Stanford Tobacco Treatment Services - Virtual Reality Treatment for Smoking Cessation

Study Protocol and Statistical Analysis Plan

NCT05220254

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Stanford Cancer Institute
A National Cancer Institute Comprehensive Cancer Center

Stanford MEDICINE

TITLE: Stanford Tobacco Treatment Services – Virtual Reality Treatment for Smoking Cessation

Version 3.18.22

Initial SRC Approval Date: 9.13.21 (for version 9.7.21)

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Regulatory Information

Study Agent: MindCotine virtual reality smoking cessation mobile app
IRB of Record: 60253
IND / IDE Sponsor: N/A
Funding Source: NCI Moonshot Supplement

STATEMENT OF COMPLIANCE

LEAD INVESTIGATOR STATEMENT

I have read and agree to the study, as detailed by this protocol document. I am aware of my responsibilities as an Investigator pursuant to the clinical trial protocol, the guidelines of Good Clinical Practice (GCP) [1], the Declaration of Helsinki [2], and the applicable Code of Federal Regulations (CFR) at Title 21 [3] and Title 45 Part 46 [4], as well as my responsibilities as a Lead Investigator, as a ClinicalTrials.gov Responsible Party under 42 CFR Part 11 [5] as promulgated pursuant to Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801), and other applicable requirements of the participating institutions including the Stanford Cancer Institute, the Stanford Hospitals and Clinics, Lucile Packard Children's Hospital, and/or the Stanford University Medical Center. I agree to conduct the trial according to these regulations, guidelines, and requirements, and to appropriately direct and assist the participating staff under my authority, and that all staff members are aware of, and trained in, their clinical trial responsibilities.

All key study personnel have completed Human Subjects Protection Training.

Site Principal Investigators are expected to assure that no deviation from, or changes to the protocol, will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB) of record, except where necessary to eliminate an immediate hazard(s) to the trial subjects.

Sponsor-Investigator's Name: Judith J. Prochaska

Name of Site: Stanford Cancer Institute
Stanford Medicine
Stanford, California

Principal Investigator's Signature: [redacted] **Date**: 3/18/22

1 FDA Guidance for Industry: current revision of the International Conference on Harmonization (ICH) Good Clinical Practice Guidelines E6.

2 World Medical Association, Declaration of Helsinki Ethical Principles for Medical Research Involving Human Patients.

3 United States Code of Federal Regulations (CFR), Title 21, "Food and Drugs."

4 CFR, Title 45 "Public Welfare;" Part 46 "Protection of Human Subjects."

5 CFR, Title 42 "Public Health;" Part 11 "Clinical Trials Registration and Results Information Submission."

STATEMENT OF COMPLIANCE

PARTICIPATING SITE PRINCIPAL INVESTIGATOR STATEMENT

I have read and agree to the study, as detailed by this protocol document. I am aware of my responsibilities as an Investigator pursuant to the clinical trial protocol, the guidelines of Good Clinical Practice (GCP) [1], the Declaration of Helsinki [2], and the applicable Code of Federal Regulations (CFR) at Title 21 [3] and Title 45 Part 46 [4], and the applicable requirements of the participating institution. I agree to conduct the trial according to these regulations, guidelines, and requirements, and to appropriately direct and assist the participating staff under my authority, and that all staff members are aware of, and trained in, their clinical trial responsibilities.

All key study personnel have completed Human Subjects Protection Training.

I assure that no deviation from, or changes to the protocol, will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB) of record, except where necessary to eliminate an immediate hazard(s) to the trial subjects.

Principal Investigator's Name: Judith J. Prochaska

Name & address of local site: 1265 Welch Road, Stanford, CA. 94305-5411

Name of Lead Institution: Stanford Medicine
Stanford, California

Principal Investigator's Signature: [redacted] **Date**: 3.15.22

1 FDA Guidance for Industry: current revision of the International Conference on Harmonization (ICH) Good Clinical Practice Guidelines E6.

2 World Medical Association, Declaration of Helsinki Ethical Principles for Medical Research Involving Human Patients.

3 United States Code of Federal Regulations (CFR), Title 21, "Food and Drugs."

4 CFR, Title 45 "Public Welfare;" Part 46 "Protection of Human Subjects."

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PROTOCOL SYNOPSIS

Study Title	tanford Tobacco Treatment Services – Virtual Reality Treatment for moking Cessation
Study Description	esting feasibility of a virtual reality app for smoking cessation among 20 atients, from the Stanford Cancer Center, who smoke cigarettes daily as art of the Tobacco Treatment Services.
Study Purpose (for ClinicalTrials.gov)	ealth Services Research
Secondary Objective(s)	uit status and attempt to quit. Learning whether those who also opted in her tobacco treatment services (e.g. NRT, counseling sessions) have fferent outcome than the ones who used the MindCotine app only
Secondary Endpoint(s)	nd of treatment assessment quit status, making a quit attempt during the ast 6 weeks, use of cessation medications, smoking reduction (EOT garettes per day compared to cigarettes per day at baseline), MindCotine sage, dropout, and adverse events.
Eligibility Criteria	aily or some day cigarette smokers (>9 cigarettes/week), English or panish fluent, has compatible smartphone, willing to interact with the app or 6 weeks, willing to complete survey assessments, no hx of seizures
Treatment and Procedural Summary	articipants are recruited during outreach as part of the Tobacco Treatment ervices. The study is proposed as a treatment option. If interested, otential participants will complete a phone screen, and if still interested, roceed to the study consent form. After the study consent form is signed, VR kit with the app code for access to the full MindCotine virtual reality rogram will be mailed to the participant. The participant will start eatment, engage in treatment for 6 weeks and complete the end of eatment questionnaire. The participant can utilize the app for up to a year they wish to. All participant data on the app will be deleted after that ear has passed. Data will be analyzed. A summary of analyses will be rovided to MindCotine. The team will decide whether to invest in lindCotine as a treatment option for patients.

Considerations

ollection, the statistical plan is descriptive in nature. Descriptive statistics .g., means/SD, frequencies, ranges) will summarize participant emographic and tobacco use characteristics, changes in tobacco use over me, MindCotine app usage, feedback on the MindCotine program, ropout, and any adverse effects. Factors that indicate feasibility will nclude (i) interest among our patient population in using the app, which ill be offered at no cost; (ii) among those patients who are interested, that ey are able to onboard and make use of the app; and (iii) patient ratings f recommending the app to others. Feasibility metrics would be at least (i) 0% interested in using the app; (ii) 75% of interested patients onboarded nd using the app; and (iii) 70% recommending the app to others. Efficacy oals will be examining tobacco use reduction and quitting with goals of at ast (iv) 50% reducing tobacco use and 10% quitting. Additionally, the uit rate among participants in this pilot will be compared to the quit rate

Study Duration

stimated study period is 9 months to recruit, complete assessments with 0 patients, and data analyses. After the initial outreach and consent, the articipant will receive their VR kit in 3-5 business days, start the ntervention, and have a final survey after the 6-week period. Data analyses

Subject Duration

he study duration is 6 weeks or 1.5 months for participants from baseline end of study.

LIST OF ABBREVIATIONS & TERMS

pp	le application	NCI	National Cancer Institute
LIA	:al Laboratory Improvement ıendments; Certification	On-study date	Defined (per OnCore) as date of subject's first research-related procedure, scan, or treatment
R	ɔlete response	PR	Partial response
SMP	Safety Monitoring Plan	SCI	Stanford Cancer Institute
DAAA	and Drug Administration ıendments Act	SOP	Standard Operating Procedures
UI	for Guidances under Stanford search Compliance Office	TTS	Tobacco Treatment Services
ICMJE	Committee of Med Journal Edito	UP	Unanticipated Problem

1. INTRODUCTION

1.1. Study Rationale

There are patients from the Stanford Cancer Center who use tobacco and have difficulty reducing their use or quitting. Tobacco use exacerbates health conditions and hinders treatment. Currently, Tobacco Treatment Services include nicotine replacement therapy, cessation medication consultations, individual counseling sessions, group counseling sessions, and referrals to the quit line. Some patients have exhausted their options in smoking cessation. The MindCotine virtual reality smoking cessation app is a novel approach to tobacco cessation, and is an option to consider adding as part of the tobacco treatment service.

