Study Protocol and Statistical Analysis Plan

Title	Development of a mHealth Intervention for Ambivalent Smokers
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NCT Number	NCT04560868
Clinicaltrials.gov identifier	1401452
Version Date	9/22/2022 for ClinicalTrials.gov

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LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
NCI	National Cancer Institute
NIH	National Institutes of Health
NRT	Nicotine Replacement Therapy
OTC	Over the Counter
PPA	Point Prevalence Abstinence
SAE	Serious Adverse Event/Serious Adverse Experience
UC	Usual Care
UP	Unanticipated Problem

PROTOCOL SUMMARY

Title	*Development of a mHealth Intervention for Ambivalent Smokers: A Pilot Feasibility Study*
Précis	Tobacco use remains the leading preventable cause of death and illness in our society. Despite this, 36.5 million US adults continue to smoke. Most of these people (70%) want to quit smoking someday but are not yet ready to quit or actively seeking treatment. That is, they are "ambivalent" about quitting. This project creates an innovative mobile health (mHealth) intervention targeted to ambivalent smokers. The trial uses a parallel, two-arm, randomized trial design. Ambivalent smokers will be randomized to receive either a control ("standard care") version or an experimental version of the app and we will compare the two.
Objective	Conduct a randomized pilot study to assess the feasibility, acceptability, and potential impact of the experimental version of the app compared to the control version.
Outcomes of Interest	As a pilot study, we do not have a single "primary outcome" of interest. Rather, we will examine a range of measures designed to inform our study objectives: assess the program's feasibility (program engagement), acceptability (ratings of satisfaction and helpfulness), impact on cognitive mediators of change (self-efficacy, outcome expectations, and motivation) and impact on indicators of smoking behavior change (quit attempts, smoking reduction, and abstinence).
Population	Participants will be recruited nationwide via advertisements on online platforms. The team will also reach out to individuals who'd previously requested to be placed on the waiting list for tobacco studies at KPWHRI. The study will recruit smokers (18 and older) who want to quit smoking someday, but not in the next month, and who are not actively using or seeking treatment to quit; own and use a smartphone at least once a week and have (or are willing to upgrade to) a current iOS or Android operating system supported by the app; are willing to install and use the study program; are current smokers and smoke at least 10 cigarettes a day (as required for use of nicotine replacement therapy); speak/read English; and are willing to use birth control if they elect to use nicotine replacement therapy

	(females). Only one member per household will be eligible. Only those installing the app will be included in the final analytic sample.
Number of Sites	This pilot study includes 1 site (KPWHRI).
Description of Intervention	We have designed a mHealth app which blends sound scientific theory, evidence-based treatment, and best practice treatment guidelines for nicotine dependence with intervention content that is also responsive to the needs and preferences of ambivalent smokers. The experimental intervention combines the following components: • Best-practice self-help guidance for quitting based on the US PHS' Clinical Practice Guidelines for treating nicotine dependence and best practice treatment recommendations (aka, **Quit Guide**) • A toolkit with other experimental features. • A **referral** to free local state tobacco quitline services . • The ability to earn and request a free 2-week starter kit of **nicotine replacement patches** • A series of 9 personal **experiments**, each designed to build motivation or teach the skills necessary to successfully cu-back or quit smoking. The control intervention also includes items 1-4 above.
Study Duration	The pilot will be carried out over a ~1 year period.
Subject Participation Duration	Each participant will be enrolled for a period of ~3 months.
Estimated Time to Complete Enrollment	Enrollment will occur over an ~8-month period.

1 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Background Information

Fifteen percent of US adults smoke and tobacco use remains the leading preventable cause of death and illness in our society.[1, 2] It kills an estimated 480,000 Americans annually and results in more than $300 billion in direct health care costs and lost productivity each year.[3] Reducing smoking prevalence is a national priority and developing behavioral treatments which optimize treatment effectiveness by using scalable interventions to extend reach is a priority for NIH.[4]

