the ages of 18-39, who have symptoms of PTSD and currently smoke cigarettes.

Number of Participants

- Phase I: 10 participants
- Phase II: 80 participants

Number of Study Sites

The study will be conducted at San Francisco VA Medical Center (SFVAMC) and affiliated Community Based Outpatient Clinics (CBOCs).

Visit Schedule Table (Optional)

Study Flow Chart (optional)

Abbreviations

Abbreviation	Explanation

Glossary of Terms

Glossary	Explanation

Table of Contents

1 - Introduction

1.1 Introductory Statement

This project aims to enhance the scalability of an office-based smoking cessation treatment protocol for veterans with posttraumatic stress disorder (PTSD), called Integrated Care (IC), by adapting it to be delivered over the telephone and incorporating mobile technology components. Mobile technology components include: (1) the Stay Quit Coach (SQC) mobile application (app) and (2) the iCO Mobile Smokerlyzer, a smartphone-compatible carbon monoxide monitor. In Phase 1 (Focus Groups), we will conduct two focus groups with up to 10 veterans who are current or former smokers, ages 18-50, to gain feedback on the manualized intervention to ensure it is acceptable to this population. In Phase 2 (Pilot Phase), we will conduct a pilot RCT in which we randomize 80 veteran smokers with PTSD, ages 18-39, to receive either (1) the telephone- and technology-facilitated intervention (n=40) or (2) the current standard of care (referral to the VA telephone Quitline [QL]) (n=40) as a control. All participants will receive a baseline (Week 0) office visit and will optionally be prescribed nicotine replacement therapy. Participants in the intervention condition will also receive eight 20- to 30-minute telephone counseling sessions and be encouraged to use the SQC app and iCO Mobile Smokerlyzer. Control participants will receive up to eight weekly proactive telephone sessions through the VA Telephone QL. Assessments will occur at baseline (Week 0), treatment end (Week 8), and at three months (Week 12) and six months (Week 24) post-randomization.

Aims: (1) to assess the feasibility and acceptability of the intervention; (2) to assess the impact of the adapted intervention on treatment retention compared to the current standard of care (i.e., referral to the VA QuitLine).

2 - Background

2.1 Background/prevalence of research topic

This project aims to examine the feasibility, acceptability, and potential efficacy of a tailored telephone- and mobile technology-delivered smoking cessation intervention for young veterans with posttraumatic stress disorder (PTSD). Smoking is a devastating and costly public health problem that disproportionately affects certain high-risk populations. According to the Centers for Disease Control, smoking prevalence in the general population has declined in recent decades(1,2), but has decreased only slightly among those with psychiatric disorders such as PTSD3 and is stable or increasing among military veterans.(2,4,5) Young veterans deployed to Iraq and Afghanistan smoke at epidemic levels ranging from 32-48%,(4,6,7) with highest risk in those with PTSD.(5) Smokers with PTSD experience high rates of lapse and treatment failure and require tailored strategies that target both PTSD symptoms and smoking urges.(12)

To address this need, researchers developed an integrated care (IC) protocol that delivers PTSD-informed cognitive behavioral therapy for smoking cessation plus pharmacotherapy.(12) Compared to Veterans Affairs (VA) smoking cessation clinic treatment, the IC protocol doubled 12-month smoking abstinence rates in veterans with PTSD. However, nonattendance and poor retention limited efficacy, with highest dropouts observed in young Iraq and Afghanistan veterans. Young veterans with PTSD have high rates of dropout from VA clinics and face numerous barriers to care.(5,13-15) Scalable and convenient telephone and mobile technology adaptations to this highly effective protocol may increase engagement and overcome barriers for young veterans. However, to date, no randomized controlled trial (RCT) has examined whether technology and telephone adaptations to the IC protocol could enhance engagement, retention, and treatment outcomes.

Individuals with PTSD are at high risk of failed quit attempts and often use smoking as a means of coping with stress, hyperarousal, and emotional numbing. Current models of smoking cessation treatment (VA smoking cessation clinic, QL) are not designed to address PTSD symptom exacerbations during quit attempts. While the IC protocol has demonstrated efficacy in improving quit rates relative to usual care in veterans with PTSD, the model fails to meet the needs of young veterans, residents of rural areas, and those who face logistical barriers to attend office visits. No RCT has yet been conducted to determine whether adaptations to the model improve retention and treatment outcomes in young veterans. To our knowledge, our proposed intervention is the first smoking cessation treatment iteratively designed and tested with young adult veterans to target the specific needs of this population. Young veterans with PTSD are at especially elevated risk of treatment failure and progression to chronic smoking. Those who reside in rural areas often lack access to care altogether. Given the health disparities faced by young veterans with PTSD, it is of urgent importance to develop cost-effective, targeted strategies to promote quitting early in life to reduce risk of tobacco-related disease and premature death in this vulnerable group.

3 - Rationale/Significance

3.1 Problem Statement

Smoking is a devastating and costly public health problem that disproportionately affects certain high-risk populations. According to the Centers for Disease Control, smoking prevalence in the general population has declined in recent decades,[1,2] but has decreased only slightly among those with psychiatric disorders such as PTSD[3]and is stable or increasing among military veterans.[2,4,5] Young veterans deployed to Iraq and Afghanistan smoke at epidemic levels ranging from 32-48%,[4,6,7] with highest risk in those with PTSD.[5] Smokers with PTSD experience high rates of lapse and treatment failure[8-11] and require tailored strategies that target both PTSD symptoms and smoking urges.

3.2 Purpose of Study/Potential Impact

Innovation: Individuals with PTSD are at high risk of failed quit attempts and often use smoking as a means of coping with stress, hyperarousal, and emotional numbing.[8,33] Current models of smoking cessation treatment (VA smoking cessation clinic, QL) are not designed to address PTSD symptom exacerbations during quit attempts. While the IC protocol has demonstrated efficacy in improving quit rates relative to usual care in veterans with PTSD, the model fails to meet the needs of young veterans, residents of rural areas, and those who face logistical barriers to attend office visits. No RCT has yet been conducted to determine whether adaptations to the model improve retention and treatment outcomes in young veterans. To our knowledge, our proposed intervention is the first smoking cessation treatment iteratively designed and tested with young adult veterans to target the specific needs of this population.

Impact: The public health impact of a scalable, tailored intervention for PTSD and smoking is high. PTSD affects both civilians and veterans[19,22] and is associated with a smoking prevalence far exceeding that of the general population, over 40%,[19-22] and related high morbidity and mortality.[19,20] Young veterans with PTSD are at especially elevated risk of treatment failure and progression to chronic smoking. Those who reside in rural areas often lack access to care altogether. Given the health disparities faced by young veterans with PTSD, it is of urgent importance to develop cost-effective, targeted strategies to promote quitting early in life to reduce risk of tobacco-related disease and premature death in this vulnerable group.

3.3.1 Potential Benefits

In PHASE 1, participants may derive satisfaction from participating in the design and development of a smoking cessation treatment delivered via telephone and technology that has the potential to benefit veterans with PTSD. For PHASE 2, participants engaging in the RCT may find that the participation promotes retention in treatment and may potentially lead to success in smoking cessation, consistent with our study hypotheses. Beyond these benefits, knowledge gained from this project could more broadly benefit veteran and civilian smokers with mental illness, young adult smokers, residents of rural areas, and high utilizers of technology.

3.3.2 Potential Risks

- Possible personal discomfort due to sensitive topics (stress, embarassment, trauma).
- Information on Illegal Drug Use: While we make every effort to maintain confidentiality, we will be asking many questions about the use of illegal substances. Given the event that confidentiality is breached and someone outside of the study finds out about a participant's illegal drug use, this can create issues in employment and benefits of a participant. Again, we will make every effort to ensure this information stays private amongst appropriate research staff.
- Nicotine withdrawal symptoms: People who quit smoking may experience withdrawal symptoms, including occasional (1 to 10%) irritability, fatigue, dizziness, restlessness, insomnia, and increased cough. These symptoms are temporary and usually go away within 2-3 weeks. Participants will have access to NRT to minimize this risk.
- Risk of use of nicotine replacement therapy (NRT): Participants will be given the option to receive nicotine replacement therapy (NRT). NRT will follow standard VA prescribing guidelines and will be based on (1) safety; (2) nicotine dependence level, and (3) participant preference. Receipt of medications in the study is optional and is not required for full participation in the trial. The potential risks of different formulations of NRT are summarized below.
- Nicotine patches: likely (> 10% risk): itching and redness of skin; less likely known risks (< 10% risk): skin rash (swollen red skin under the patch), diarrhea, an upset stomach, muscle aches, increased blood pressure, trouble sleeping or nightmares.
- Nicotine lozenges: likely (> 10% risk): diarrhea, upset stomach, muscle aches, increased blood pressure, trouble sleeping or nightmares.
- Nicotine gum: likely (> 10% risk): hiccups, nausea, coughing, heartburn, headaches, flatulence, fast heart rate, increased blood pressure, trouble sleeping, flatulence (gas), occasional muscle ache in the jaw may occur due chewing the gum, occasional sore throat or sore mouth, or potential ulceration of the mouth.
- Rare but serious risks of any NRT: There may be an increase in the possibility of a heart attack or stroke if participants continue to smoke while using the nicotine patch, lozenges, or gum at the same time. For this reason, you should not smoke while using these NRT products.
- Nicotine overdose symptoms are less common (< 10% risk) and may include very bad headache, confusion, dizziness, weakness, cold sweat, blurred vision, chest pain, and/ or vomiting.
- Pregnancy: NRT has not been deemed safe for use by pregnant women. The risks of using NRT during pregnancy are unknown.
- Accidental poisoning: NRT poisoning is a risk for participants with small children.