1.2. Background

1.2.1. Overview of study intervention

Patients who use tobacco are identified from Stanford Cancer Clinics, and our Tobacco Treatment Specialist reaches out to them to engage in tobacco cessation. If a patient is interested in the VR treatment option, patients will be checked on whether they would be able to use the VR intervention (e.g. smokes, smartphone compatibility, language fluency), and then is sent the intervention kit. Patients will be followed up with post intervention to check on effectiveness of the treatment. Participation in the 6-week VR intervention is voluntary and will not affect access to other tobacco treatment options. Treatment outcomes will be analyzed with pre/post survey data and app use frequency data.

Data obtained from the 20 patients trying out this intervention will inform whether MindCotine is a worthwhile treatment option to offer. If MindCotine proves to be effective among our patients, we may have another treatment option for our patients, especially for those who have exhausted their smoking cessation options.

MindCotine is the first virtual reality intervention for smoking cessation with pilot results supporting remote and self administration feasibility. Abstinence rates in their pilot study had similar results to other studies with smoking cessation apps.
(http://www.jmir.org/2020/7/e17571/)

In the pilot study, the average age of the participants was 41, supporting that the users do not necessarily have to be tech savvy. This suggests that MindCotine may be an effective digital health intervention for our patients, who tend to be older.

1.2.2. Mechanism(s) of Action for Stanford Tobacco Treatment Services – Virtual Reality Treatment for Smoking Cessation

The MindCotine 6-week training period consists of a playlist of audiovisual content (2D, audio, Virtual Reality) lasting from 2 to 10 minutes each, and a series of CBT-based self-reflective questions. The participant can select their Quit-Date at any given time, and will receive notifications accordingly. The 2D and audio activities are based on formal mindfulness exercises

based on breathing techniques, body scan, recognition of thoughts, emotions, and the impulse of smoking.

The VR therapy exercises include the following topics:
1. The Act of Smoking
2. RAIN meditation
3. Stress at work
4. Bodily sensations
5. Deep emotions
6. Nicotine anonymous
7. Alcohol as a trigger

Each content consists of a 2-minute animated environment to induce meditative states of mind, 6 minute of exposure with real people, and 2 more minutes of animated environment to again, induce a meditative mindset.

1.2.3. Clinical Experience

MindCotine is the first virtual reality intervention for smoking cessation with pilot results supporting remote and self administration feasibility. This pilot studied 120 participants from Buenos Aires, Argentina (mean age 43.2 years, SD 9.50; 47.5% female). Abstinence rates in their pilot study had similar results to other studies with smoking cessation apps. Follow up rates were >90% for both the treatment and control groups. At postintervention, the treatment group reported 23% abstinence compared with 5% of those in the control group (χ^2 =8.3; *P*=.004).

In the pilot study, the average age of the participants was 41, supporting that the users do not necessarily have to be tech savvy. This suggests that MindCotine may be an effective digital health intervention for our patients, who tend to be older. Long term outcomes have not been studied.

The manuscript of the pilot trial can be found on (http://www.jmir.org/2020/7/e17571/).

Our Tobacco Treatment Services has grown, and we are exploring novel treatments that incorporate technology for scalability. A manuscript of the project's progress is available at https://doi.org/10.3390/ijerph17062101

1.2.4. Importance of the Clinical Trial

The purpose of the Tobacco Treatment Service is to expand access to and engagement in tobacco cessation treatment services at the Stanford Cancer Center to patients and their family members. The project utilizes technological innovations to deliver provider education; optimize chart documentation, referral, and team communications; and extend treatment service delivery. Adding VR treatment is an option we are considering for patients who would like to quit smoking.

For patients with cancer and use tobacco, helping them quit can: Reduce treatment side effects (e.g. from surgery, radiation, and/or chemotherapy); Increase the effectiveness of treatment; Decrease the risk of cancer recurrence or of the development of other types of cancers; and improve overall well-being and quality of life.

1.3. Potential Risks and Benefits

1.3.1. Known Potential Risks of MindCotine

The virtual reality simulation could potentially trigger seizures. Those with a history of epilepsy should not use this treatment option.

There is also the possibility of side effects from the virtual reality simulation. Symptoms may include dizziness, disorientation, nausea, sweating, or headaches.

1.3.2. Known Potential Risks of Study Procedures

Given that the pilot study aims to see feasibility of VR program in reducing tobacco smoking, we do not envisage that participation in the study will be associated with elevated risk. We are not assessing suicidal ideation in our questionnaires. Some risk is always present in studies that involve human participants. Such risk may include the following:

1. Data Protection and Privacy: All study data are gathered on a HIPAA compliant web platform that resides behind Stanford security firewalls and has been tried and tested by the University for several years, thus actual risk from data breach for study data is low. All assessments, including the screening utilizing HIPAA compliant survey administration tool commonly used by Stanford University in its clinical trials (Qualtrics or REDCap). Given the high data protection safeguards embedded within Qualtrics or REDCap, there is little risk to the subject associated in regards to their privacy and/or confidentiality.

Research material obtained from human subjects will involve behavioral and psychological assessments including self-report questionnaires. All data will be obtained specifically for purposes of this pilot study. Data that are obtained from the Qualtrics/REDCap surveys will be stored and protected within Qualtrics/REDCap.

Data that are obtained via MindCotine: MindCotine established a connection app-server with secure layer; Data are encrypted while traveling the Internet. MindCotine have servers within the Google infrastructure with the highest standards of security and privacy. Emails will be asked for during app registration. IP addresses will be temporarily collected for Firebase (part of the app infrastructure) to work. All participant data on the app will be deleted a year after starting the app.

Only members of the research team (PI, post-doc, research assistant) will have access to the data. The clinical and research teams will have access to PHI, as described with IRB 48420. MindCotine requires emails for user registration with their app. Otherwise, no PHI is required.

Data sharing: Data shared between MindCotine and Stanford will be conducted using Stanford Medicine Box and secure email. MindCotine will share user data with the Stanford team. After the data are merged by the Stanford team, identifiers will be removed and each row of participant data will be assigned a number from 001-020. The Stanford team will analyze the data and provide a summary of outcomes (overall demographics, overall engagement with tobacco treatment interventions opted into at initial outreach, cessation outcomes) to MindCotine. The summary of outcomes will not have any identifiable information, and will describe the pilot sample.

2. Potential Upset due to Survey Questions: Foreseeable risks to subjects include the possibility that some assessment questions and/or treatment procedures may be upsetting to subjects. Experience at Stanford with similar populations has indicated that the risk of emotional upset during the assessments is low and if it occurred, the upset would likely not be serious in nature and temporary. Such risks will be minimized by asking a small amount of questions for tobacco use assessment, compatibility with the program satisfaction with program, and likelihood of recommending the program. Potential participants will also be informed that they may drop out of the study at any time and if requested, appropriate treatment referrals would then be given.

3. Risk of treatment avoidance due to engagement with the intervention. No treatment is being withheld. The pilot study offers the VR program to 20 participants as an option of the Tobacco Treatment Service, allowing for participants to also engage in other tobacco cessation treatment.

1.3.3. Known Potential Benefits

May help patients reduce smoking or help them quit.

2. STUDY DESIGN, OBJECTIVES, AND OUTCOMES

2.1. Study Design

2.1.1. Overall Design

The intervention model of this study is **Single Group.**

2.1.2. Primary Purpose of the Study

Health Services Research: To test feasibility of the MindCotine virtual reality program for smoking cessation among 20 patients. After the pilot, the team will decide whether to invest in MindCotine as a treatment option to offer to patients.

2.1.3. Study Cohorts / Arms / Groups

Pre/post-intervention design. Participants' tobacco use will be compared at two timepoints: Enrollment, and End of treatment.

2.1.4. Scientific Justification for Study Design

This study is a pilot to test feasibility of the app among patients from the Stanford Cancer Center who smoke cigarettes daily. There will be 20 kits available for testing feasibility. Outcomes will be assessed pre-intervention and post-intervention.

Factors that indicate feasibility will include (i) interest among our patient population in using the app, which will be offered at no cost; (ii) among those patients who are interested, that they are able to onboard and make use of the app; and (iii) patient ratings of recommending the app to others. Feasibility metrics would be at least (i) 20% interested in using the app; (ii) 75% of interested patients onboarded and using the app; and (iii) 70% recommending the app to others. Efficacy goals will be examining tobacco use reduction and quitting with goals of at least (iv) 50% reducing tobacco use and 10% quitting. Not feasible would be indicated by **less than** (i) 20% interested in using the app; (ii) 75% of interested patients onboarded and using the app; and (iii) 70% recommending the app to others.