Most smokers (~70%) want to quit someday but are not yet ready to quit.[5] These 'ambivalent smokers' are not actively seeking treatment, but many are receptive to treatment when offered. Prior research has shown that ambivalent smokers can reduce their smoking levels,[6] and in our prior work, we found ambivalent smokers are also willing to enroll in clinical trials when it is clear the goal is to help them explore their willingness to quit or to answer questions about the quitting process, as opposed to asking for a commitment to stop smoking, and many even successfully quit.[7, 8] Others have shown that setting a goal of smoking reduction increases quit rates among ambivalent smokers, particularly when counseling is paired with a stop-smoking medication.[9-13] So there is good reason to expect interventions targeting ambivalent smokers can be effective, particularly if they are designed to be sensitive to smokers' ambivalence, but the research with this population is relatively limited and insufficient to inform the design of interventions for ambivalent smokers beyond suggesting it is reasonable to encourage smoking reduction and provide pharmacotherapy. Thus, it is important to look to also look to theory to inform the content and design of these cognitive behavioral interventions. For example, Fagerstrom suggests ambivalent smokers require softer, more gradual intervention approaches, even if they contain much of the same basic behavioral and pharmacological strategies that are effective with smokers who are ready to quit.[14] This recommendation is consistent with the evidence cited above[7-13] and with West's PRIME theory of motivation, which suggests motivation and stage of change are highly fluid and change quickly over time.[15] As a result, West argues that rather than excluding these smokers from intervention, we need to modify interventions to be more engaging to ambivalent smokers. This perspective is a paradigm shift for some but could be an important tactic for helping reduce smoking prevalence. However, most available cessation treatments and most treatment development research target the minority of smokers who are ready to quit, not the majority who are not actively trying to quit. This results in critical gaps in both the evidence base and available treatment programs. The proposed study will address these gaps by pilot testing a theoretically-grounded intervention which combines cognitive behavioral principles with pharmaco-therapy for ambivalent smokers.

1.2 Rationale

To date, no published trials have tested a mHealth intervention for ambivalent smokers, but there is strong rationale for doing so. 77% of US adults own a smartphone, including those with only a high school education (69%), who make $30,000-$49,999 a year (69%), and persons of color (Hispanics, 75%, black 72%)[16]—that is, demographic groups with high smoking rates.[17] We've also found that most ambivalent smokers who use smartphones are interested in

mHealth apps for smoking: 75% told us they would consider using a cessation app, 88% were interested in an app to help them reduce their smoking, and 91% were interested in an app that could help them decide "if , when, or how" to quit.[18]

mHealth interventions are a reasonable strategy for reaching ambivalent smokers and research is needed to develop and evaluate interventions which can be broadly disseminated via mHealth platforms. The current study addresses this research gap.

1.3 Potential Risks and Benefits

1.3.1 Potential Risks

The primary risks of participation include a breach of confidentiality and emotional upset or embarrassment due to assessment and intervention. If people quit smoking, they could experience nicotine withdrawal symptoms (such as irritability, cravings to smoke, difficulty concentrating, headache, constipation, trouble sleeping). Participants who "earn" and elect to use the free trial of over-the-counter (OTC) NRT patches could experience additional side-effects (most commonly, rash/skin irritation at patch site, headache, nausea, and indigestion). Participants will be informed of all anticipated risks in the informed consent.

Participants can choose not to participate in this trial. While no publicly available treatments currently exist for smokers who are not ready to stop smoking, those who elect to quit can purchase OTC NRT from their local pharmacy and can seek assistance quitting by calling 1-800-Quit-NOW to enroll in their local state tobacco quitline or by contacting their personal health care provider.

2.3.2 Potential Benefits

All participants may receive some satisfaction or indirect benefit from contributing to this research. People who quit smoking may experience positive gains such as improved health and well-being. An additional benefit for all participants is receipt of free smoking cessation treatment via the mHealth app.

2 OBJECTIVES

2.1 Study Objectives

The primary objective of this pilot study is to evaluate the feasibility, acceptability, and potential effectiveness of a scalable mHealth intervention targeted to ambivalent smokers.

The secondary objective of this study is to plan for a future randomized efficacy trial to test the program.

2.2 Study Outcome Measures

As a pilot study, we do not have a single "primary outcome" of interest. Rather, we will examine a range of measures designed to inform our study objectives: assess the program's feasibility (program engagement), acceptability (ratings of satisfaction and helpfulness), impact on cognitive mediators of change (self-efficacy, outcome expectations, and motivation) and impact on indicators of smoking behavior change (quit attempts, smoking reduction, and abstinence).

Outcomes will be used to assess whether the intervention warrants further refinement and whether a future randomized efficacy trial is warranted.