- Potential drug-drug interactions or difficulty metabolizing NRT: NRT may interact with the metabolism of other medications.

4 - Study Objectives

4.1 Hypothesis

We hypothesize that a higher proportion of intervention participants will complete four or more weekly sessions compared with control participants.

4.2 Primary Objective

Aim 1: To iteratively adapt the evidence-based IC treatment manual into a technology- and telephone-facilitated smoking cessation treatment for veterans with PTSD, informed by stakeholder (CAP) and veteran (focus groups) feedback; and to examine the *feasibility* and *acceptability* of this intervention in young adult veteran smokers with PTSD.

Aim 2: To assess the impact of the adapted intervention on *treatment retention* compared to the standard of care (referral to VA Telephone Quitline).

4.3 Secondary Objectives (if applicable)

Exploratory Aims: We will examine the effect of the technology- and telephone-facilitated intervention on daily cigarette, e-cigarette, and smokeless tobacco use; nicotine dependence (Fagerström Test of Nicotine Dependence[16] [FTND]), and PTSD symptom levels (PTSD Checklist-5[17] [PCL-5]) at Weeks 8, 12, and 24; and bioverified seven- and 30-day point prevalence abstinence at Weeks 12 and 24.

5 - Study Design

5.1 General Design

We propose a three-year, two-phase study comprised of (1) a nine-month Community Advisory Panel (CAP) plus veteran Focus Group phase, in which we iteratively adapt the IC protocol to be delivered over the telephone and incorporate technology components and gather feedback through focus groups with up to 10 veteran current or past smokers; and (2) a two-year Pilot RCT in which we examine the feasibility and acceptability of the intervention and assess its efficacy in improving treatment retention in young adult veteran smokers with PTSD. We will also preliminarily examine its impact on use of cigarette, e-cigarette, and smokeless tobacco use; PTSD symptom severity; and seven and 30-day point prevalence abstinence rates at three and six months post-randomization.

PHASE 1: For the Community Advisory Panel (CAP), we will assemble key stakeholders (i.e., leading professionals in the areas of veteran behavioral health and/or smoking cessation), as well as Focus Groups with up to 10 veterans ages 18-50 (current or past smokers) to adapt the manual to be delivered over the telephone and incorporate SQC app and iCO mobile Smokerlyzer.

PHASE 2: In the second phase, we will conduct a pilot RCT in which we randomize 80 veterans with PTSD ages 18-39 to receive either (1) the telephone-and technology-facilitated PTSD-informed treatment (intervention condition, n=40) or (2) a QL control condition (n=40) over eight weeks. Assessments will occur at Weeks 0, 8, 12, and 24.

5.1.1 Study Duration (if applicable)

The three year study includes: (1) a nine-month Community Advisory Panel (CAP) and Focus Group phase and (2) a two-year Pilot RCT.

5.1.2 Number of Study Sites

The study will be conducted at San Francisco VA Medical Center (SFVAMC) and affiliated Community Based Outpatient Clinics (CBOCs).

5.2.1 Primary Outcome Variables

We will assess feasibility as follows: a) proportion of those eligible among those screened; b) proportion enrolled among those eligible; c) the rate of enrollment per month; d) adherence to medications; e) study completion rate.

We will assess acceptability by collecting quantitative and qualitative data about the acceptability of the overall intervention and its components (telephone sessions, SQC app, iCO mobile CO monitor) at follow-up assessments. Quantitative measures will include an acceptability measure developed by our team and the Client Satisfaction Questionnaire.

5.2.2 Secondary and Exploratory Outcome Variables (if applicable)

We will examine the effect of the technology- and telephone-intervention on daily cigarette, e-cigarette, and smokeless tobacco use; nicotine dependence (Fagerström Test of Nicotine Dependence16 [FTND]) and PTSD symptom levels (PTSD Checklist-517 [PCL-5]) at Weeks

8, 12, and 24; and bioverified seven- and 30-day point prevalence abstinence at Weeks 12 and 24.

5.3 Study Population

- Phase I: Veterans between the ages of 18-50 who currently smoke cigarettes.
- Phase II: Veterans between the ages of 18-39 who have symptoms of PTSD and currently smoke cigarettes.

5.3.1 Number of Participants

- Phase I: 10 participants
- Phase II: 80 participants

5.3.2 Eligibility Criteria/Vulnerable Populations

Inclusion Criteria:

- PHASE 1

1. Male and female Veterans
2. Ages 18 to 50 (inclusive)
3. Self-identifies as current or prior smoker
4. Participant is smartphone (iOS or Android) user or comfortable using a smartphone
5. Ability to attend two focus groups and review the treatment manual before each session

- PHASE 2

6. Male and female Veterans eligible for VA services
7. Ages18 to 39 (inclusive)
8. Meets lifetime criteria for PTSD using the DSM-V
9. Smoked at least 5 cigarettes per day for 15 of past 30 days
10. Participant interested in smoking cessation and willing to receive interventions
11. Participant is a smartphone (iOS or Android) user or comfortable using a smartphone
12. Female participants must have a negative urine pregnancy test and must be practicing an effective method of birth control (e.g., surgically sterile, spermicide with barrier, male partner sterilization; or abstinent and agrees to continue abstinence or to use an acceptable method of contraception, as listed above, should sexual activity commence)
13. Ability to attend screening appointment in-person or via V-tel at San Francisco VA or associated clinic and participate in 8 weekly sessions, follow-up sessions at Weeks 12 and 24, and monthly nicotine replacement check-ins

Exclusion Criteria:

- PHASE 1

14. Psychiatrically or medically unstable in the clincial judgment of the PI or study physician based on chart review

- PHASE 2

15. Psychotic disorders, bipolar disorder, dementia, moderate to severe substance use disorders, or other psychiatric disorders judged to be unstable in the clinical judgment of the PI or study physician
16. Clinically significant unstable medical conditions, in the clinical judgment of the PI or study physician
17. Female participants who are pregnant
18. Concurrent participation in another smoking cessation study

6 - Methods

6.1 Intervention

Description of the Intervention: The intervention that we are designing and testing will be telephone- and technology-facilitated, PTSD-informed treatment for smoking cessation in young veterans with posttraumatic stress disorder (PTSD).

6.1.1 Description of Intervention

The original treatment manual includes eight weekly sessions focusing on tobacco use and PTSD psychoeducation, behavioral coaching tailored for smokers with PTSD, scheduling a quit date in Session 5, and providing skills for relapse prevention. PTSD-specific skills include: controlled breathing, coping plans to manage trauma-related triggers, and strategies to manage anxiety sensitivity, emotional numbing, and low mood (see Figure 4). Consistent with the office-based manual, sessions will occur weekly, with identical duration to the original IC protocol (20-30 minutes per session), and will include use of a modified workbook tailored to the manual. Telephone sessions will be scheduled weekly and phone calls will occur proactively (therapist calls participant). The content of the revised manual and workbook will be thematically similar in approach, topic areas, and content to the office-based manual, but will be revised to include: (1) an interactive question-and-answer format aimed at engaging the participant more actively during telephone sessions; (2) prompts instructing participants to access the workbook at the beginning and end of sessions to minimize interruptions; and (3) prompts directing the participant to utilize the SQC app and iCO Smokerlyzer. SQC app will be populated with personalized information such as reasons for quitting, a coping plan for managing PTSD and smoking triggers, and a medication plan. The iCO Smokerlyzer enables participants to test their breath CO level anywhere and download the readings to their smartphones for review during telephone counseling sessions.

Session	Week	Core Content of Eight Intervention Sessions
1	1	Assess nicotine dependence, identify reasons for quitting, encourage med adherence if prescribed meds; introduce behavioral plan to reduce cigarette use; reinforce SQC app and iCO use
2	2	Set quit date, identify smoking triggers and PTSD symptoms related to smoking; introduce controlled breathing and coping plans for triggers and PTSD symptoms; reinforce SQC app and iCO use
3	3	Review assignment to practice coping with smoking triggers and PTSD symptoms, develop action plan to manage triggers and

		symptoms, assess adherence with medications; reinforce SQC app and iCO use
4	4	Implement behavior changes to prepare for quit date while managing PTSD symptoms; reinforce SQC, iCO use
5 (Quit Week)	5	Review assignment to practice coping with smoking triggers and PTSD symptoms, develop action plan for quit date, introduce relapse prevention; coordinate with prescriber reinforce SQC app and iCO use
6	6	Reinforce coping plans, SQC app and iCO use, controlled breathing, adherence with medications
7	7	Assess for PTSD symptom exacerbations associated with cigarette reduction and/ or cessation
8	8	For non-abstinent patients: reset quit date, reinstate appropriate treatment

6.1.2 Method of Assignment/Randomization

Eligible participants will be randomized to one of two conditions (intervention or control condition) in a 1:1 ratio according to a computer-generated code provided by the study biostatistician.