Given the novelty of the program (virtual reality app) and our older patient population, we are interested in seeing do patients have interest in using the program, are they able to onboard at a distance (from home), do they make use of the app, and would they recommend the app to others. We also will examine whether they reduce or quit their tobacco use. If the metrics above are met, we would consider adding MindCotine to the choices available.

2.1.5. Treatment Assignment

Open-label: No study blinding.

2.1.6. Justification for Dose(s)

N/A.

2.1.7. End of Study Definition

A participant is considered to have completed the study if they have completed their end of treatment assessment after the 6-week intervention.

2.2. Objectives

Learning whether MindCotine is a feasible smoking cessation option among 20 patients from the Stanford Cancer Center who smoke cigarettes daily. Learning whether less tobacco use is associated with utilizing multiple tobacco cessation options.

2.2.1. Primary Objective

Learning whether MindCotine is a feasible smoking cessation option among 20 patients from the Stanford Cancer Center who smoke cigarettes daily.

2.2.2. Secondary Objective(s)

Learning whether less tobacco use is associated with utilizing multiple tobacco cessation options.

2.3. ClinicalTrials.gov Registration, Outcomes, and Results

This study is not an applicable clinical trial (ACT) per FDAAA 2007, does not meet the criteria for mandatory study registration at ClinicalTrials.gov, does not have direct NIH funding, and will not posted in the Stanford Clinical Trials Directory. Therefore, this study will not be registered at ClinicalTrials.gov.

3. SUBJECT SELECTION

3.1. Eligibility Criteria and Participant Eligibility Checklist

Inclusion and Exclusion Criteria are provided on the Eligibility Checklist which may be extracted from this document for use in screening potential subjects.

The Participant Eligibility Checklist must be completed in its entirety for each subject prior to registration (see Section 3.4 Registration / Enrollment). The completed, signed, and dated checklist is retained in the subject's record. Screening results will be collectively documented on the Study Participant Log (see references in Appendix A).

Participant Eligibility Checklist

I. Protocol Information

Protocol Title:	Stanford Tobacco Treatment Services – Virtual Reality Treatment fo Smoking Cessation
Principal Investigator:	Judith Prochaska

II. Subject Information

Subject name / Unique ID: /

III. Eligibility Criteria

3.1.1. Inclusion Criteria

1. Daily or some day cigarette smoker (>9 cigarettes/week)	☐		Identified as a cigarette smoker in Epic; Phone s
2. Age 18+	☐		18+ on Epic
5. Available to interact with a smartphone app for 6 weeks	☐		Phone screen
6. Available to complete the EOT assessment at en of 6-weeks	☐		Phone screen
8. Confirm phone, email, address during consent	☐		ICF, Epic

3.1.2. Exclusion Criteria

Prospective Participants Must NOT Meet ANY of These Exclusion Criteria	Yes		Supporting Documentation

* All subject files must include supporting documentation to confirm subject eligibility.

V. Statement of Eligibility

By signing this form of this trial I verify that this subject is:

☐ eligible for participation in the study ☐ ineligible for participation in the study

Signature:

Signature:

3.1.3. Lifestyle Considerations

- No Restrictions. The participant can access the app at any time of day. Interaction with the app is estimated to take 10 min per day.

3.1.4. Screen Failures

Participants consent to participate in the clinical trial, but who do not meet 1 or more Eligibility Criteria during the screening procedures are considered Screen Failures.
Screen Failures will not be considered enrolled subjects, although they **WILL** be tracked on the Screening Log (with reason for ineligibility) and in the OnCore study management system. Individuals who do not meet the criteria for participation in this trial, ie, screen failure, because of **smartphone compatibility** may be rescreened. Potential subjects who are re-screened will be assigned the same sequence number and OnCore subject identifier as for the initial screening. If a screen failure occurs and the person requested their information to not be kept, the decision will be honored but the screen will count towards the number of screen failures of that day.

3.2. Recruitment and Retention Procedures

3.2.1. Recruitment

Potential participants may be identified by the following methods:

- Review of the medical records of new or existing oncology patients for potential subjects who meet eligibility criteria.
    - Patients who use tobacco are identified from Stanford Cancer Clinics, and our Tobacco Treatment Specialist reaches out to them to engage in tobacco cessation. The VR pilot will be brought up as an option (phone script available). If a patient is interested in the VR treatment option, patients will be going through a phone screen (with consent) on whether they would be able to use the VR intervention (e.g. smokes, smartphone compatibility, language fluency), and if eligible and interested, proceeds to the informed consent process. After that, the intervention kit will be mailed to the participant, the participant interacts with the intervention and is followed up with an end-of-treatment survey after the 6-weeks.

3.2.2. Retention Procedures

None. After enrollment, participants will be contacted at the end of the 6-week intervention. Unless the participant reaches out to the team during the intervention period, there is no expected contact with the participant until the end of the 6-week period.

3.3. Informed Consent Process

Study participants will provide written informed consent prior to the conduct of any study-specific procedures in accordance with institutional policies via online. For Spanish speaking patients, the consent form will be translated by Stanford Hospital Translation Services prior to recruitment. The study is completely remote, and the consent form will be provided via online link.

3.4. Registration and Enrollment

3.4.1. Subject Registration Procedures

All subjects who provide informed consent for this study will be registered in the Stanford OnCore Enterprise Research System ("OnCore") database within 5 days of the date of consent, regardless of the outcome of any eligibility screening.

Subject identification numbers will be sequentially assigned **for the entire study.**

The Stanford study team will review eligibility for each subject, and provide the 3rd signature on the Eligibility Checklist, which confirms and documents eligibility. Once confirmed by Stanford, the subject will be promptly registered in OnCore (within 5 business days) and the subject's OnCore accrual status will be updated. At this time, the subject can begin study treatment procedures.

	Judith Prochaska 650-724-3608
@stanford.edu	jpro@stanford.edu

3.4.2. Subject Enrollment Procedures

For this study, a subject is enrolled on the study when registered per Section 3.4.1; has meet eligibility per the screening procedures; and has been otherwise accepted into the study.

Each week, the Tobacco Treatment Specialist generates an Edge Report that lets them know which patients have been identified as a tobacco user at the Stanford Cancer Center or satellite clinics. Any patients referred to the Tobacco Treatment team by a nurse practitioner or doctor of medicine will be included for outreach as well. Of the patients identified as a tobacco user and seen at the Stanford Cancer Center or satellite clinics, 74% are reached for initial outreach by the TTS. Of those reached, 34% engage in treatment. The study will be offered to all the patients reached at this initial outreach. The initial outreach involves contacting the patients with up to two phone calls. We do not know if these patients are interested in the app; Interest in the app will be considered for feasibility. We expect the study to be brought up as an option, along with the other tobacco treatment offerings (i.e. behavioral counseling, cessation medication), during a phone call with each patient up till enrollment stops.

If a patient expresses interest in the study, they will be directed to the phone screen conducted by the TTS. To enroll in the study, patients must pass the phone screen, and if eligible, sign the informed consent form on via Adobe Sign. Enrollment will stop after 20 informed consent forms have been signed. Enrollment will not focus on certain tumor types.

Should any interest in the study come up after we've finished enrollment, we'll note it but also inform the patient that we have filled enrollment for the study. This may happen if a patient who has screened, but has not signed the informed consent form, asks for some time to think about participating in the study. Patients who ask for some time to consider participation will be told only 20 spots are available and may fill; No spots will be held to wait on a response.

4. STUDY INTERVENTION

4.1. Investigational Drug / Device / Procedure: *MindCotine*

4.1.1. Name

MindCotine

4.1.2. Dose and Administration

Mobile app program. Can be used at any time. Duration intervention is estimated up to 10min a day for 6 weeks.

4.1.3. Regulatory Status of MindCotine

MindCotine is approved for marketing in the United States, for the indication(s) of tobacco cessation. This indication includes is for the use described in this study. Regulatory authorization to conduct this study is pursuant the definition of an IND-Exempt study.

4.1.4. MindCotine Preparation, Handling, Storage, and Accountability .

4.1.4.1. Acquisition and Accountability

MindCotine will send 20 VR kits to the Stanford team. These kits will include the MindCotine brochure (details what to expect with the VR smoking cessation program), cardboard headset, wristbands, stickers, and an activation code for accessing the full program. The program is an app is downloadable from the app store. These kits will be mailed out by the Stanford team to the 20 participants. Once the kit reaches the participant, that kit belongs to the participant; Nothing needs to be returned.