2.2.1 Primary

The primary outcomes of interest that will be explored are:

- Seven-day point prevalence abstinence (PPA) at 3-month follow up;
- Total program log-ins to the assigned program during the study period at 3 months post-enrollment;
- Self-reported presence of an intentional quit attempt lasting at least 24 hours since study enrollment by 3-month follow up.

2.2.2 Secondary

Key secondary outcomes that will be explored at the 1-month follow up only:

- Self-report of no smoking in the past 7 days.

Key secondary outcomes to be explored at both the 1 and 3-month follow up include:

- Overall satisfaction with assigned program;
- Helpfulness ratings for each personal experiment, as well as satisfaction ratings of the associated experimental program features;
- Self-report rating of motivation for quitting;
- Self-report ratings of self-efficacy for quitting smoking;

Secondary outcomes to be explored at the 3-month follow up only:

- Cumulative duration of assigned program utilization in minutes, based on automated program tracking data.

2.2.3 Other Secondary & Exploratory Outcomes

Given the exploratory nature of this pilot study we will also examine a range of other potential secondary outcomes to include: program duration days, number of days quit attempts were maintained, any quit attempt, NRT earned, NRT requested, NRT used, program component contact time, use of each intervention component, number of personal experiments completed, stage of change, utilization badges earned, change in smoking rate, and self-reported outcome expectations, motivation and self-efficacy for staying quit; self-efficacy for enacting related behavioral skills targeted in the experimental intervention.

3 STUDY ENROLLMENT AND WITHDRAWAL

3.1 Subject Inclusion Criteria

In order to be eligible to participate in this study, a participant must meet all of the following criteria (see also Eligibility Screen in Appendix D):

- 18 years of age or older;
- Speak/read English;
- Want to quit smoking someday, but not planning to quit in the next month;
- Are not actively using or seeking treatment to quit;
- Smoked at least 100 cigarettes in their lifetime and smoked in the last 7 days;
- Own and use a smartphone and use it at least weekly;
- Are comfortable reading text on the screen or in text messages;
- Willing to install the study app on their smart phone and use it;
- Have a current iOS or Android operating system or are willing to update to one;
- Are willing to use birth control if elect to use NRT during the study (females).

3.2 Subject Exclusion Criteria

Individuals will be excluded if they:

- Smoke less than 10 cigarettes per day
- Self-report a lifetime history of dementia, manic depression, bipolar disorder, or schizophrenia;
- Have medical contraindications for NRT (i.e., recent heart attack, an arrythmia, or currently pregnant);
- Another household member is enrolled in the pilot study (based on self-report or mailing addresses on file for participants)
- Study staff are unable to verify the phone number or email address provided (i.e., unable to complete the enrollment process)
- Do not install the app during the study period

3.3 Strategies for Recruitment and Retention

<u>Recruitment</u>:

Our primary strategy will be to recruit a nationwide sample of smokers using online postings, ads and message boards (e.g., Craigslist, Facebook, online newspapers).

If recruitment lags, we will seek IRB approval to expand enrollment to smokers enrolled in Kaiser Permanente Washington or recruit via community flyers.

Interested smokers will be directed to call the toll free study number at KPWHRI to learn more about the study and be screened for eligibility. We will adjust our recruitment posting, as needed, to ensure we meet our recruitment goal. Each participant will then be followed for ~3 months post-enrollment.

Retention:

Several steps will be taken to ensure participant retention, as follows:

- Participants will be compensated a $25 e-gift card for completing the baseline and each follow-up survey, for $75 total compensation.
- Participants will receive an additional $20 e-gift card for providing timely biochemical confirmation of their smoking status via saliva testing following the 3-month survey.
- Assessments will be kept brief and will be available for completion online. If not completed online within 2 weeks, they will be offered by phone.
- We will collect multiple forms of contact information in order to track participants, including: mailing address, email address, and phone number(s).

3.4 Treatment Assignment Procedures

3.4.1 Randomization Procedures

Randomization will be automated using a stratified block randomization scheme. Participants will be randomized following completion of the online baseline survey. We will stratify by cigarettes per day (>15 vs. <15) and frequency of smartphone use (daily vs. non-daily) since these factors might influence quitting smoking and program participation. Half will be randomized to each of the two study arms (control vs. experimental). Following randomization, participants will receive instructions on how to download and set up and access their assigned program on their smart phone.

3.4.2 Masking Procedures

Participants will be blinded to their study arm.

Staff completing follow-up surveys by phone will be blinded to participants' treatment arm until the last section of the survey, which will contain additional satisfaction questions for the experimental arm.