6.1.3 Selection of Instruments/Outcome Measures

Aim 1: Feasibility and Acceptability of the Intervention

· Feasibility: We will calculate the: a) proportion of those eligible among those screened in rural and urban areas; b) proportion enrolled among those eligible; c) the rate of enrollment; d) adherence to medications (percentage of days participant takes NRT of total days prescribed); e) total number of sessions completed in each condition; f) iCO and SQC app usage data (intervention participants only); and g) study completion rate. To assess NRT adherence and estimate app usage data, participants will be asked to record daily medication adherence in a paper log using the TLFB method with specific anchor dates in a calendar, which will be mailed to the study team at each assessment time point. Pharmacy refill data will be reviewed at each time point to confirm TLFB self-report of medication adherence.

· Qualitative Interview (Acceptability): We will conduct a 20-minute semi-structured, audio-recorded telephone interview at Week 8 with intervention condition participants only to

collect in-depth feedback about user satisfaction with features of the overall intervention and its components (telephone sessions, SQC app, iCO monitor). We will use a framework of open-ended questions based on an interview guide developed by the study team, similar to that used in the focus groups with the CAP (see 3B.4), but with a greater emphasis on the acceptability of the intervention and its individual components (telephone sessions, SQC app, iCO monitor) in a therapeutic context during a quit attempt. We will inquire about individual features of each component of the intervention and perceived helpfulness; feasibility and acceptability in rural and urban settings; acceptability of the intervention in a military/ veteran cultural context; anticipated barriers and facilitators of implementation; the balance of adequate therapeutic intervention versus time burden; scheduling; cost-effectiveness; and issues of mobile device accessibility and connectivity. Audio-recordings of the interviews will be transcribed and relevant portions about acceptability of the intervention will be noted.

· System Usability Scale (SUS)[72,85]: The SUS is a brief, reliable and valid instrument to measure perceptions of usability of technology devices, with higher scores reflecting greater usability (maximum score of 100). We will administer the SUS for the SQC app and iCO monitor at Weeks 8, 12 and 24 follow-ups in the intervention condition only.

· Acceptability questionnaires: Participants will complete a questionnaire developed by our team to rate the protocol from 1-10 in the following areas: perceived helpfulness, understandability, and likelihood of use at Weeks 8, 12, and 24 follow-ups in the intervention condition only. The Client Satisfaction Questionnaire-8, a validated measure of client satisfaction with behavioral interventions, will also be administered. Total mobile app data usage of iCO and SQC will be recorded and participants will be asked to record usage of iCO or SQC apps daily on the TLFB paper log (see Section 3C11).

Aim 2: Retention (Attendance)

We will record attendance at each weekly session in both conditions during the eight-week study period. For intervention participants, the study team will document attendance and duration of each visit (target 20-30 minutes). For control participants, the study team will contact participants once weekly and inquire about their participation in the QL session for that week and estimate the number of minutes in each QL session. Per VA guidelines, intervention participants will receive a reminder call the day before each weekly appointment and will receive three outreach calls after a missed appointment before the visit is considered a no-show. Rescheduled appointments must be completed within the week of the originally scheduled visit; those that are not will be considered a no-show. Patients who decide to stop treatment or stop attending treatment in both conditions will be invited to complete follow-up assessments.

Exploratory Aims: Tobacco Use and PTSD Symptoms

Use of cigarette, e-cigarette, and chewing tobacco: We will use the TLFB method to record use of nonprescribed nicotine and tobacco products for past 30 days at Week 0 (baseline) and at Weeks 8, 12, and 24.[71] Seven-day and 30-day point prevalence abstinence will be assessed at 12 weeks and 24 weeks and will be defined as (1) no smoking and no use of e-

cigarette or non-cigarette tobacco on any of the seven and 30 consecutive days prior to the assessment, respectively; and (2) salivary cotinine levels < 10 nanograms/milliliter.[86] For participants using NRT and for those who reported use of smokeless tobacco, e-cigarettes during the study, abstinence status will be independently verified by a friend or family member. Participants with missing salivary cotinine or those unable to obtain verification from a friend or family member will be considered non-abstinent. Participants will be provided with postage-paid mailers, a collection kit, and detailed instructions for saliva collection and will be asked to collect specimens, store them in their home freezer, and mail them to our lab, where they will be batch shipped on dry ice to the Salimetrics lab for analysis.

· Nicotine dependence: We will administer the FTND at Weeks 0, 8, 12, and 24.

· PTSD symptoms: We will administer the PCL-5 at Weeks 0, 8, 12, and 24.

6.1.4 Intervention Administration

Intervention Condition: Participants will receive (1) eight 20- to 30-minute telephone sessions [initial session is aproximately 45-60 minutes]; and use (2) technology components (SQC app and iCO Smokerlyzer) between sessions. The therapist will proactively contact participants for each telephone session and use the accompanying workbook. At Week 0, participants will download the SQC app to their personal smartphones and be instructed to use SQC as much as desired between sessions. Participants will receive a brief training and orientation about features of SQC and will populate SQC with personalized information (planned quit date, triggers to smoke and coping plan, reasons to quit, and medications prescribed) in the weeks leading to the quit attempt (Week 5). At Week 0, participants will also receive an iCO Smokerlyzer mobile device for their personal use and will download the compatible Covita iCO app to their personal smartphones that displays CO readings. They will receive training on use of the iCO monitor and app and will be encouraged to measure CO levels as much as desired throughout the study period. Information will be stored on the apps on individuals' personal devices (no personal identifiers will be used and data will not be sent to or from participants, with anonymized data from the apps remaining on participants' phones).

Treatment Fidelity: Fidelity maintenance (1) ensures that the treatment delivered is the treatment intended, thereby safeguarding internal validity, (2) minimizes the influence of therapist effects,[80] and (3) facilitates dissemination and implementation by providing training programs and quality assurance procedures. Treatment fidelity ratings are a critical part of adherence to CONSORT guidelines as applied to psychosocial interventions.[81] Adherence to the treatment model, which is improved through fidelity maintenance procedures, is associated with improved outcomes in both research and clinical implementation.[82,83] The therapist will undergo a two-hour initial training with the PI, who is well-versed at delivering the original IC protocol. The therapist will then will attend a weekly supervision meeting with the PI. We will ensure a minimum of one hour of supervision per week for every four cases. Treatment sessions will be audiotaped using a telephone recording device that allows both sides of the conversation to be recorded. The PI will randomly select 10% percent of the audiotapes for adherence ratings by research clinical evaluators. This type of intensive

supervision will ensure therapist fidelity,[80] thereby minimizing threats of the internal validity of the study.

Control condition: Consistent with the current standard of care in VA clinics in rural areas, controls will be referred to the proactive VA Telephone QL.[55,84] Participants will receive instructions to call the VA QL[55,84] in Week 1 and will then request to receive weekly proactive telephone calls thereafter. They will be asked to track their weekly participation in QL sessions and duration of each session and will be instructed to request follow up calls weekly from the QL counselor for up to seven weeks thereafter (eight total). We selected the VA QL as a control because it accurately represents real-world treatment provided to veterans in VA settings, particularly in rural areas. The VA QL is a national toll-free number available to veterans that allows them to speak with a smoking cessation counselor for as many weekly sessions as needed (minimum recommended five sessions, more as needed) to develop a quit plan and receive counseling, strategies to prevent relapse, and weekly proactive follow-up calls based on National Cancer Institute guidelines. Sessions provide evidence-based smoking cessation counseling, but no resources or skills to manage mental health symptoms, such as PTSD symptoms, are provided.

6.1.5 Reaction Management

Participant safety will be a paramount concern during this research project. Participants will include veterans who are eligible for VA health care, including emergency or urgent care. Should any adverse events, medical or mental health emergencies occur during the course of the study, participants may seek emergency or urgent care at SFVAMC or their nearest emergency room. If a participant is injured as a result of being in this study, VA will ensure that treatment is made available at a VA medical facility. The costs of such treatment will be covered by the Department of Veterans Affairs. The Department of Veterans Affairs does not normally provide any other form of compensation for injury. Participants will be provided with the contact information for VA Regional Counsel in case they have any questions.

6.2 Assessments

Psychiatric history: VA electronic psychiatric record review (including current psychiatric diagnoses, current treatment, and any documentation of psychiatric acuity in past 30 days) will be reviewed by the PI at Week 0.

Clinician-Administered PTSD Scale (CAPS): The CAPS is a 30-item, structured interview that is the gold standard for DSM-V PTSD diagnosis and will be administered at Week 0 to assess for lifetime PTSD.

M.I.N.I. Neuropsychiatric Inventory: The M.I.N.I. 6.0 is a structured interview for DSM-V diagnosis of psychiatric disorders and will be administered at Week 0.

Timeline Follow-Back (TLFB): Use of cigarettes, e-cigarettes, chewing tobacco, and tobacco products using TLFB (past 30 days), which uses a calendar with specific anchor dates to identify the quantity and frequency of use. TLFB will be given at Weeks 0, 8, 12, and 24.

Medical history: VA electronic medical record review; medical history, medications and over the counter supplements; drug allergies will be completed by the PI at Week 0.

Demographic questionnaire: Age, education, relationship status, military branch and occupational specialty, deployment history, and living arrangements will be obtained at Week 0.