4.1.4.2. Formulation, Appearance, Packaging, and Labeling

MindCotine is packaged as a mobile app program. The app is downloadable from the app store. The VR kit MindCotine has for their users primarily is for providing a cardboard headset so an immersive VR environment can be achieved, and the activation code provides full access to the program.

4.1.4.3. Storage and Stability

The MindCotine app is available on mobile. No particular storage requirements aside from space for the app on the phone. The cardboard headset should be durable in most environments. Neither the phone nor cardboard headset should get wet.

4.1.4.4. Preparation

Preparations include downloading the app and utilizing the activation code; and assembling the cardboard headset from the VR kit. MindCotine is available for support if the participant decides to reach out to them. Participants can always reach out to the study team for questions.

4.1.5. Investigational Agent Supply

MindCotine is supplying the VR kits. The Stanford team will be handling the shipping to participants.

The mailing address and local contact phone number for MindCotine Inc. is:

Name: MindCotine, Inc.
Address: 2021 The Alameda Street, San Jose, CA 95126
Phone: 1-669-240-9137

4.1.5.1. Investigational Agent Ordering

MindCotine is supplying the VR kits. The Stanford team will be directly handling the shipping to participants. The Stanford team will coordinate shipping details with MindCotine.

The mailing address and local contact phone number for MindCotine Inc. is:

Name: MindCotine, Inc.
Address: 2021 The Alameda Street, San Jose, CA 95126
Phone: 1-669-240-9137

4.2. Comparator / Control Agent:

N/A

5. TREATMENT PLAN

5.1. Treatment Assignment

After the subject is determined to be completely eligible to participate in the study, the OnCore sequence number, a unique subject identifier, will be sequentially assigned. There is no randomization or blinding

5.2. Treatment Dose

N/A. No dosage.

5.3. Treatment Schedule

Comparison is post-treatment to pre-treatment among the participants.

5.4. Treatment Duration

The intervention period is 6-weeks. Estimated participation of 10 min per day interacting with the program.

5.5. Subject Medication Diary

N/A.

5.6. Pre-Treatment Criteria

Participants will undergo a phone screen before eligibility is determined. Participants should be daily cigarette smokers, English or Spanish fluent, have a compatible smartphone, available to complete survey assessments, willing commit to the intervention, and not have a history of epilepsy.

5.7. Dose Modifications and Dose-limiting Toxicities

Adverse event documentation and reporting is described in Section 7.

N/A, not a drug. If VR sickness is experienced during the intervention, the participant can remove themselves from the environment by taking off the headset.

5.8. Concomitant Medications, Procedures, and Supportive Care Guidelines

N/A

5.9. Criteria for Removing Subjects from Study Intervention and/or Study

Subjects are free to withdraw consent and discontinue participation in a study at any time without prejudice to further treatment. The investigator may discontinue a subject from treatment intervention or the entire study for medical or administrative reasons. The following reasons may lead to discontinuation from the study intervention or the entire study.

- Withdrawal of consent
- Study non-compliance
- Investigator discretion

If the subject elects to withdraw consent from further treatment with the study intervention, or is withdrawn by the investigator, it will be confirmed and documented if the subject will consent to continue to be followed per protocol, if applicable. The rationale for the investigator's decision to discontinue treatment will be clearly documented.

5.10. Duration of Follow-Up

After completion of treatment (ie, date of last treatment / intervention *6-weeks post enrollment)* subjects will be followed up soon after with an end of treatment survey after the intervention or removal from study or until death, whichever occurs first. Should the study team learn of any severe adverse events during the intervention period, Dr. Prochaska will be notified and the team will proceed according to her instructions.

5.11. Study Completion or Discontinuation

The study will be complete when the last study data, including all follow-up data, has been collected, and analysis is complete. This is expected to occur within a couple of months after the final study participant has completed their end of treatment assessment, which includes questions on tobacco use, satisfaction with the program, likelihood of recommending the program, and questions on whether VR side effects were experienced.

Subjects will no longer be followed or subject data collected as part of this study once the study is complete per this section.

Conditions may be discovered during the conduct of the study by the investigator, regulatory authorities, or other oversight bodies that indicate that the study should be terminated prematurely. The reasons that may warrant termination include, but are not limited to:

- The study is determined to be non-feasible, including inadequate accrual
- Determination of unexpected, significant, and/or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility
- Business decision by the Principal Investigator, institution, or funding source, etc

Written notification will be provided by the investigator to the IND/IDE sponsor, the funding entity, and regulatory authorities as appropriate, including the IRB of record.

6. STUDY PROCEDURES AND ASSESSMENTS

6.1. Schedule of Events

Schedule of Events

	Screening			Wk 3		Wk 5			Wk 8		Wk 10	Wk 11	
Phone consent	**X**												
Smartphone compatibility	**X**												
TTS cessation services	**X**												
Notes	Ideally the EOT survey is completed as close as possible to 6-weeks. It's possible the study team will attempt follow up for up to three times after the intervention period.												
Recruitment				**X**		**X**			**X**		**X**		

6.2. Description of Procedures and Assessments

6.2.1. Efficacy Assessments

1. Patients who use tobacco are identified as part of the Tobacco Treatment Program. The Tobacco Treatment Specialist reaches out to these patients and offers tobacco cessation resources, and the pilot study will be offered as a part of this. Recruitment of 20 participants is estimated to take approximately 3 months.
2. If a patient expresses interest in the pilot study, they will go through a phone screen consent and questionnaire. Inclusion criteria includes daily or some day cigarette smoking, English or Spanish fluency, have compatible smartphone, willing to commit to the intervention and complete the surveys, and no history of epilepsy.

3. Informed Consent: If a patient is eligible for the study, and would like to proceed, they will go through an informed consent process provided via online link. The Tobacco Treatment Specialist will be available to go through the consent form with the patient. If signed, they will be enrolled in the pilot study, and a copy of the signed consent form can be provided via secure email or by mail.
4. Within two business days of the informed consent, a study research team will keep track of signed consents and keep track of participants, including demographics, any tobacco cessation resources the participant also wanted to use, date of screening, when the kit was mailed out, and when end of treatment will be.
5. Within two business days of the informed consent, the study team will mail out a VR kit to the participant. The VR kit should reach the participant in 3-5 business days.
6. Once the VR kit is received, the participant can have full access to the MindCotine app and start the intervention.
7. The participant interacts with the app for 6-weeks.
8. After the 6-week intervention, the study team reaches out to the participant to complete the end of treatment survey. If the team is unsuccessful with reaching the participant after 3 attempts, the participant will be considered "lost to follow up". The end of treatment assessment will include questions on tobacco use, satisfaction with MindCotine, likelihood of recommending MindCotine to others, and whether VR side effects were experienced.
9. Any adverse effects learned of will be tracked.
10. MindCotine will provide user app data from the 20 participants.
11. The study team will link the app data to the survey data and remove identifiers.
12. Dr. Prochaska will conduct data analysis.
13. The study team will provide a summary of outcomes to MindCotine.
14. The study team will decide on whether to invest in MindCotine as a tobacco treatment option for patients.
15. Dr. Prochaska may disseminate outcomes.

6.2.2. Safety and Other Assessments

During screening, patients who have a history of epilepsy are not eligible for the pilot study. The VR environment may be triggering for these patients.

At end of treatment, VR side effects will be assessed.

We do not anticipate serious adverse events as a result of an app designed for smoking cessation. Should any become known to the team, Dr. Prochaska will be notified within 24 hours upon learning of that information, and the team will proceed according to her directions. All SAEs will be documented. Dr. Prochaska is a licensed clinical psychologist and has led multiple clinical trials.

7. ADVERSE EVENTS AND REPORTING PROCEDURES

References for SCI adverse event (AE) policies and practices are provided in Appendix A.

7.1. Adverse Event Definitions

An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An adverse event can be any unfavorable and unintended sign or symptom, including abnormal laboratory findings, or disease, that is temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse reaction is any event that is caused by a drug or device, ie, possibly-, probably-, or definitely-related to the use of the drug or device.

Except as otherwise explicitly defined within this section, **this also includes all events of clinical deterioration such as tumor relapse, recurrence, or upstaging, or new cancers**.