Staff who interpret the saliva test results will be blinded to participants' study arm.

3.5 Subject Withdrawal

3.5.1 Reasons for Withdrawal

Participants are free to withdraw from participation in the study at any time upon request. Individuals will be asked their reason for drop out and may be asked to provide information on the primary outcome variables if drop out occurs within ~ one month of a scheduled follow-up assessment.

An investigator may terminate a study subject's participation in the study if:

- Any adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation. For example, the participant is found to be ineligible after enrollment (e.g., prior household member enrolled).

3.5.2 Handling of Subject Withdrawals or Subject Discontinuation of Study Intervention

Participants who request to drop out will be given the option to withdraw from participation in the intervention only, but to still participate in the follow-up evaluations. Participants who refuse this offer and request to completely withdraw from the study will no longer be contacted. However, previously obtained data will be retained with subject consent.

Budget permitting, we may attempt to recruit replacement participants for drop-outs. Persons who withdraw as a result of an adverse event will be referred for appropriate care.

3.6 Premature Termination or Suspension of Study

This study may be prematurely terminated if, in the opinion of the investigator, the sponsor, or the IRB there is sufficient reasonable cause. Written notification, documenting the reason for study termination, will be provided to the investigator and/or sponsor by the terminating party. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.

If the study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

4 STUDY INTERVENTION

The study uses a parallel, two-arm, randomized trial design. Ambivalent smokers will be randomized to either an experimental or control intervention.

4.1 Description

Both arms will receive an mHealth intervention consisting of:

- Best-practice self-help guidance for quitting based on the US PHS' Clinical Practice Guidelines for treating nicotine dependence and best practice treatment recommendations (aka, **Quit Guide**)
- Ability to track how many cigarettes they smoke a day, calculate what they would save if they stopped smoking, read motivational testimonials from others, and take notes within the app on things they've learned.
- A **referral** to their local state tobacco quitline.
- The ability to earn and request a free 2-week starter kit of **nicotine replacement patches.**

Experimental participants will also receive:

- A series of 9 personal **experiments**, each designed to build motivation or teach the skills necessary to successfully cut-back or quit smoking. They may also receive reminder prompts to complete experiments which are not initiated or started.

-Proprietary Intervention Detail Redacted-

4.2 Administration of Intervention

Subjects will download the app to their smart phone using instructions emailed to them and have access to the intervention for the full study period.

Experimental participants will earn badges for each experiment they attempt (whether they succeed or not). Participants in both arms can earn badges for viewing/using other program content.

4.3 Assessment of Subject Compliance with Study Intervention

System-generated program utilization data will be tracked during participants' study enrollment. This will include the total number of program log-ins (both arms), features used, duration of time engaging with the program. Participant use of the program will also be assessed via self-report.

5 STUDY SCHEDULE

5.1 Screening and Enrollment

Interested smokers will phone the study toll free number to request a call back in response to ads placed online. Smokers currently on KPWHRI's wait list for smoking-related research studies may also be contacted and invited to be screened.

Study staff will administer an eligibility screening questionnaire to interested smokers by phone. Those found to be eligible will be read an informed consent script and then emailed a link to the study information sheet to read. The study team may email a PDF as a back-up method if a participant is unable to open the information sheet using the link provided.

If after reviewing the information sheet they elect to join the study, they will be instructed to complete the online baseline survey within the next 7 days. The study will consider an eligibility screening to 'expire' after 14 days of non-response and a new eligibility screening questionnaire will be required.

5.2 Baseline and Randomization

Consenting participants will be emailed a link to complete the online baseline survey. Following completion of the baseline survey, they will be automatically randomized and provided instructions for accessing their assigned version of the app on their smartphone. Staff will be available to assist with this, as needed. Randomization date is Day 0.

5.3 1 and 3-month Follow-up Assessments

Self-reported follow-up data will be assessed at 1 and 3-months post-enrollment using an online survey with phone follow-up.

Following completion of all study activities (3 month assessment and cotinine verification, if applicable, or a failure to complete the 3 month survey in the allowed timeframe), staff will turn off participant's access to the app from the back-end administrative dashboard.

5.4 Biochemical Verification – In-Home Cotinine Saliva Test

The original study plan included biochemical confirmation of abstinence at 3 month follow-up. Due to a programming error, not all non-smokers were identified and flagged for this assessment, so this was dropped in the final plan.