Tobacco use history: Age at initiation of cigarettes, e-cigarettes, and smokeless tobacco; history of quit attempts; longest time abstinent from cigarettes; current exposure to cigarettes in household will be obtained at Week 0.

Contemplation Ladder:[78] We will administer this brief measure of motivation to quit at Weeks 0, 8, 12, and 24.

Fagerström Nicotine Dependence Questionnaire (FTND):[16]The FTND is a validated instrument to evaluate the intensity of physical addiction to nicotine. It will be administered at Weeks 0, 8, 12, and 24.

PTSD Checklist-5 (PCL-5): The PCL-5 is a 20-item self-report measure that assesses the 20 *DSM-V* symptoms of PTSD. The PCL-5 will be administered at baseline and at Weeks 0, 8, 12, and 24.

System Usability Scale (SUS): The SUS is a brief, reliable and valid instrument to measure perceptions of usability of technology devices, with higher scores reflecting greater usability (maximum score of 100). We will administer the SUS for the SQC app and iCO monitor at Weeks 8, 12 and 24 follow-ups in the intervention condition only.

Urine Pregnancy: At baseline and Week 4, female participants will complete a urine pregnancy test.

Acceptability questionnaire: Participants will complete a questionnaire developed by our team to rate the protocol from 1-10 in the following areas: perceived helpfulness, understandability, and likelihood of use at Weeks 8, 12, and 24 follow-ups in the intervention condition only. Total mobile app data usage of iCO and SQC will be recorded and participants will be asked to record usage of iCO or SQC apps daily on the TLFB paper log.

Focus Groups and Qualitative Interview: We will conduct semi-structured, audio-recorded telephone interviews (1) during the Focus Group Phase; and (2) at Week 8 of the Pilot RCT (with intervention condition participants only) to collect in-depth feedback about user satisfaction with features of the overall intervention and its components (telephone sessions, SQC app, iCO monitor). We will use a framework of open-ended questions based on interview guides developed by the study team. The semi-structured interview guides (attached) were developed using standard methodological approaches in qualitative research. We will inquire about individual components of the manual and perceived helpfulness; feasibility and acceptability of use in a real-world context; cost-effectiveness and scalability; acceptability in a military and veteran cultural context; role of stigma; and anticipated barriers and facilitators of implementation in both rural and urban settings. We will also discuss the strengths and weaknesses of traditional telephone-delivered sessions as compared with newer smartphone technologies for session delivery (i.e., mobile video

chat platforms such as FaceTime, Skype, Google Hangouts, Zoom, or Jabber video conferencing), and will inquire about participants' experiences with and opinions about these methods. Interactive video teleconferencing systems and/or video chat platforms may appeal to young veterans as a more flexible alternative to office visits. Conversely, sessions delivered over traditional telephone calls are extremely low cost; do not incur WiFi charges; lack concerns of privacy, technical issues, and connectivity; and may be more easily scalable than video chat/ teleconferencing approaches.Participants in the experimental condition will complete an **acceptability questionnaire developed by our team** to rate each section of the manual on a scale from 1-10 in the following areas: (1) perceived helpfulness, (2) understandability, and (3) likelihood of use, as well as the **Client Satisfaction Questionnaire-8 (CSQ-8)**, an eight item instrument designed to measure satisfaction with an clinical intervention ranging from 8-32, with high scores indicating greater satisfaction.

6.2.1 Efficacy

Although examining efficacy is not a primary aim of the study, we will complete the following measures to preliminarily examine efficacy:

Use of cigarette, e-cigarette, and chewing tobacco: We will use the TLFB method to record use of nonprescribed nicotine and tobacco products for past 30 days at Week 0 (baseline) and at Weeks 8, 12, and 24.[71] Seven-day and 30-day point prevalence abstinence will be assessed at 12 weeks and 24 weeks and will be defined as (1) no smoking and no use of e-cigarette or non-cigarette tobacco on any of the seven and 30 consecutive days prior to the assessment, respectively; and (2) salivary cotinine levels < 10 nanograms/milliliter.[86] For participants using NRT and for those who reported use of smokeless tobacco, e-cigarettes during the study, abstinence status will be independently verified by a friend or family member. Participants with missing salivary cotinine or those unable to obtain verification from a friend or family member will be considered non-abstinent. Participants will be provided with postage-paid mailers, a collection kit, and detailed instructions for saliva collection and will be asked to collect specimens, store them in their home freezer, and mail them to our lab, where they will be batch shipped on dry ice to the Salimetrics lab for analysis.

Nicotine dependence: We will administer the FTND at Weeks 0, 8, 12, and 24.

PTSD symptoms: We will administer the PCL-5 at Weeks 0, 8, 12, and 24.

6.2.2 Safety/Pregnancy-related policy

Safety will not be assessed as a primary outcome measure.

6.2.2.1 Adverse Events Definition and Reporting

The PI will be responsible for following adverse event reporting requirements. These responsibilities include reviewing the accuracy and completeness of all adverse events reported; compliance with IRB policies for reporting adverse events and serious adverse events; reporting any safety issues to the IRB; and closely monitoring research volunteers at

each study visit and telephone contact for any new Adverse Events (AEs) or Serious Adverse Events (SAEs).

Adverse event definition

Adverse Events (AEs) will be collected using the definition of the UCSF IRB and International Conference on Harmonization (ICH) for Clinical Safety Data Management (ICH-E2A), according to which an adverse event is "any untoward medical occurrence in a patient or clinical investigation participant administered a pharmacological product which does not necessarily have to have a causal relationship with this treatment." An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the study intervention. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures including laboratory test abnormalities.

Serious adverse event definitionResearch staff will immediately notify the study physician in the event of a serious adverse event (SAE). In the event of one that is life-threatening or requires hospitalization, the participant's medical status will be monitored and the decision of whether to withdraw the participant from the study will be made on an individual basis by the study physician based on severity and nature of the medical problem. For all adverse reactions that are serious, life-threatening, or require hospitalization, the principal investigator and research coordinator will notify the UCSF IRB and the Federal Drug Administration (FDA) using the standard procedures provided by each agency. An FDA adverse reaction form will be completed at that time.

E.1.d. Participant Withdrawal

Participants will be withdrawn from the study if:

- in the clinical judgment of the investigator, the participant's clinical condition worsens substantially and it is felt to be in the participant's best interest to obtain alternative treatment, including, but not limited to, additional psychotherapy, pharmacotherapy, hospitalization, etc.

- the participant becomes pregnant. Should a participant become pregnant at any time during the study the participant will immediately discontinue nicotine replacement therapy. Study medication will not be tapered.

6.2.3 Pharmacokinetics (if applicable)

N/A

6.2.4 Biomarkers (if applicable)

In the RCT, abstinence from tobacco will be bioverified with salivary cotinine levels, which is described in the study consent form (no additional consent needed). For salivary cotinine samples, participants will be provided with postage-paid mailers, a collection kit, and detailed instructions for saliva collection and will be asked to collect specimens, store in their

home freezer, and to mail to our lab, where they will be batch shipped on dry ice to the Salimetrics lab for analysis. Study personnel will be trained in biosafety procedures for handling saliva samples per VA and UCSF guidelines. Salivary cotinine specimens will be stored and batch shipped using deidentified subject identification numbers on dry ice to the Salimetrics laboratory for analysis and samples will be destroyed after completion of analysis. Results will be mailed to the research coordinator and the PI, Dr. Herbst, and stored in the locked cabinet and encrypted database.

6.3.1 Study Schedule

(Please see attachment "Schedule of Measures and Procedures" in addition to narrative below.)**Description of the Intervention:** The intervention that we are designing and testing will be telephone-delivered and technology-facilitated, PTSD-informed treatment for smoking cessation in young veterans with posttraumatic stress disorder (PTSD).**PHASE 1: Community Advisory Panel (CAP) and Focus Groups**

To develop the treatment manual with community input, we will assemble a CAP consisting of veteran and nonveteran stakeholders. We will also recruit up to 10 veterans, ages 18-50, who are former or current smokers to participate in two Focus Group sessions. From these focus groups, we will solicit qualitative and quantitative feedback about the treatment manual (IC Manual) and its components. Using feedback from both the Focus Group and the CAP, we will adapt the existing, evidence-based IC protocol to be delivered via telephone and incorporate the use of the SQC app and iCO Smokerlyzer. Following the two Focus Groups with veteran smokers, we will meet quarterly (including through Phase 2 of the study) with the CAP to consult on all aspects of the project, such as recruitment, disseminating best practices into VA and community settings, and implementation strategies. The CAP will be comprised of individuals who work in VHA and community agencies and serve veterans and/or treat nicotine dependence. At study end, we will hold a summary meeting with the CAP and the study team to discuss dissemination of results and best practices.**Time commitment for Focus Group participation** is as follows:

- Informed consent (up to 30 minutes)
- Collection of basic demographic data (15 minutes)
- Two study visits that each include an audiorecorded focus group to obtain feedback about the treatment manual (up to 60 minutes each). The audio-recordeings of the focus groups will be transcribed by a HIPAA-compliant transcription service used by our team. Audio-recordings will be uploaded and saved in the research drive on the VA server and then immediately erased from audio-recording devices.