Within the scope of this study and protocol, adverse device effects, ie, events that have a serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device may be referred to as "serious adverse events (SAEs)."

Serious adverse events (SAEs) are defined per the FDA definition at 21CFR§312.32(a) and ICH GCP E6. An adverse event is considered "serious" if, in the opinion of the PD, investigator, or sponsor, it results in ANY of the following.

- Death
- Life-threatening adverse event with an **actual and immediate risk of death** [21CFR§312.32(a)]
- Inpatient hospitalization or prolongation of existing hospitalization, except planned hospitalization or hospitalization only for study conduct will not be considered SAEs
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Event jeopardizes the subject and may require medical or surgical intervention to prevent one of the outcomes listed here

7.2. Classification of Adverse Events

7.2.1. Severity of Event

NCI CTCAE version 5.0 is used to assess the severity of adverse events in this study.

7.2.2. Adverse Event Attribution to Intervention or Study

For this study, all recorded adverse events will assessed on the basis of whether or not the adverse event was caused by / due to (ie, related) to the study intervention(s). AEs, serious or otherwise, will be attributed by the Principal Investigator or qualified designate to study treatment in accordance with the definitions below.

Definitely Related. There is clear evidence to suggest a causal relationship, other possible contributing factors can be ruled out. The clinical event, includi abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologic or phenomenologically definitive, with use of a satisfactory rechallenge proced necessary. **Probably Related**. There is evidence to suggest a causal relationship, and th influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of th study intervention, is unlikely to be attributed to concurrent disease or other dr or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition. **Potentially / Possibly Related**. There is some evidence to suggest a causal relationship (eg, the event occurred within a reasonable time after administrati the trial medication). However, other factors may have contributed to the ever (eg, the participant's clinical condition, other concomitant events). Although ar adverse event may rate only as "possibly related" soon after discovery, it can b flagged as requiring more information and later be upgraded to "probably relat	These are treated as **"Related"**
Unlikely to be related. A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes causal relationship improbable (eg, the event did not occur within a reasonable after administration of the study intervention) and in which other drugs or chem or underlying disease provides plausible explanations (eg, the participant's clir condition, other concomitant treatments). **Not Related**. The adverse event is completely independent of study interventi administration, and/or evidence exists that the event is definitely related to anc etiology. There must be an alternative, definitive etiology documented by the	These are treated as **"Not Related"**

In addition, for adverse events determined "Not Related" to the study intervention(s), the Principal Investigator or qualified designate will attribute the event to the study or procedures according to the definitions above. Note that adverse events can be determined related to both the intervention(s) and/or the study / procedures.

7.2.3. Expectedness of Event

The Principal Investigator or qualified designate will also assess all recorded adverse events on basis of event severity, frequency (if applicable/assessable), and the established product risk information described within the product Investigator Brochure; the FDA-approved product labeling (if an approved agent); and/or this protocol document, as to whether the events are "expected" or "not expected" relative to the study interventions and/or the study / procedures.

Note that unexpected adverse events may have reporting requirements as described elsewhere in this section.

7.2.4. Time Period of Event Assessment and Follow-up

Once the participant signs the consent form, any adverse event that occurs during their study period (approx.. 6-weeks) will be kept track of once the study team learns of the event.

All possibly study related SAEs will be followed until resolution.

7.3. Potential Adverse Events and Risks

Potential adverse events and risks were described at Section 1.3.1 Known Potential Risks.

In addition to the summary risks described in Section 1.3.1, adverse events described by severity and frequency within the informed consent are considered anticipated, ie, not unexpected. Procedural risks described in Section 1.3.1 are considered anticipated.

7.4. Adverse Event Monitoring and Collection

Untoward medical events experienced by a study subject during the study intervention period (6-weeks) will be considered an adverse event (AE), regardless of whether or not considered intervention-related. All events of disease progression or second cancer will be recorded as a serious adverse event (SAE) using the Preferred Term appropriate for the clinical finding.

7.4.1. Case Report Forms for Adverse Event Reporting

Both SAEs and non-serious adverse events will be described in source documentation and listed on study-specific Case Report Forms (CRFs or eCRFs).

Adverse events will be recorded on a log (see references in Appendix A) providing the unique subject identifier, event preferred term, CTCAE body system, date of occurrence, date of resolution; and type of resolution. All signs, symptoms, significant laboratory findings, AND diagnoses should be recorded, regardless of relationship, except as described in this document. A single "overarching" diagnosis should not be solely entered as the adverse event term in lieu of the full list of observed signs, symptoms, and significant laboratory findings, which may include the diagnostic preferred term.

Types of resolution are:

- "Resolved," ie, to Grade 0 (or baseline if a pre-existing condition)
- "Continuing" and stable (includes downgrades from a higher grade to a lower grade)
- "Deceased" (due to any cause while on-study)
- Lost-to-follow-up.
- **NOTE**: "Hospitalized" is not an outcome.

Any pre-existing condition that worsens in severity or frequency should be recorded as a new adverse event, except as described in this document.

7.5. Adverse Events of Special Consideration

7.5.1. Second vs Secondary Malignancy

7.5.1.1. Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). A second malignancy is by definition a serious adverse event (SAE), and will be recorded and reported accordingly.

7.5.1.2. Secondary Malignancy

In the context of a clinical study, a secondary malignancy is a cancer caused by chemotherapy, radiation, or the investigational agent/intervention. A secondary malignancy is not considered a metastasis of the initial neoplasm, but nonetheless, a secondary malignancy is by definition a serious adverse event (SAE), and will be recorded and reported accordingly. Secondary malignancies are usually described as one of the following:

- Leukemia secondary to oncology chemotherapy [eg, acute myelocytic leukemia (AML)]
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

By definition, secondary malignancies are adverse events that are both serious and related to the research, and should be anticipated to be an Unanticipated Problem (UP) and reported accordingly. If also determined to be related to the study treatment, and not described by the Investigator Brochure or package insert as known to be associated with the study agent, the secondary malignancies may also necessitate Expedited Reporting to FDA, eg, an IND Safety Report to the IND.

7.5.2. Progressive Disease

Progressive disease will be reported by the clinical signs or symptoms of disease progression. If the event is Grade 5 fatal and signs/symptoms of disease progression are not available / informative for the event, the CTCAE v5.0 preferred term “Disease Progress” may be used.

7.5.3. Other Adverse Events of Special Considerations

None.

7.6. Adverse Event Reporting

Reportable adverse events, based on relatedness (attribution) to the study agent; expectedness, severity (Grade 1 to 5), seriousness (Yes/No), or any other aspect of the investigation, will be reported as described below.

- Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat; and head congestion should be reported as "upper respiratory infection").

- Serious adverse events (SAEs) per the definition at 21CFR§312.32 will be reported to the investigator **within 24 hours of the knowledge of the event**. Possibly study related SAEs will be reported to the MindCotine.
- SAEs will be reported to the SCI Data and Safety Monitoring Committee (DSMC) by submission to CCTO-Safety. The event must be described on either the SCI SAE form (see references in Appendix A), or a study-specific form. If applicable, the Form FDA 3500A (see Section 7.6) for mandatory IND Safety Reports may be substituted. The report will be sent by **secure** email to CCTO-safety@stanford.edu at the time of the **first** notification to MindCotine (if possibly study related); or the IRB of record. The SAE form must be signed by the investigator. CCTO-Safety will process the SAE report into OnCore, and the DSMC will review the event. See the SCI Data Safety and Monitoring Plan (DSMP).
- All **Unanticipated Problem (UPs)** associated with the use of a drug, biologic, or device will be reported as follows.
    - Note that for the purposes of Stanford IRB Unanticipated Problem reporting, subjects are considered to be study participants when consented, ie, events during screening and/or pre-treatment through that subject's official end of study participation may qualify as reportable.
    - To the Stanford IRB, by the Stanford Protocol Director, if an adverse event meets the Stanford IRB's current definition of an Unanticipated Problem (UP) as specified by the IRB document "Events and Information that Require Prompt Reporting to the IRB" (GUI-P13), per the timeframes defined therein. See also Section 9.4 Data and Safety Monitoring Plan. In addition to event triggered expedited UP reports, all UPs should be summarized in the Continuing Review, with, as applicable, a discussion of any change in assessment of risk (ie, different than previously described).
    - To the SCI Data and Safety Monitoring Committee (DSMC), by submission to CCTO-Safety / OnCore as an SAE (see SAE reporting to DSMC above. See also the SCI DSMP).