6 STUDY PROCEDURES /EVALUATIONS

Standard operating procedures for the study will be detailed in the Manual of Procedures (MOP), which will be provided to study staff prior to study start-up. Overviews of the procedures are provided here. Data collected will be directly entered into our electronic data collection system.

7 STUDY OVERSIGHT

According to NCI's Policy for Data and Safety Monitoring of Clinical Trials (*http://deainfo.nci.nih.gov/grantspolicies/datasafety.pdf*), the method for monitoring patient safety should be commensurate with the level of risk. For Phase I and II trials, a DSMB is not required and data safety can be monitored by the study PI and/or project manager.

For the current low risk pilot study, the study PI will be responsible for monitoring the data integrity and patient safety as outlined above.

8 ASSESSMENT OF SAFETY

8.1 Specification of Safety Parameters

This is a minimal risk behavioral intervention. Nevertheless, adverse events (AEs) and serious adverse events (SAEs) will be recorded and reported over the course of the study.

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Project staff with participant contact will be trained to identify potential AEs and SAEs and instructed to report them immediately to the study PI and the project manager.

8.1.1 Severity of Event

The following scale will be used to grade the severity of adverse events:

1) Asymptomatic or mild symptoms; no intervention needed (non-serious);
2) Moderate: minimal, local, or non-invasive intervention indicated; limiting on ADL (non-serious);
3) Severe or medically significant but not immediately life threatening; hospitalization or prolonged hospitalization needed; disabling; limited self-care ADL (serious);
4) Life-threatening; urgent intervention required (serious);
5) Death related to AE (serious).

8.1.2 Non-serious Adverse Event Reporting

Non-serious AEs will be reported annually to the IRB.

8.1.3 Serious Adverse Event Reporting

All serious AEs will be reported within 48 hours, consistent with KPWHRI IRB policy and NIH guidelines. All participants learned to be deceased, regardless of the cause of death or relatedness to the program, will be reported to the IRB. The IRB will work with the PI to ensure additional agencies (e.g., NIH, etc.) are notified as required. All SAEs will be followed until satisfactory resolution or until the PI deems the event to be chronic or the patient to be stable.

8.1.4 Expected Adverse Reactions

Expected adverse events include:

- Upset due to participation in research assessments. Such reactions are expected to be mild and transient.
- Nicotine withdrawal. Participants who chose to quit smoking may experience nicotine withdrawal symptoms such as irritability, cravings to smoke, difficulty concentrating, headache, constipation, and trouble sleeping.

- NRT side-effects. Participants who chose to use the optional OTC NRT patches may experience side-effects such as rash/skin irritation at patch site, headache, nausea, and indigestion. These adverse events are expected, transient, and generally mild to moderate intensity. While NRT use is considered safer than smoking, female participants will be advised to use birth control while using NRT.

8.2 Time Period and Frequency for Event Assessment and Follow-Up

Reportable events will be recorded in the data collection system throughout the study. Events will be followed for outcome information until resolution or stabilization.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation.

8.3 Characteristics of an Adverse Event

8.3.1 Relationship to Study Intervention

The Study PI will determine is AE's are deemed possibly related to the individual's study involvement. The following guidelines will be used.

- Associated – The event is temporally related to the study participation and no other etiology explains the event.
- Not Associated – The event is temporally independent of study participation and/or the event appears to be explained by another etiology

8.3.2 Expectedness of SAEs

The Study PI will be responsible for determining whether an SAE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

8.4 Unanticipated Problem

8.4.1 Definition

The Office for Human Research Protections (OHRP) considers unanticipated problems (UP) involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 Unanticipated Problems Reporting to IRB and NCI

Incidents or events that meet the OHRP criteria for unanticipated problems will be reported to the IRB within 48 hours of when the team is made aware of the event.

Unanticipated problem reports will include:

- Appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- A detailed description of the adverse event, incident, experience, or outcome;
- An explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem

The IRB will determine if other immediate action is required (e.g., suspension of recruitment, protocol closure, etc.). Temporary or permanent suspension of an NIH-funded protocol will be reported to the NCI Program Official responsible for the grant.

8.5 Halting Rules

Study halting may occur as required by the IRB or NCI. The study PI may temporarily suspend enrollment pending review by these authorities if warranted based on the presence, type, or frequency of SAE's or other changes in the study protocol which may place participants at greater than anticipated risk.