Time commitment for CAP participation

is as follows:

- An organizational meeting at study start (45-60 minutes)
- Quarterly meetings throughout the study period, i.e., both Phase 1 and Phase 2 (45-60 minutes each)

- Final summary meeting at study end (2 hours)

PHASE 2: Pilot Randomized Controlled Trial (RCT)

We will

conduct a pilot randomized controlled trial (RCT) in which we randomize

80 veteran smokers with PTSD ages 18-39 to receive either (1) the telephone- and technology-facilitated PTSD-informed treatment (intervention condition) over eight weeks, or (2) standard care: VA Telephone Quitline (control condition) over eight weeks. Participants in both conditions will be offered and encouraged to use nicotine replacement therapy (NRT), as this is a component of standard care for smoking cessation; however, use of NRT is optional and not required for participation.

Participants will not be the same as those recruited for the Phase 1 focus group.

Time commitment for the RCT

is as follows:

- Informed consent (up to 30 minutes)
- Initial screening visit at Week 0 (1-2 hours)
- Initial prescriber office visit to be offered nicotine replacement therapy (NRT) at Week 0 (30-45 minutes)
- Randomization to receive either (1) eight weekly telephone counseling sessions (20-30 minutes each), plus use of technology components (intervention condition); or (2) referral to the VA Quitline for up to eight weekly proactive sessions (control condition).
- Monthly check-in calls with study psychiatrist blinded to group assignment to monitor NRT throughout the 24 week period
- Follow-up Assessments will be completed at Weeks 8, 12, and 24. For intervention participants, this will include a 30-minute, audio-recorded semi-structured interview at Week 8 to gather detailed acceptability feedback about the intervention. (up to 2 hours each)

Participants in both conditions will:

(1) Complete an initial screening visit that is expected to last up to 2 hours and will include a series of questionnaires assessing eligibility criteria and will including meeting with the study physician to review medical history and information about NRT. For females, the physician visit will include a urine pregnancy test to verify that participants are not pregnant. (Note: At female participants' monthly check-in wth the study physician (primarily for monitoring NRT), the physician will confirm that the participant is not pregnant and continuing to use an accepted form of birth control (per verbal report). Any female participant who has become pregnant will be withdrawn from the study.) (2) Be offered nicotine replacement therapy

(NRT) at baseline (Week 0), per VA prescribing guidelines, nicotine dependence levels, and participant preference.

Participants in the intervention condition will receive:

(1) Eight telephone counseling sessions targeting PTSD symptoms related to smoking lapse. Content of sessions is consistent with that delivered in the Integrated Care (IC)[12] study for veteran smokers with PTSD. The firstof these sessions will last approximately 45-60 minutes, and the remaining seven sessions will last 20-30 minutes. (2) Use of the Stay Quit Coach (SQC) app between sessions. SQC is a public domain, no-cost mobile app designed by our co-investigators at the National Center for PTSD to complement the IC protocol with evidence-based tools to support smoking cessation, such as motivational messaging and coping tools for managing PTSD symptoms associated with smoking lapse.(3) Use of the Covita Bedfont iCO Smokerlyzer, a mobile carbon monoxide (CO) monitor, compatible with iOS and Android smartphones, that provides CO readings to the user at any time in order to self-monitor progress in quitting. The Covita iCO mobile app is used with the iCO Smokerlyzer to display CO readings.**Participants in the control condition will receive:** Weekly proactive telephone sessions through the VA telephone Quitline, a proactive telephone quitline available to all veterans for up to eight weeks. Participants will initiate the first call and subsequent calls will be made by the Quitline counselor.**Primary outcomes to be measured include:**

(1) Treatment retention as measured by total number of sessions completed in both conditions;(2) Data related to feasibility (rates of recruitment, dropout, and adherence to treatment in both conditions in residents of rural and urban areas); and(3) Quantitative and qualitative data about acceptability (satisfaction, convenience, ease of use) of the overall intervention and its components (telephone sessions, SQC app, iCO Mobile Smokerlyzer CO monitor) in the intervention condition only.

Specifically, we will conduct a 20-minute semi-structured, audio-recorded telephone interview at Week 8 with intervention condition participants only to collect in-depth feedback about user satisfaction with features of the overall intervention and its components (telephone sessions, SQC app, iCO monitor). We will use a framework of open-ended questions based on an interview guide developed by the study team, similar to that used in the focus groups with an emphasis on the acceptability of the intervention and its individual components (telephone sessions, SQC app, iCO monitor) in a therapeutic context during a quit attempt. Interviews will be audio-recorded and transcribed by a HIPAA-compliant transcription service used by our team. Audio-recordings will be uploaded and saved in the research drive on the VA server and then immediately erased from audio-recording devices.

Outline for Week 8 Qualitative Interview

- Individual features of each component of the intervention (telephone sessions, SQC app, iCO monitor)and perceived helpfulness
- Feasibility and acceptability in rural and urban settings

- Acceptability of the intervention in a military/ veteran cultural context -Anticipated barriers and facilitators of implementation
- Balance of adequate therapeutic intervention versus time burden --Scheduling issues
- Cost-effectiveness
- Mobile device accessibility and connectivity, including WiFi and battery usage

Secondary outcomes to be measured include:

(1) Self-reported cigarette, e-cigarette and smokeless tobacco use assessed by Timeline Follow-Back (TLFB)[76];(2) PTSD symptom severity assessed by PTSD Checklist-5 (PCL-5)[17];(3) Nicotine dependence assessed by Fagerström Test for Nicotine Dependence (FTND)[16] at Weeks 0, 8, 12, and 24; and(4) Bioverified seven and 30-day point prevalence abstinence rates assessed by self-report and confirmed with salivary cotinine levels (or independent verification by friend or family member if on NRT) at Weeks 12 and 24. (Details on the saliva collection process and use to assess point prevalence abstinence base on cotinine content of saliva are further explained in the attached documents: "Cotinine Saliva Collection" and "Oral Swab Collection Instructions".)

6.3.2 Informed Consent

For potential participants, research staff will conduct brief pre-screening interviews and answer any questions about the study during the initial screening phone call. After this pre-screening interview, the more in-depth screening visit (which includes the formal consent process) will be scheduled. Potential participants will be given as much time as they desire to review study information and ask questions before deciding if they want to move forward with the consent process. The informed consent process will be conducted by trained research assistants in private rooms within the Addiction Psychiatry Research Program.

All study staff who obtain informed consent will be directly trained by the PI and will undergo mandatory VA and UCSF research training on informed consent procedures. Staff will have the opportunity to observe more experience research staff in obtaining informed consent.

If there is any concern regarding a prospective participant's capacity to consent, the research staff conducting the consent will contact the principal investigator who will meet with the prospective participant in order to make a decision regarding capacity to participate in the study.

6.3.3 Screening

Search of San Francisco VA Medical Center (SFVAMC) medical records: Study staff will use CPRS to search the SFVAMC medical records for veterans who have a tobacco use disorder and/ or PTSD. The first and last names, last 4 of SSN, telephone number(s), and mailing address of identified veterans will be documented in a password-protected recruitment database that is stored on the secure VA network, in a study drive accessible only to study personnel.

When: The process of screening for eligibility will commence as soon as all approvals have been obtained from all regulatory bodies. The pre-screening and screening process will be maintained steadily until we have reached our target enrollment.

By Whom: The primary people will be involved in determining eligibility for study participation will be the research coordinator, study physician, and principal investigator (i.e., "study staff"). However, mental health and primary care providers will also assist in identifying veterans who may be eligible and referring them to the study.

How: Recruitment will be accomplished through: (1) opt-out letters mailed to veterans identified via CPRS medical record review; (2) direct outreach to patients via posted notices and cards placed in patient areas; (3) asking clinicians to refer patients to the study; and (4) phone calls made to potential participants only if referred to us by a clinician who has obtained permission for study staff to make contact. In attempting to connect with potential participants by phone, the study staff will only make three attempts by phone. If study staff are unable to reach the potential participant, then a follow-up letter (**see Follow-Up Letter General**) will be sent to the mailing address, inviting the person to reach out if they are interested in the research study.

Opt-out letters will be mailed to potential participants (as identified above) describing how the PI obtained their names and addresses and why these letters are being sent to them (**See Opt-Out Letter**). A unique recruitment ID# will be filled in by hand (by the study coordinator) prior to sending the opt-out packet to a potential participant. The letter will vaguely identify the research study and will invite veterans to call the study staff. A pre-addressed, stamped postcard will be included in the letter which a patient can return to indicate that they do not wish to be contacted for this study (**See Opt-Out Postcard**).

We will wait to contact potential participants for 2 weeks after the initial mailing to allow them time to opt-out if they do not wish to be contacted. If the team receives no returned "opt-out" postcard within 14 days after the original mailing, we will attempt to contact the veteran by telephone, but will adhere to strict confidentiality. We will speak only to the patient once identified. If study staff were to reach a non-study participant, he/she would state only that they are calling from the SFVAMC and will not disclose any information pertaining to the study. If a patient states that he/she does not wish to be in the study, we will respectfully not call again. If an opt-out letter is returned due to an incorrect mailing address, we will attempt to contact the potential participant by phone. If we are unable to reach a potential participant after 3 attempts, we will stop all efforts to make contact.

Once the potential participant has completed the informed consent and screening process (see Section 7.9—Research Plan and Procedures), study staff will determine eligibility based on review of screening data, chart review, and urine sample (pregnancy test) results.