Serious adverse events (SAEs) will be reported to the IRB of record and to the DSMC in accordance with the applicable guidelines and regulations.

Serious adverse events (SAEs) will be reported to the IRB of record in accordance with the applicable guidelines, regulations, and SOPs (see references in Appendix A).

7.7. Adverse Event Records

The investigator will retain adverse event source data, supporting documentation of attribution and seriousness, and copies of official adverse event reports or SAE CRFs, as well as documentation of informal communications (such as telephone calls or emails) in accordance with the current version of Stanford School of Medicine standard operating procedure SOP-005 "Identifying and Reporting Adverse Events" (see references in Appendix A).

7.8. Risk Mitigation

Dr. Prochaska will be informed of all SAEs that occur during the study within 24 hours upon learning of the event, and the participant will be follow up with as appropriate.

8. CORRELATIVE / SPECIAL STUDIES

None

8.1. Correlative Studies Background

None

8.2. Laboratory Correlative Studies

None.

9. REGULATORY CONSIDERATIONS AND DATA REPORTING

9.1. Review and Approval of Protocol by IRB and SCI SRC

This protocol, the proposed informed consent, and all forms of information related to the study that will be provided to the subjects (eg, questionnaires, handouts, written instructions, diaries, advertisements used to recruit subjects, etc) will be submitted to, reviewed, and approved by the SCI Scientific Review Committee (SRC) and the Stanford Administrative Panels on Human Subjects in Medical Research of the Research Compliance Office (ie, the Stanford IRB) ") prior to initiation of the research. Any changes made to the protocol will be submitted as a modification and will be approved by the IRB of record prior to implementation.

This study will be conducted in accordance with the iteration of the protocol that is currently IRB-approved.

9.2. Protocol Compliance and Deviations

9.2.1. Compliance with the Protocol

No deviation or changes from the procedures and process described by the IRB-approved protocol, except those necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial [eg, change in study monitor(s), change of telephone number(s)], will be knowingly permitted without review and approval by the IRB of record.

9.2.2. Protocol Deviations

Any deviation (or violation) from the IRB-approved protocol, including those that eliminate an immediate hazard or are administrative in nature, will be documented and explained in the study

site file. All deviations at the Stanford clinical that meet the reporting requirements defined in the Stanford University HRPP Policy Guidance "Events and Information that Require Prompt Reporting to the IRB" GUI-P13 with be reported to the Stanford IRB by the Stanford investigator within the defined timeframes. All deviations will reported to the Stanford IRB either annually in the IRB continuing review, or individual as IRB Prompt Reports (within 5 or 10 working days, see GUI-P13).

For all studies monitored by the SCI Data and Safety Monitoring Committee (DSMC) as defined in Section 9.3 Data and Safety Monitoring Plan, all deviations, exceptions, and/or violations of the protocol, as well as deviations, exceptions, and/or violations to applicable IRB policies and overarching regulations, will be reported to the SCI data Safety and Monitoring Committee (DSMC). Accordingly, as the DSMC only reviews reports recorded in OnCore, such events will be promptly submitted in the OnCore record for the study, per the current SCI DSMC SOP.

9.3. Data and Safety Monitoring Plan

The Principal Investigator is responsible for monitoring the conduct of the study including oversight of safety and protocol compliance. On an ongoing basis, the Principal Investigator will review safety data and identify any changes to the research necessary to ensure the appropriate measures and monitoring necessary for participant safety. In addition to the Principal Investigator's safety monitoring role, the SCI DSMC will conduct data and safety monitoring activities for this study.

9.3.1. Monitoring

The Principal Investigator will be the monitoring entity for this study. The study data safety monitoring plan (DSMP) must be commensurate with the risk of the study design with adequate measures for oversight of data and safety monitoring. The Principal Investigator will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and GCP. This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the Principal Investigator will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the Principal Investigator's monitoring efforts will be communicated to the respective IRB of record and appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

9.3.1.1. Investigator Monitoring

Pursuant to the Guideline for GCP, monitoring is defined as the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s).

The Principal Investigator is responsible for self-monitoring the progress of the trial on a continuous basis. Self-monitoring includes, but is not limited to, those items that will be reviewed during an audit (see also Section 9.5).

9.4. Data Management

Source documents for all research data will be retained in accordance with all applicable regulations and institutional requirements for data retention. These materials will be made available for monitoring and/or auditing by SCI DSMC, other monitoring body and/or regulatory agencies.

9.4.1. Data Management Plan

The study data will be collected via the **REDCap or Qualtrics** central online database, with password-protected access limited to the study team .

The Stanford Principal Investigator will provide a data monitoring plan describing how and when the Stanford Principal Investigator and/or designates will monitor the study. The monitoring will be adequate to assure that the valid consent is obtained and documented; the per-protocol data are collected; records and databases are maintained with adequate and accurate participant case histories; adverse events are reported; clinical protocol is maintained; and the study is conducted according to the established procedures of the IRB of record. Original source documents include clinical charts and hospital, laboratory, and pharmacy records.

9.5. Site Documentation and Management

The following information will be maintained by the Principal Investigator at the participating site.

- Delegation of Authority Log, indicating study role, training date, on-study date (date of first research-related procedure or scan), and off-study date
- Financial Disclosure Forms and updates
- Copies of all correspondence with the IRB of record, including all approval letters and approved template informed consent documents, in chronological order by date.
- Copies of all correspondence with the local Scientific Review Committee, including approval letters, renewals, and other types of communication.
- Study agent accountability log
- Serious adverse event (SAE) log, documenting the subject, date, event, relatedness, follow-up, and outcome, with dates of communication to the IRB of record and Oncore/CCTO-Safety (Stanford site).
- Log of Deviations (ie, excursions form the protocol not authorized by the Stanford investigator and approved by the IRB). The Log of Deviations must be maintained in OnCore.
- Laboratory documentation, including copies of local site CAP and CLIA certificates, State licenses, laboratory director CV and medical license, with laboratory normal values/reference ranges for all labs used in the study.
- Printed, dated copy of roster for IRB of record, for each year of the study.

9.6. FDA Oversight

9.6.1. Investigational New Drug (IND) Application Considerations N/A

9.6.2. Investigational Device Exemption (IDE) Application Considerations

Exempted Device Investigation

This study describes the use of a device in a study that is considered to not require an Investigational Device Exemption (IDE), as elucidated at 21CFR§812.2(c). This study will be submitted to the IRB of record, and their approval obtained, before the study is initiated.

10. STATISTICAL CONSIDERATIONS

A pilot study (n=20), with short-term outcomes, and limited data collection, the statistical plan is descriptive in nature. Feasibility metrics would be at least (i) 20% interested in using the app; (ii) 75% of interested patients onboarded and using the app; and (iii) 70% recommending the app to others. Efficacy goals will be examining tobacco use reduction and quitting with goals of at least (iv) 50% reducing tobacco use and 10% quitting. Descriptive statistics (e.g., means/SD, frequencies, ranges) will summarize participant demographic and tobacco use characteristics, changes in tobacco use over time, MindCotine app usage, feedback on the MindCotine program, dropout and any adverse effects. The quit rate among participants in this pilot will be compared to the quit rate for our tobacco treatment service as a clinical benchmark.

10.1. Statistical Plan

A pilot study (n=20), with short-term outcomes, and limited data collection, the statistical plan is descriptive in nature.

10.1.1. Method of Treatment Assignment

All 20 participants will receive the VR kit with an activation code to access the full MindCotine program.

10.1.2. Sample Size Determination

This is a pilot study to see if MindCotine is feasible for patients from the Stanford Cancer Center who smoke. MindCotine will be providing 20 VR kits for free for this purpose. The sample size is N=20. We view a sample size of 20 as sufficient to gain an initial understanding of interest in the program and use of the program in our patient population.

10.1.3. Minimization of Bias

App usage is collected from the MindCotine app – it is not self-reported. Assessment items collecting feedback on MindCotine are non-leading. Standard measures of participant characteristics and tobacco use are utilized.

10.2. Study Endpoints

Feasibility metrics would be at least (i) 20% interested in using the app; (ii) 75% of interested patients onboarded and using the app; and (iii) 70% recommending the app to others. Efficacy goals will be examining tobacco use reduction and quitting with goals of at least (iv) 50% reducing tobacco use and 10% quitting.