9 CLINICAL SITE MONITORING

Clinical site monitoring will not be done for this study; however, the NCI reserves the right to conduct independent audits or clinical monitoring as necessary.

10 STATISTICAL CONSIDERATIONS

10.1 Study Hypotheses

We hypothesize that by engaging in the experiments, ambivalent smokers in the intervention arm will have successive mastery experiences which will build their confidence and positive outcome expectations (i.e., belief that *I can control my smoking* or *I can quit when I am ready*) and, in turn, will better motivate them to change their smoking behavior, including making a successful quit attempt and, possibly, quitting smoking. We also expect that experimental participants will be more likely to use the provided nicotine replacement patches and tobacco quitline referral than are control participants.

10.2 Sample Size Considerations

The primary analytic goals of this pilot study are to assess feasibility and to estimate the magnitude of intervention effects on study outcomes. The target sample size (n = 60) for this pilot is based on recommended guidelines for estimating effect sizes in behavioral treatment development research[22] and not on our anticipated intervention effect size. By design, the pilot trial is not powered to evaluate efficacy or to test for statistically significant differences between intervention groups.

10.3 Final Statistical Analysis Plan

All summaries and analyses will be limited to randomized individuals who installed the app using a modified intent-to-treat approach, whereby participants are labeled by their randomization group regardless of app usage. However, when assessing self-reported satisfaction with specific app features, analyses will be restricted to participants who both self-report use of the feature and whose automated data confirm this use. This is done to eliminate ratings from people who either did not use each feature or recall its use, both of which could invalidate users' ratings.

First, descriptive statistics will be used to characterize the baseline sample. Summaries across arms for outcomes of interest 1- and/or 3-months post-baseline will be conducted in addition to counts of Experiments completed in the experimental arm.

Similar statistical methodology will be used to conduct inference for all outcomes. Regression models will be fit using generalized estimating equations with robust standard errors and an exchangeable working correlation. When applicable for a given outcome, the regression model will be fit to outcomes collected at both time points simultaneously, even if reported separately. For each binary outcome of interest—such as 7-day PPA and having a successful 24-hour smoking quit attempt—we will initially attempt to estimate relative risks (RR) of the outcome in the experimental app relative to the control app using a Poisson regression model. When outcomes are too rare to obtain estimates of relative risks, we will fit linear regression models to binary outcomes and estimate risk differences (RD) of the outcome instead. Linear

regression models will be fit to continuous outcome data—including number of program log-ins, Likert scales for self-efficacy and satisfaction and average number of cigarettes smoked per day—to estimate mean differences in the outcome across app versions. All point estimates will be accompanied by 95% confidence intervals and *P*-values from two-sided Wald tests.

All app comparisons will adjust for the assigned app, number of cigarettes smoked at baseline, and when applicable, the time of survey collection and interaction between follow-up time and assigned app. The latter interaction allows for results to be presented separately at one and 3-months post-baseline. If the outcome measure is collected at baseline and not identical across all participants at baseline, we will additionally adjust for the outcome measure at baseline. With this adjustment, the estimated average difference across study arms may also be interpreted as the average difference in change from baseline across arms. Depending on differences identified between arms at baseline that were not avoided despite randomization by chance, additional potential confounders may be adjusted for.

Outcomes collected via follow-up surveys are subject to missingness; however, per convention, missing data for smoking cessation outcomes will be imputed as smoking or failing to successfully quit smoking for at least 24 hours. For these outcomes, additional sensitivity analyses will be conducted using (1) complete cases only and (2) completed assessments using multiple imputation by chained equation[24] with 10 imputed data sets created with logistic regression imputation using Barnard-Rubin adjusted degrees of freedom[25]. For all other outcomes, analyses will use complete cases only. Further sensitivity analyses may consider modification of the effect of intervention on the primary outcomes by gender.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate treatment and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Study staff will permit authorized representatives of NCI and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

12 ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

12.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. IRB approval of the protocol and consent processes must be obtained before any subject is enrolled. Any amendment to approved study materials will require re-review and approval by the IRB before the changes are implemented in the study.

12.3 Informed Consent Process

Each person will provide consent to be screened for eligibility by phone. If screened eligible, they will provide verbal consent and be emailed a link to a study information sheet for their records. The study team may email a PDF as a back-up method if a participant is unable to open the study information sheet using the link.