6.3.4 Recruitment, Enrollment and Retention

6.3.5 On Study Visits

MEDICATION MANAGEMENT

Initial visit: The PI will meet with each participant at baseline (Week 0) prior to randomization to prescribe NRT (patch, gum, and/or lozenge) if desired, following a VA prescribing algorithm consistent with current prescribing guidelines.12,79 The session will be either in-person or through the telemedicine (V-tel) clinical services at the SFVAMC CBOCs. NRT will follow standard VA prescribing guidelines and will be based on (1) safety, (2) nicotine dependence level, and (3) participant preference. All participants will be instructed to set a goal of stopping cigarette, e-cigarette, and smokeless tobacco use during the course of study.

NRT monitoring: Following the initial visit, a study psychiatrist who is blinded to group assignment will contact participants in both conditions once monthly by phone to monitor for NRT side effects, adjust dosing, and renew refills. Participants who decline NRT will also receive a brief monthly check-in call to eliminate any potential therapeutic effect of these calls on study outcomes. All participants will remain on NRT as long as is clinically indicated throughout the 24-week study period, as determined by the study psychiatrist. Participants may contact the psychiatrist with any side effects or concerns related to NRT.

STUDY INTERVENTION PERIOD

Intervention condition: Details on the weekly telephone counseling sessions are provided in Section 6.1.4. Study therapists will conduct the sessions from private offices at SFVAMC, and veterans will participate via phone from their home or other location that is convenient for the.

Control condition: Details on the QL control condition are also provided in Section 6.1.4. QL sessions are also conducted via phone, and veterans will participate, as frequently as desired, from their home or other location that is convenient for the.

6.3.6 End of Study and Follow Up

Follow-Up: Follow-up Assessments will occur at Weeks 8, 12, and 24. They will be conducted by phone (reminder call day before) and last up to 2 hours each. Details on the measures administered at these Follow-up Assessments are provided in Section 6.2. Participants who withdraw from the study may receive care through the SFVAMC Smoking Cessation Clinic and/or the Quitline as desired.

6.3.7 Removal of Subjects

Rules for Withdrawing Study Participants from the Study Interventions: Participants will be withdrawn from the study if, in the opinion of the DSMB or the PI, there is: sustained clinically significant worsening of symptoms, unacceptable adverse events judged to be related to study interventions, or any other clinically significant medical (e.g., pregnancy), psychiatric, or substance-use related poor outcome that makes continued study participation unsafe in the clinical judgment of the PI or DSMB members.

6.4.1 Statistical Design

Data analytic plan: Prior to analysis all data will be examined for anomalous and missing values and described in detail. The description of the data is a key aspect of this work as it

informs future studies. Qualitative data (Focus groups and Aim 1) will undergo thematic analysis using a hybrid qualitative methodology incorporating deductive and inductive approaches. For the preliminary codebook for interviews, we will start with deductive codes (based on the interview guide and prior literature). Iteratively, we will add inductive codes (using grounded theory methodologies[89-91]). We will apply codes (phrases that explicitly describe segments of data) to relevant quotations for data sorting. Once a preliminary codebook has been created, a minimum of two coders will assist with coding and will apply initial codes as well as develop new codes following review of each additional transcript. All coders will document the process of creating new codes and any changes in previously determined codes. We will hold weekly meetings with coders to aid in calibration of coding and review and discuss discrepancies if necessary. We will calculate inter-rater reliability (Cohen's k for codes) and will resolve discrepancies to ensure consistent code application across raters and over time (.80 or above will be considered acceptable). We will identify themes (recurring and unifying concepts) during iterative thematic analyses until saturation is reached.[90,92] ATLAS.ti software will be used to organize the unstructured interviews objectively. Quantitative Data: To evaluate feasibility (Aim 1) we will calculate the: a) proportion of those eligible among those screened; b) proportion enrolled among those eligible (goal ≥ 50%); c) the rate of enrollment (goal four participants per month); e) adherence to NRT in those prescribed NRT, defined as total days taking NRT divided by total days prescribed NRT (goal ≥ 70% adherence in intervention condition); e) study completion rate in both conditions. We will also examine iCO and SQC app usage patterns (number of days each app is used per participant self-report and total data used by each app over the study period) in intervention condition participants and examine the relationship between app usage and study outcomes. To assess acceptability (Aim 1) we will calculate the percentage of participants in the intervention condition who rate each of the technology components as moderately acceptable or higher as measured by the SUS[72,73] and the self-report questionnaire assessing acceptability of the telephone manual (objective: ≥ 75% participants rate SUS ≥ 70 for iCO and SQC and rate telephone sessions as "moderate" or higher acceptability). Qualitative data will be combined with the quantitative acceptability data in a mixed methods analysis for cross-validation of the techniques. Failure to meet the feasibility and acceptability objectives will drive a major revision of the study protocol for future studies. We will also compare retention rates of the two treatment conditions (proportion of participants in each condition that engages in four or more sessions) (Aim 2 Hypothesis) and in seven- and 30-day point-prevalence smoking abstinence rates, FTND scores, and PCL scores (Exploratory Hypotheses) at Weeks 8, 12, and 24. The randomization procedure should result in covariate effects being distributed equally between the treatment conditions. If, however, the preliminary analyses indicate the treatment conditions vary on potentially confounding variables such as age or number of previous quit attempts, these covariates will be included in a multivariate model. Comparing treatment conditions that include time as a factor, the prototypical model will be a nonlinear mixed-effects model for dichotomous outcomes. Given the limited number of assessment points, the most parsimonious model will be a general linear model for each outcome. Planned contrasts among the intervention condition will directly test each hypothesis. Quantitative

analyses will be performed with SPSS. Results will be reported using CONSORT guidelines and the World Health Organization (WHO) mHealth Technical Evidence Review checklist on mobile Health evidence reporting and assessment (mERA).[93]

6.4.2 Sample Size Considerations

Power Analysis: The primary aim of this pilot study is to gather relevant information including preliminary outcomes, to evaluate feasibility and acceptability for the purpose of refining our intervention and to provide empirical data for recruitment, attrition and effect size estimation for a future RCT. Therefore, the sample size of n=80 was determined primarily by practical and clinical reasons and not driven by estimated effect sizes. We do plan to evaluate the key outcomes, however, so we estimated the minimally detectable effect sizes for those tests. Results indicate that a total sample of at least 60 completers with planned contrasts as described in the Analysis section should provide adequate power to detect large effect sizes.

6.4.3.4 Analysis of Subject Characteristics

Means or proportions of participants will be compared across the various categories of VA facilities by age, race/ethnicity, gender, level of education, employment, military branch and era, and marital status. Prior to testing the study hypotheses, the distributions of all variables will be examined to ensure that they have adequate range and variance and meet all necessary assumptions of the statistical methods to be used. Cronbach's alpha will serve as the index of internal reliability for this step. Primary analyses will be performed by intent to treat. All patients who are assigned a treatment condition will be considered enrolled.

6.4.5 Handling of Missing Data

Missing data can arise from several sources, including participant dropout or participant failure to complete occasional measures. For the analyses of smoking outcomes, we will conduct analyses in two ways: a complete-case approach using observed data, and to assume missing as the negative outcome (e.g., missing=non-abstinent) to obtain a range of the intervention effects. We will use the maximum likelihood approach of the mixed model to accommodate missing outcome variables without bias under the assumption of missing at random, meaning that missingness is random conditional on observed variables. This is a reasonable assumption for missing data not under the participants' control and sporadic missing items on measures.

7 - Trial Administration

7.1 Ethical Considerations

1) Risk of Distress or Embarrassment: To protect against risks of distress or embarrassment, researchers will inform participants that participation is voluntary. They will be informed that they may choose to not respond to any question asked at any point in the study, may stop a session at any time, or end their participation in the study at any time. The PI and other study team members have substantial experience and expertise in these issues from work in prior research studies. To minimize risk of distress associated with completion of self-report forms, we have chosen self-report assessments that are unlikely to lead to participant distress. Acceptability questionnaires administered during the CAP are at very low risk of contributing to clinically significant distress.

2) Exacerbation of PTSD symptoms: This risk will be minimized by providing participants in both conditions with support and behavioral intervention designed to facilitate smoking cessation with a minimal amount of stress. All participants will be able to continue or seek any mental health treatment at any point in the study. Referrals for psychotherapy and/ or emergency behavioral health services will be made when deemed necessary.

3) Nicotine withdrawal symptoms (RCT only): To minimize withdrawal symptoms, both conditions will receive treatment; there is no placebo condition in this trial. All participants will be offered NRT and will be counseled about the symptoms of nicotine withdrawal and coping strategies.

4) Use of NRT (RCT only): To minimize risks of adverse effects of NRT, the risks, benefits and alternatives of these medications will be discussed in detail by Dr. Herbst, PI, in the office visit at Week 0 prior to randomization in all participants. Each participant's medical and medication history will be reviewed in detail and prescribing practices will follow VA prescribing guidelines, which includes assessment of nicotine dependence level, assessment of safety and risks and benefits for the participant, review of medical record and medication history, and participant preference. Prior to initiation of the medication trial, verbal informed consent will be obtained from participants at this face-to-face visit. Participants will be provided with a wallet card with the study psychiatrist's contact information and will be encouraged to contact her with any side effects or other concerns related to prescribed medications. Following the initial visit, a study psychiatrist, blinded to group assignment, will contact participants in both conditions monthly by phone to monitor for side effects, adjust dosing or discontinue medication, and renew refills as needed. The potential risks of different formulations of NRT are summarized below.

