NCT04525222

An mHealth Mood Management Tool (Actify!) to Improve Population-level Cessation

FRED HUTCHINSON CANCER CENTER

Current version: 6/13/2022

Version 1	6/11/2020
Version 2	10/14/2021
Version 3	1/25/2022
Version 4	6/13/2022

Title of Protocol:
An mHealth mood management tool to improve population-level cessation

Investigators List:		
Jaimee Heffner, PhD	Associate Member, FHCRC	(206) 667-7314
Edit Serfozo	Project Manager, FHCRC	(206) 667-2428
Biostatistician:		
Kelsey Baker	Cancer Center Biostatistical Shared Resource	(206) 667-6655

SPONSOR: National Institute on Drug Abuse*,* Grant Number: 1R34DA050967

PROTOCOL SYNOPSIS

Protocol Title	An mHealth mood management tool to improve population-level cessation
Protocol Number	
Protocol Sponsor	National Institute on Drug Abuse
Trial Phase	Phase 1
Trial Type	Pilot RCT 2 arm
Clinical Indication	Smoking cessation
Study Objectives	Conduct a pilot, randomized controlled trial (n=240) to test the primary outcome of treatment acceptability and secondary outcomes of efficacy and mechanism of change at 8-week follow-up for two smartphone applications for smoking cessation: the novel Actify app, which integrates Behavioral Activation Treatment for Depression (BAT-D) with US Clinical Practice Guidelines (USCPG) vs. the National Cancer Institute's QuitGuide app, which is based on USCPG. Specifically, we will: a) compare the treatment groups on user satisfaction and app utilization (treatment acceptability) b) preliminarily compare the effects of the interventions on 30-day point prevalence smoking abstinence (efficacy) and behavioral activation (mechanism of change)c) determine whether there is evidence of differential efficacy in smokers with vs. without pre-quit depressive symptoms
Study Design	2-arm randomized controlled pilot trial with 1:1 parallel assignment
Population	Adult smokers with and without depressive symptoms
Primary Endpoints	Treatment acceptability: • Satisfaction (user satisfaction ratings of the assigned app at 8 weeks post-randomization) • Utilization (total number of log-ins to the assigned app at 8 weeks post-randomization)
Secondary Endpoints	Treatment efficacy (e.g., smoking abstinence), changes in theory-based mechanisms of change. Smoking abstinence outcomes: • Primary: Self-reported 30-day point prevalence abstinence (PPA) from smoking at 8 weeks post-randomization • Secondary: Self-reported 30-day PPA from smoking at 6 months post-randomization; Biochemically-confirmed 30-day PPA from smoking at 8 weeks and 6 months post-randomization; Self-reported and biochemically confirmed 7-day PPA from smoking at 8 weeks and 6 months post-randomization; Self-reported and biochemically confirmed 30-day PPA from cigarettes and other non-medicinal nicotine/tobacco products at 8 weeks and 6 months, including e-cigarettes

	Mechanisms of change outcomes: • Change in behavioral activation from baseline to 8 weeks post-randomization • Change in depressive symptoms from baseline to 8 weeks post-randomization
Type of control	Standard-care smoking cessation app (QuitGuide)
Treatment Groups	2 arm; Actify vs QuitGuide
Treatment Schedule	The treatment period is 8 weeks. Participants will be encouraged to use their assigned app as desired during that time.
Number of trial subjects	N=240
Estimated duration of trial	21 months
Duration of Participation	6 months

ABBREVIATIONS

BAT-D	Behavioral activation therapy for depression
PPA	Point Prevalence Abstinence
USCPG	US Clinical Practice Guidelines

Table of Contents

1.0 GENERAL INFORMATION

This document is a clinical research protocol for a randomized, controlled 2-arm pilot trial that will be conducted in compliance with the IRB-approved protocol, associated Federal regulations, and all applicable IRB requirements. The research plan is consistent with Stage IB of the NIDA Stage Model for Behavioral Intervention Development. We will use these pilot data to optimize the treatment and study design and to prepare for a rigorous test of the efficacy of Actify in a subsequent R01.