Informed consent will include permission for contacting participants by push notification/mail/email/text to remind them of follow-up surveys and other study events and permission to collect all study data and track their use of the program. It will also include permission to order a 2-weekly supply of NRT patches from an online pharmacy and have it sent to participants' homes, for those participants meet the study requirements to receive the NRT and also specifically request for it to be mailed to them. (Note: receipt of the NRT is optional for participants.)

Participants are free to refuse to answer any survey questions or drop out of the study at any time. Participants will be instructed how to discontinue involvement in the intervention or drop out of the study as part of the consent process.

12.4 Exclusion of Women, Minorities, and Children (Special Populations)

Individuals of any gender or racial/ethnic group may participate. Children under the age of 18 years will be excluded.

12.5 Subject Confidentiality

Appropriate steps will be taken to safeguard participant confidentiality. This includes the following:

- KPWA is a HIPAA covered entity and complies with all HIPAA regulations regarding data security. All study files will be maintained in a centralized location on the KPWHRI

departmental server. Access to this data is password protected and subject to the same security protections as other confidential health plan data. Access will be limited to staff working on this study and require access to these files. All staff are trained in appropriate security protections, computer passwords are changed on a regular basis, and all staff sign annual confidentiality agreements.

- Participants' identities will not be shared with anyone other than relevant team members at KPWHRI as needed to perform their study roles.
- Electronic communications we send will not contain personal health information (PHI) other than references to smoking and participant first names.
- Biochemical confirmation of smoking abstinence will be remotely monitored using a secure video conference software for Apple and Android devices. The software does not store or access PHI, uses encrypted video streaming to protect confidentiality, and does not allow video sessions to be recorded, to further protect patient confidentiality.
- Participant information will not be stored on their phones. Data generated by the app will be encrypted when transmitted and then securely stored in a back-end database behind the KP firewall. Access will be limited to staff who need it, who will log-in using their NUID or other secure password (as recommended by KP).
- Data exported from the backend database will be stripped of identifiers before being stored or analyzed.
- Data from study surveys (collected in REDCap) will not be tied to personal identifiers.

12.6 Future Use of Identifiable Data

Identifiable information will be destroyed within 5 years of the end of the study, consistent with HIPAA and our IRB requirements.

We have no plans to retain identifiable information beyond this period. If this plan changes, we will obtain appropriate IRB approval and participant consent.

13 DATA HANDLING AND RECORD KEEPING

13.1 Data Management Responsibilities

Data collected will be captured in electronic records (e.g., REDcap).

Final datasets will be saved electronically, clearly labeled and stored in a secure project folder on the KPWHRI server accessible only to study staff.

No electronic participant data shall be overwritten by study staff. As necessary, variables may be recoded into new variables for analyses, but will done in a way to preserve the original record. All changes will be documented.

13.2 Types of Data

Data for this study will include eligibility screening, baseline and follow-up assessments, web analytics monitoring the program use, confirmation of smoking abstinence, and safety data.

13.3 Data Capture Methods

- Eligibility screening and consent will be completed by telephone and documented in REDCap.
- The baseline assessment will be completed by participants online in REDCap.
- Participants will be sent a link to complete the 1 and 3-month follow-up surveys online in REDCap. If unresponsive to the online survey, study staff may attempt to administer the assessment by phone.
- Video-based confirmation of smoking abstinence will be conducted using a secure telemedicine program. Participants will use saliva test kits mailed to them by the study. Results of biochemical confirmation of abstinence will be recorded in REDCap by study staff and a photo of the de-identified saliva test securely saved to the study files.
- Adverse events may be self-reported to study staff via email or by phone. Events will be documented in study records and followed up for resolution and stabilization, as appropriate. Adverse events will not be reported or tracked through the intervention/app.
- All electronic records will be kept in a 21 CFR Part-11 compliant data capture system, which includes password protection.

13.4 Study Records Retention

All study data will be maintained for at least 5 years after the conclusion of the study. At that time, consistent with HIPAA guidelines, identifying information and linking files will be destroyed unless consent to retain these files is granted by study participants or the IRB.

13.5 Protocol Deviations and Violations

All staff will immediately report protocol deviations and violations to the KPWHRI Project Manager, who will inform the PI. Deviations will be considered any noncompliance with this clinical trial protocol, Good Clinical Practice, or the Manual of Procedures.

Protocol deviations will be reported annually to the IRB. Protocol violations will be reported to the IRB in a timely manner.

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