Risks of Any NRT:

- Cardiovascular risk: Participants with history of heart attack or stroke will require medical clearance from a VA primary care physician prior to receiving NRT during the study.

- Risk of overdose: To minimize risk of overdose, Dr. Herbst and the study psychiatrist to be named will adhere to VA prescriber dosing guidelines. Participants will be advised not to smoke while using NRT products. Participants will be advised that if these symptoms occur,

they should stop using NRT and will be told to contact the study team and/ or seek emergency care immediately, depending on severity of symptoms.

- Pregnancy: Due to the unknown risks of NRT in pregnancy, participants who are pregnant will be excluded at screening (self-report of pregnancy and/ or urine pregnancy test). Women of childbearing age will be advised to either avoid NRT or use an effective form of contraception if they accept NRT therapy during the study.

- Poisoning: Parents of small children should store NRT out of reach of children to prevent a child from consuming them and being poisoned.

- Potential drug-drug interactions or difficulty metabolizing NRT: The PI will review the medical history in the medical record, medication list including over the counter and herbal supplements, and will perform a thorough clinical assessment at the medication management visit to minimize risk of drug-drug interactions. Should side effects occur, the study psychiatrist will adjust or discontinue the medication.

Risks of specific formulations of NRT:

- Skin irritation (patch) may be relieved by the use of 1% hydrocortisone or Eucerin cream available over-the-counter, and avoiding reapplication of the patch to the same site.

- Insomnia (patch) may be managed by removal of the patch at night during sleep.

- Irritation in the mouth or jaw (gum or lozenge) can be managed by adjusting and/ or discontinuing the medication by the study psychiatrist.

- Other nonspecific side effects (diarrhea, an upset stomach, muscle aches, increased blood pressure) can be managed through dose reduction or adjustment, switch to alternative form of NRT, or discontinuation of NRT, depending on clinical presentation and evaluation of the PI.

Monitoring to ensure safety: Participants will be monitored in the following ways:

- At the screening visit, they will undergo a diagnostic interview and will be assessed for psychiatric acuity to ensure that participation is safe and participants are sufficiently stable to participate.

- Review of the VA electronic medical record, collection of medical and psychiatric history, and psychiatric diagnostic interview will be conducted at screening to ensure safety of participation.

- Medication management evaluation will be conducted prior to randomization at Week 0 to evaluate the safety, risks, and benefits of NRT in each participant per VA prescribing guidelines.

- Study psychiatrist blinded to group assignment will contact participants by telephone in both conditions once monthly to monitor NRT throughout the 24week study period.

- Participants will be provided with emergency contact information for the study team, study psychiatrist, and PI as well as the VA Suicide Prevention Hotline and those of nearest VA facilities and counselled to call or present for emergency care as needed.

Provision of emergency medical or psychiatric care: Participant safety will be a paramount concern during this research project. Participants will include veterans who are eligible for VA health care, including emergency or urgent care. Should any adverse events, medical or mental health emergencies occur during the course of the study, participants may seek emergency or urgent care at SFVAMC or their nearest emergency room. If a participant is injured as a result of being in this study, VA will ensure that treatment is made available at a VA medical facility. The costs of such treatment will be covered by the Department of Veterans Affairs. The Department of Veterans Affairs does not normally provide any other form of compensation for injury. Participants will be provided with the contact information for VA Regional Counsel in case they have any questions. Finally, we have identified a Medical Monitor, Anne Richards M.D., who will oversee all aspects of safety monitoring throughout the study, and will assemble a Data and Safety Monitoring Board (DSMB) consisting of three experienced clinician-researchers: Dr. Richards, Psychiatrist, SFVA/ UCSF; Raj K. Kalapatapu M.D., Psychiatrist, UCSF; and Beth Cohen M.D, Internal Medicine physician, SFVA/ UCSF.

7.2 Institutional Review Board (IRB) Review

The study sponsor, California Tobacco-Related Disease Research Program (TRDRP), will receive an annual report with study progress. In addition, the UCSF Committee on Human Research and VA Institutional Review Board will perform continuing review of the study once annually.

7.3 Subject Confidentiality

To protect confidentiality, participants will receive a participant identification number that will be used throughout the study. The study team will use best practices to protect participant confidentiality in keeping with HIPAA, UCSF, and VA, including maintenance of files in locked cabinets, storage of participant information in a password protected database on a secure, and encrypted VA server. Researchers will maintain control over all hard-copy research materials, including interview audio-recordings and transcripts by keeping them within their personal control during the conduct of research or by keeping them in a locked filing cabinet at the SFVA. Audio-recordings will not include any identifying information and will be downloaded to the VA server immediately. Computer files containing interview transcripts, the key linking interview numeric codes to actual participant names, audio-recordings of interviews, post-interview reflective memos will be anonymized using a numeric code and will be kept in an encrypted file behind the VA firewall and on a password protected computer in the investigator's locked office. In manuscripts, reports, publications, and other documents, the names of individual research participants will be deidentified. All technology apps to be used in the RCT will not contain any personally identifying information. Participants will be instructed to password protect their phones. To preserve confidentiality in the Community Advisory Panel, no psychiatric diagnostic information will be collected. Participants will not maintain any identifying information in the apps used in the study (SQC, iCO).

7.4 Deviations/Unanticipated Problems

Unanticipated problems will immediately be reported both verbally and in writing to the VA Research and Development Office, the UCSF Committee on Human Research, and the study sponsor.

7.5 Data Quality Assurance

Treatment Fidelity: Fidelity maintenance (1) ensures that the treatment delivered is the treatment intended, thereby safeguarding internal validity, (2) minimizes the influence of therapist effects,[80] and (3) facilitates dissemination and implementation by providing training programs and quality assurance procedures. Treatment fidelity ratings are a critical part of adherence to CONSORT guidelines as applied to psychosocial interventions.[81] Adherence to the treatment model, which is improved through fidelity maintenance procedures, is associated with improved outcomes in both research and clinical implementation.[82,83] The therapist will undergo a two-hour initial training with the PI, who is well-versed at delivering the original IC protocol. The therapist will then will attend a weekly supervision meeting with the PI. We will ensure a minimum of one hour of supervision per week for every four cases. Treatment sessions will be audiotaped using a telephone recording device that allows both sides of the conversation to be recorded. The PI will randomly select 10% percent of the audiotapes for adherence ratings by research clinical evaluators. This type of intensive supervision will ensure therapist fidelity,[80] thereby minimizing threats of internal validity.

7.5.1 Data Collection

Participant Database

We have developed a recruitment database for tracking research participants which is housed on a VA-secured server, behind a firewall, and is backed up regularly. There are several layers of protection regulating access to this database. First, it can only be accessed through a VA-authorized computer, which requires registration with the VA and creation of a computer account and password. Second, individuals must be granted access through the Database Manager. Third, individuals must log in using a unique username and password. These multiple steps ensure that only authorized research staff will be able to access this highly protected database. The Project Coordinator and Database Manager will manage this study database to ensure continued security.

Information Database

The study team will develop a secure database to store and manage participant data. The database will be accessible only by individuals (1) with an authorized VA user account and (2) who are granted access to the server by the Database Manager with permission from the Principal Investigator. tudy data (e.g. self-report questionnaire, assessment documentation) will be collected and stored using individual's study ID numbers. This database will not contain any Patient Health Information (PHI) and will only use participant's study ID numbers. All data, before entry, will be reviewed to ensure that it is void of PHI.

Data Management Tools

A detailed Data Management Plan (DMP) is created for each study in the database system. The DMP describes the data management practices and policies of how the data will be managed, to document the activities of the study database build, validation, entry, cleaning and database lock. Related Standard Operating Procedures and Guidelines drive the flow process.

A query resolution tracking system is designed to allow communication between data managers and the study coordinators in identifying data issues and resolutions. All data issues will be closed out at time of database lock.

A query reports generator is available to provide users the ability to generate standardized report listings. These reports provide an overall summary of study progress, enrollment progress, and study timelines and metrics within the research program.

Data Governance

Data Collection Interface:

The Addiction Research Program Data Management Core offers various data collection methods best suited on the data measure collected. These include:

- Electronic Data Capture via the Qualtrics HIPAA compliant web-based data collection platform.
- Microsoft Access using Data Entry Forms and Switchboard Dashboard
- Microsoft Access linked tables/objects with server
- Microsoft ADP (access data project) with server
- Bulk loads from files of various formats
- At a point of entry, data values are subjected to consistency edit checks (e.g. range and type verification, missing data). Scoring algorithms are applied where appropriate. Once data is entered into the database, edit checks are run for accuracy.

Data Collection:

· Informed Consent Documents: Informed consent documents will be kept in a locked cabinet in a secure area on site at SFVAMC. Only research staff will have access to the locked cabinet. Data containing identifying information will be filed separately from de-identified study data.

· Self-report, neurocognitive measures, and screening assessments: Self-report and other assessments will be entered by participants and study staff into the Qualtrics HIPAA compliant web-based collection platform. Self-report questionnaires will be built using Qualtrics software and customized for compliance with HIPAA regulations. Survey data entered into Qualtrics will be hosted by a secure server at UCSF, then downloaded at the

VA, and stored electronically on the secure server, and stored behind the VA firewall in the SQL server database described above. Survey data will be deidentified, password protected, and only accessible to study staff. All pen and paper documents will reside in a locked cabinet at the SFVAMC.