10.2.1. Primary Endpoint

App feasibility and acceptability – that is, interest in using the app, onboarding to the app, and recommending the app to others.

10.2.1.1. Relevant Subset for Primary Objective / Outcome

Interest in using the app will be calculated as 19 out of out of the total number of patients invited to use the app minus 1.

Onboarding of the app will be calculated as the number who register with the app out of the 20 patients provided with the program.

Recommending the app to others will be calculated for the N=20 participating.

10.2.1.2. Endpoint Definition for Primary Objective / Outcome

i) Agreement to use the app

ii) Onboarding of the app

iii) Endorsing that they would recommend the app to others

10.2.1.3. Assessment Methods for Primary Objective / Outcome

i) Intake interview will track the number of declines

ii) MindCotine app will record registration

iii) Survey

10.2.1.4. Measurement Time Points for Primary Objective / Outcome

i) Intake interview

ii) Intervention period

iii) EOT

10.2.1.5. Response Review

There is no drug dosage involved. The study ends after the last participant completes their EOT assessment. Data analysis will be comparing pre- with post-treatment.

10.2.2. Secondary Endpoint(s)

Quitting, making a quit attempt during the past 6 weeks, use of cessation medications, smoking reduction (ie., change in cigarettes per day from baseline), MindCotine usage, MindCotine dropout, and adverse events.

10.3. Interim Analyses

N/A. Pilot study of N=20.

10.3.1. Stopping Rules

N/A. Pilot study of N=20.

10.4. Primary Analysis

Interest in using the app will be calculated as 19 out of out of the total number of patients invited to use the app minus 1. The total number of patients invited to use the app meaning the number of patients presented with this study as a possible treatment opportunity during the TTS's outreach calls.

Onboarding of the app will be calculated as the number who register with the app out of the 20 patients provided the program.

Recommending the app to others will be calculated for the N=20 participating.

10.4.1. Primary Analysis Population

Full sample N=20.

10.4.2. Primary Analysis Plan

Interest in using the app will be calculated as 19 out of out of the total number of patients invited to use the app minus 1.

Onboarding of the app will be calculated as the number who register with the app out of the 20 patients provided the program.

Recommending the app to others will be calculated for the N=20 participating.

10.5. Secondary Analysis

Frequency calculation of the number of participants who report being tobacco free at the end of treatment divided by the full sample size (N=20). We will assume those who drop out to be still using tobacco.

Frequency calculation of quit attempts, use of cessation medications, MindCotine dropout, and adverse events. We will calculate the mean change in reported cigarettes per day from baseline to EOT. We will calculate mean scores for MindCotine app usage.

10.5.1. Secondary Analysis Population

Full sample N=20.

10.5.2. Secondary Analysis Plan

Frequency calculation of quit attempts, use of cessation medications, MindCotine dropout, and adverse events. We will calculate the mean change in reported cigarettes per day from baseline to EOT. We will calculate mean scores for MindCotine app usage.

10.5.3. Sample Size

N=20.

10.5.4. Accrual estimates

4 patients a month.

10.5.4.1. Sample size justification

Initial pilot to examine feasibility and acceptability.

10.5.4.2. Effect size justification

N/A. This pilot study is not powered to test efficacy.

10.5.4.3. Criteria for future studies

If found to be feasible to deliver and acceptable among our patient population, we will consider a larger evaluation powered to test efficacy.

10.6. Descriptive Statistics and Exploratory Data Analysis

Per responses above, this pilot study is descriptive in nature.

11. REFERENCES

Gali K, Pike B, Kendra MS, Tran C, Fielding-Singh P, Jimenez K, Mirkin R, Prochaska JJ. Integration of Tobacco Treatment Services into Cancer Care at Stanford. *International Journal of Environmental Research and Public Health*. 2020; 17(6):2101. https://doi.org/10.3390/ijerph17062101

Goldenhersch E, Thrul J, Ungaretti J, Rosencovich N, Waitman C, Ceberio M. Virtual Reality Smartphone-Based Intervention for Smoking Cessation: Pilot Randomized Controlled Trial on Initial Clinical Efficacy and Adherence. J Med Internet Res 2020;22(7):e17571. URL: https://www.jmir.org/2020/7/e17571 DOI: 10.2196/17571

12. PROTOCOL HISTORY

ıendment ʏersion) Date *	Change Summary
1 9.7.21)	ıdated to respond to tabled comments.

* Latest version date should match footer date of the current protocol

13. APPENDICES

13.1. Appendix A. References for Stanford Cancer Institute Policies & Practices

Relevant Stanford Cancer Institute (SCI) process, policies, and documentation include the following.

Standard Operating Procedures (SOPs):

- Stanford School of Medicine standard operating procedure SOP-005 "Identifying and Reporting Adverse Events." This document is available on the Spectrum website.

http://med.stanford.edu/spectrum/b4_research_quality/b4_3_standard_operating_procedures.html.

- SCI Scientific Review Committee (SRC) Policies and Procedures

http://med.stanford.edu/content/dam/sm/cancer/documents/PRMSDocuments/SRC_SOP.pdf.

- SCI Institutional Data and Safety Monitoring Plan.

http://med.stanford.edu/cancer/research/trial-support/dsmc.html.

- SCI Data Management in Clinical Investigations

http://med.stanford.edu/content/dam/sm/ccto/sunet_id_resources/regulatory_documents/sop/SOP-Data%20Management.pdf.

Logs and Forms:

- The SCI Adverse Event Log (editable):

http://med.stanford.edu/content/dam/sm/ccto/sunet_id_resources/coordinator_documents/Adverse%20Event%20Log.pdf.

- SCI Serious Adverse Event Report Form (editable):

http://med.stanford.edu/content/dam/sm/ccto/sunet_id_resources/coordinator_documents/SAE_CRF.pdf.

- Sample Study Participant Log (editable):

http://med.stanford.edu/content/dam/sm/ccto/sunet_id_resources/coordinator_documents/Subject_Log_07.29.11.doc.

Guidelines:

Current Stanford University IRB policies and procedures:

- Stanford University Human Research Protection Program (HRPP) Policy Manual at:

http://researchcompliance.stanford.edu/hs/hrpp/Documents/hrpp_entire.pdf.

- Stanford University HRPP Policy Guidance Events and Information that Require Prompt Reporting to the IRB GUI-P13 at:

http://humansubjects.stanford.edu/research/documents/Events-Info-Report-to-IRB_GUI03P13.pdf.

- Stanford University HRPP Unanticipated Problem reporting process is defined at Section 3.10, in the Human Research Protection Program (HRPP) Policy Manual

http://researchcompliance.stanford.edu/hs/hrpp/Documents/hrpp_entire.pdf.

Other regulatory documentation and resources

- The Common Terminology Criteria for Adverse Events (CTCAE) **version 5** are available at:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50, see https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5.0.xlsx OR https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

- The International Conference on Harmonization (ICH) Guideline on Good Clinical Practice (ICH GCP E6r1), including adverse event reporting, is available at:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf.

These links may change from time to time, and will be updated in this template as needed. Consult issuing authority as needed.