· Audio-recorded interviews: A member of the study team will audio-record qualitative interviews on site using a portable recording device. No identifiers will be used during the interviews. The study staff will then log in to a secure VA computer and download the audio-recordings to the SFVAMC research server, which will then be uploaded to a HIPAA compliant transcription service used by VA researchers, Viva Transcription. Once downloaded, the audio-recorded interviews will then be erased from the recording device.

Saliva specimens to be collected, schedule, and amount:

Laboratory studies will include salivary cotinine , a biomarker of recent tobacco use. Participants will collect the saliva samples themselves. Staff will instruct participants to provide a saliva sample through a straw into a cryovial. Prior to saliva collection, volunteers will rinse their mouths two times with water, and then complete saliva collection ten minutes later. Each specimen will contain 2 ml of saliva. The following amount is needed: cotinine= 75 microliters. A total of 2 ml of saliva per specimen will allow for biomarkers to be assayed in each sample.

After collection participants will store the samples in a personal cooler container provided by the study, placed in their freezer, and shipped in a prepackaged Fedex shipping package the next day. Upon receipt of the sample, research coordinator will then store the samples at -80 C and batch shipped on dry ice to the Salimetrics laboratory. They will then be analyzed at the laboratory using standard procedures. Results will be mailed to the research coordinator and the PI Dr. Herbst. Only subject IDs will be used and no personal identifiers will be on the samples or the results.

Storage: Upon receipt of the specimens, the research coordinator will label the specimens with participant ID numbers (no unique identifiers), added to a tracking database, and stored at -80 Celsius in freezers at the SFVAMC for no more than 4 months. The coordinator will ship the specimens via FedEx overnight in batches on dry ice to Salimetrics laboratory for analysis. The specimens will not be stored for future use. Laboratory results will be mailed to the study coordinator, who will then manually enter results into the password-protected study database. Dr. Herbst, PI will also receive a copy of the lab results.

Participants will be provided with information about salivary sampling during the informed consent process and will have the opportunity to decline participation based on that information. Participants will be informed that they may withdraw consent at any time, and we will destroy any samples that have been stored. Participants are not required to follow any dietary restrictions or special instructions prior to the saliva collection.

Labs performing evaluations and special precautions: All study personnel who collect, handle, and store the saliva specimens will undergo annual biosafety training at the SFVA and TAFB and will be supervised by the PI to ensure adherence to good clinical laboratory practices (GLP).

Study personnel will receive training on best practices for saliva collection per the instructions of the assay manufacturer, Salimetrics. All standard precautions will be followed. Study personnel wear gloves and use only approved cryovials labeled with participant IDs. Specimens will be stored and batch shipped on dry ice using FedEx 24 hour shipping to the Salimetrics laboratory for analysis.

7.5.1.1 Access to Source

Only members of the study team will have access to study records, data, and specimens. For quality assurance purposes, VA regulatory personnel may access study records to perform yearly audits of research studies conducted at the SFVAMC. Authorized representatives of related regulatory agencies, such as the University of California, San Francisco's Committee on Human Research, SFVAMC Research and Development Office, and the study sponsor (TRDRP) may also review study records as appropriate.

7.5.1.2 Data Storage/Security

Disposition of Data: All data will reside in the Research Program server on the VA network, with paper consent forms and other documents in a locked cabinet in at the SFVAMC.

7.6 Study Records

Regulatory documents, consents forms, data from interviews and self-report measures, transcribed audiorecordings, and laboratory reports are all considered study records.

7.6.1 Retention of Records

At the present time, the VA does not allow destruction of research records; therefore, we will store the data securely and indefinitely. Once the study is closed, we will work with the Clinical Research Office at the SFVAMC to arrange long term storage of data at an approved facility. Transfer and access of records will be arranged by the Clinical Research Office.

7.7 Study Monitoring

The study sponsor (TRDRP) will receive annual progress reports. In addition, UCSF CHR and SFVAMC will perform annual Continuing Review of the study. Finally, the Data Safety Monitoring Board (DSMB) will meet biannually to review the project.

7.8 Data Safety Monitoring Plan

The Data and Safety Monitoring Plan (DSMP)

The DSMP for this project consists of:

- A Data and Safety Monitoring Board (DSMB)
- A schedule of DSMB meetings to review study data and events
- A list of study data and event items to be reviewed by the DSMB
- Procedures for communicating DSMB findings to the UCSF IRB, and other appropriate entities
- A plan for conducting and reporting interim analysis

- Stopping rules
- Rules for withdrawing study participants from the study interventions

Note: These elements of the DSMP are described below:

The Data and Safety Monitoring Board (DSMB)

The Data and Safety Monitoring Board (DSMB) is a group of three physicians who are clinicians as well as clinical researchers, and who are not study investigators. They have expertise in the areas of clinical psychiatry, clinical psychopharmacology, posttraumatic stress (PTS), and substance use disorders. The composition of the DSMB is: Anne Richards, M.D., M.P.H., Staff Psychiatrist, SFVAMC; Raj K. Kalapatapu, M.D., Psychiatrist, UCSF; and Beth Cohen, M.D., Internal Medicine, SFVAMC.

The DSMB will meet quarterly to review data reports prepared by the PI regarding the progress of the study and will monitor patient enrollment, retention, outcomes, adverse events, and other issues related to patient safety. The DSMB will make recommendations to the PI as to whether the study should continue or be modified or terminated. The DSMB can consider patient safety or other circumstances as grounds for early termination. Any member of the DSMB can ask for a meeting of the group if he/she feels that it is necessary, based upon the data.

During the course of the study, reports will be prepared and distributed to the Data and Safety Monitoring Board on a quarterly basis. In order for the Data and Safety Monitoring Board to discharge their duties for overseeing the study and the rights of the patients, they will receive analyses of the primary outcome measures and the important exploratory measures on a quarterly basis. The DSMB will receive reports of serious adverse events (SAEs) within 72 hours of their occurrence. DSMB Minutes will be prepared by the Study Coordinator within 5 working days after each quarterly DSMB meeting.

Data Safety Monitoring Board Plan

Anne Richards, MD, MPH, is an Assistant Clinical Professor at UCSF and Staff Psychiatrist at the SFVAMC. Her clinical and research interests are in the area of PTSD. Dr. Richards will serve as Research Monitor. At a minimum, the research monitor: (1) may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research; (2) shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the UCSF Committee on Human Research (CHR) can assess the monitor's report; (3) shall have the responsibility to promptly report their observations and findings to the IRB or other designated official. As Research Monitor, Dr. Richards will review all unanticipated problems involving risk to subjects or others, serious adverse events and all subject deaths associated with the protocol and provide an unbiased written report of the event. The medical monitor will comment on the outcomes of the event of problem and in case of a serious adverse event or death, comment on the relationship to participation in the study.

The Research Monitor will also indicate whether he/she concurs with the details of the report provided by the principal investigator (PI). Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reports of events resulting in death will be promptly forwarded to the TRDRP.

Schedule of DSMB Meetings

The DSMB will meet semi-annually.

List of Study Data and Event Items to be Reviewed by the DSMB

Data reports prepared by the PI regarding the progress of the study will include patient enrollment, retention, analyses of the primary outcome measures and important exploratory outcome measures, adverse events, serious adverse events, and other items related to patient safety.

Procedures for Communicating DSMB Findings to Appropriate Regulatory Bodies

The PI will communicate DSMB findings in the form of copies of the minutes of each quarterly DSMB meeting, within 10 working days following each meeting. Reports will be sent to the UCSF IRB and SFVAMC Human Research Protection Program (HRPP), and additionally to TRDRP if appropriate.

Rules for Withdrawing Study Participants from the Study Interventions

Participants will be withdrawn from the study if, in the opinion of the DSMB or the PI, there is: sustained clinically significant worsening of symptoms, unacceptable adverse events judged to be related to study interventions, or any other clinically significant medical, psychiatric, or substance-use related poor outcome that makes continued study participation unsafe in the clinical judgment of the PI or DSMB members.

7.9 Study Modification

Study modifications will occur as needed based on ongoing review by the study team in collaboration with the DSMB. Modifications will be submitted through the SFVA Research and Development Office and the UCSF CHR. No modifications will be implemented until approval is obtained.

7.10 Study Discontinuation

The study would be discontinued in the following circumstances:

1. Risks of participation are determined to greatly exceed potential benefits; or

2. Risk of participation in one arm of the study is determined to greatly outweigh that of the other.

7.11 Study Completion

Completion date will be three years from study start, which will be determined by approval date of the UCSF IRB. Estimated completion date 11-12/2020. The UCSF CHR will be notified by the study team when it reaches the data analysis phase and human subjects activities have been completed.

7.13 Funding Source

Funding source is the Tobacco-Related Diseases Research Program (TRDRP).

7.14 Publication Plan

The PI holds primary responsibility for timely publication of results. In the data analysis phase in Year 3 Quarter 4, the PI will work with the study team to disseminate results through manuscript preparation, presentations, and ongoing reporting to the study sponsor.

Appendices

Appendix #	Name	Title	Section	Topic

List of Tables