13.2. Appendix B. Other appendices as needed

13.2.1 Questionnaires

Screening section:

3. How many cigarettes did you smoke in the past 7 days?	_____	andard
4. Are you currently using any other tobacco products? (select all that apply)	a. E-cigarettes/vaping devices b. Non-tobacco nicotine products (e.g. Zyn) c. Cigars, cigarillos, little filtered cigars d. Heated tobacco (IQOS) e. Blunts f. None	iginal question
6. Do you use a smartphone? If No, pt is not eligible.	a. Yes b. No	iginal
7. What smartphone device and version do you use? If a or c is selected, pt not eligible. Phone is not compatible. If e is selected, check with MindCotine on compatibility if they do not screen out in later questions.	a. Older than iPhone 4 b. iPhone 4 or newer c. Older than Android version 4.1 d. Android version 4.1 or newer e. Other/Unknown	iginal

8. Would you be available to interact with a smartphone app for a 6 week period? If No, pt is not eligible.	a. Yes b. No	iginal
9. Would you be available to answer questions about the program at the end of the 6 week period? If No, pt is not eligible.	a. Yes b. No	iginal
Thank you for your responses. Unfortunately it does not look like this treatment option is a good fit for you. We are happy to share other treatment options available to you. If patient asks why, can explain: The treatment option... **[Q1]** is offered for current cigarette smokers. **[Q3]** is offered to those who smoke more frequently. This is so we can better understand if the intervention is useful. **[Q5]** is not designed in other languages. **[Q6, Q7]** works on newer smartphones. **[Q8, Q9]** is being tried out with a limited amount of patients to see whether it is an option worth offering to our patients in the future and for this to work out, we would like		**reen out**
Thank you for your responses. [for staff] *Go through phone consent. Then set up with intervention if consent is obtained.*		**reen in**

[for staff] *After screen in, keep track of patient, their start date, demographics, and do end of treatment when it's time.*

End of Treatment:

3. Are you currently using any other tobacco or nicotine products? (select all that apply)	a. E-cigarettes/vaping devices b. Non-tobacco nicotine products (e.g. Zyn) c. Cigars, cigarillos, little filtered cigars d. Heated tobacco (IQOS) e. Blunts	Original
4. Are you currently using any quit smoking medications?	a. Chantix b. Bupropion c. NRT (patches, gum, lozenges, spray)	Original
If still smoking – 5. During the past 6 weeks, have you stopped smoking cigarettes for one day or longer because you were trying to quit smoking?	a. Yes, stopped smoking cigarettes for one day more in an attempt to quit b. No, did not stop smoking cigarettes for one or more	ASPiRE (modified
6. How would you rate the MindCotine program?	a) Excellent b) Good c) Fair	CSQ-8 (adapted
7. If a friend was in need of quitting smoking, would you recommend MindCotine to them?	a) No, definitely not b) No, I don't think so c) Yes, I think so d) Yes, definitely	CSQ-8 (adapted
8. Did you experience any of the following when using the MindCotine app?	**1. Dizziness** None Mild Moderate Severe **2. Nausea** None Mild Moderate Severe **3. Disorientation** None Mild Moderate Severe **4. Sweating** None Mild Moderate Severe **5. Headache**	Original for assessing side effe of VR

13.2.2 Recruitment Guide

The Tobacco Treatment Specialist (TTS) will contact patients as part of IRB 48420. Below is a script in navy blue for when the TTS offers different treatment options. Note: Wording may be slightly altered to allow for organic conversation or clarity.

We have a pilot study going on that involves a mobile-based virtual reality program to help quit smoking. The study is to help decide on whether we should invest in the virtual reality program to offer as part of our tobacco treatment services. The virtual reality treatment involves learning skillsets to aid with quitting smoking, and the treatment can be done remotely. We are looking to recruit 20 participants. If you're interested, would you like to go through the screening interview to see if you can participate in the study?

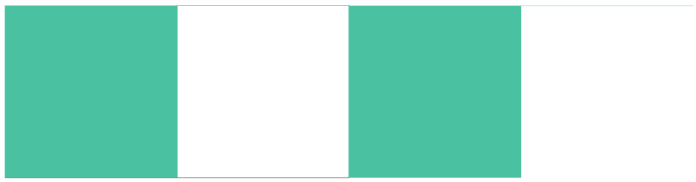
Or

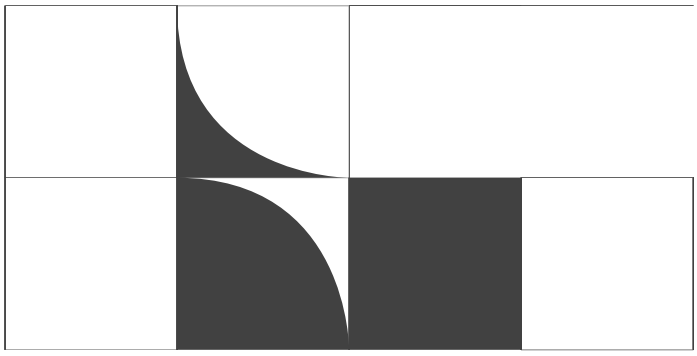
I wanted to let you know about a new opportunity we have available. It is a mobile-based virtual reality program for quitting smoking. The program teaches skills for quitting smoking and is very visual. The treatment can be done at home from your phone. We have 20 of the kits available to test out. If you're interested, would you like to go through some screening questions to see if the program would be a good fit for you?

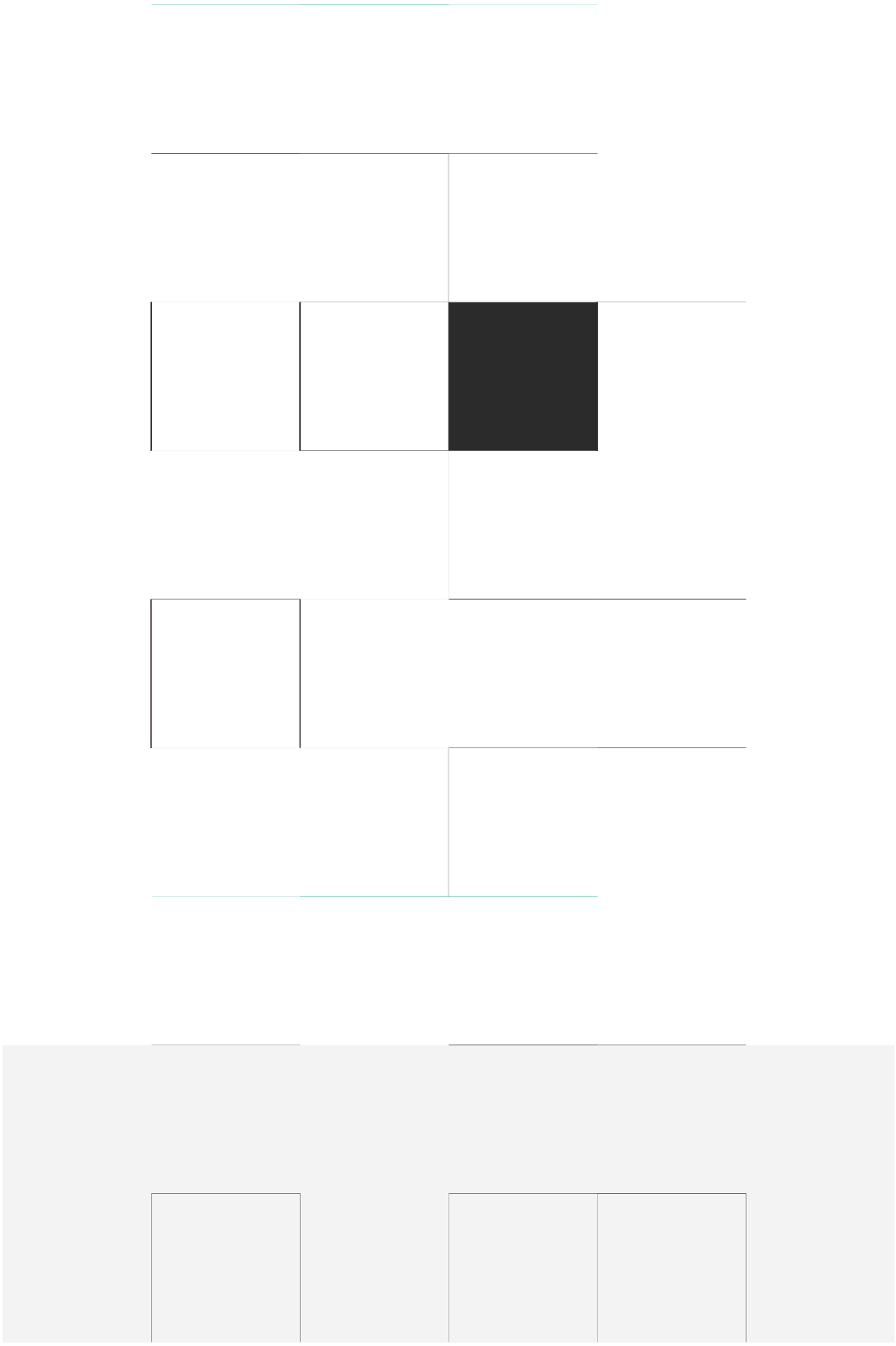
If yes, proceed to phone screen.

If no, continue engagement as part of IRB 48420.

13.2.3 MindCotine Brochure








HOW TO INCREA
YOUR CHANCES
STAY QUIT
MIND
MIND

SRC Pre-review Comments and Recommendations:

Reviewer will input text comments here for return to the author / study team.