Rationale.
Cigarettes are the most deadly drug in the US. The number of deaths annually from cigarette smoking (~480,000) is over three times greater than the number of alcohol-related deaths (~88,000) and drug overdoses per year (~52,000) combined. Helping current smokers to quit is a public health priority. There are numerous forms of assistance available, yet they all have suboptimal outcomes for a large group of smokers: those who experience depressive symptoms before or during a quit attempt. Prior to making a quit attempt, 40- 55% of smokers report depressive symptoms. Because depressed mood and other forms of negative affect are also common nicotine withdrawal symptoms, mood management strategies have the potential to benefit a majority of treatment-seeking smokers. Indeed, our pilot data suggest that 83% of smokers interested in using a cessation app endorse mood difficulties as a barrier to quitting.

Behavioral activation therapy for depression (BAT-D) is a novel addition to standard smoking cessation interventions that can address depressive symptoms as a risk factor for treatment failure. **Scientific premise**: Two pilot studies and one fully-powered randomized, controlled trial support the efficacy of BA-based treatments for smoking cessation delivered in face-to-face format. Delivery through an mHealth app would make this treatment widely disseminable as a standalone public health intervention. There are currently no BA- based mHealth treatments for smoking cessation with established efficacy.

More detailed rationale can be found below in section 2.0.

Overview of Study Design.
This project involves conducting a pilot, randomized controlled trial (n=240) to test the primary outcome of treatment acceptability and secondary outcomes of efficacy and mechanism of change for the behavioral activation app (Actify) vs. the USCPG-based app for smoking cessation (QuitGuide). We will test the interventions using an 8-week treatment period, and, consistent with the evaluation period in our previous cessation app pilot study, our primary outcomes will be assessed at the 8-week end-of-treatment mark. We will also collect 6-month follow-up data to assess long-term outcomes.

1.1 Protocol Title: An mHealth mood management tool to improve population-level cessation
1.2 Sponsor Information: National Institute on Drug Abuse, Grant Number: 1R34DA050967
1.3 Investigator Information: Jaimee Heffner, PhD, (206) 667-7314
1.4 Contractors and Consultants for the Study (if applicable):
Jennifer McClure, PhD (Kaiser Permanente, Seattle);
Stacey Daughters, PhD (University of North Carolina at Chapel Hill);
Elisardo Becoňa Iglesias, PhD (University of Santiago de Compostela, Spain)

2.0 INTRODUCTION TO THE PROTOCOL

2.1 Introduction

Cigarette smoking remains the leading preventable cause of death in the United States. The number of deaths annually from cigarette smoking (~480,000) [1] is over three times greater than the number of alcohol-related deaths (~88,000) [2] and drug overdoses per year (~52,000) [3] combined. Only 6% of smokers each year are able to successfully quit [4]. Novel interventions are needed to target the key factors that maintain smoking.

2.1.1 Problem: Depression is prevalent and interferes with smoking cessation. Mood management treatments can help, but effective options accessible at the population level do not currently exist.

2.1.1.a. Prevalence of depressive symptoms among smokers. The estimated prevalence of current (past 12 months) major depressive disorder among smokers is 11% [5]. Depressive symptoms that do not meet full criteria for a mood disorder are even more prevalent, particularly among treatment-seeking smokers. Among callers to a state tobacco quitline, 41% reported current depressive symptoms on the Patient Health Questionnaire-9 (PHQ-9) [6]: 25% met criteria for a major depressive episode and an additional 16% reported depressive symptoms that fell below the diagnostic threshold [7]. We have found similarly high rates of depression among smokers enrolled in our trials of technology-delivered cessation treatments. In a recent trial of web-based Acceptance and Commitment Therapy (ACT) for smoking cessation [8], over half (56%) of the 2637 study participants screened positive for depression on the Center for Epidemiological Studies Depression (CES-D) [9] scale. Approximately 40% of participants in a pilot trial of smartphone-delivered ACT [10] screened positive for depression. This high prevalence of depressive disorders and symptoms observed among treatment-seeking smokers (i.e., 40-55%) in both clinical and research settings likely reflects the greater difficulty of quitting for these smokers and consequently greater need for assistance.

2.1.1.b. Evidence that depressive symptoms have a negative impact on quitting is robust. Observational population [11, 12] and clinical studies [13] have shown that both mood disorder diagnoses and depressive symptoms predict a lower likelihood of long-term cessation. Quit rates for people with mood disorders are between 17% (for major depressive disorder) and 60% (for bipolar disorder) lower than for people without mood disorders [14-17]. In smoking cessation trials, depressed mood at the time of a quit attempt predicts failure to quit smoking [7, 18-21], as does emergence of depression and other forms of negative affect during the post quit period [22]. Data from our trial of group-delivered cessation therapy suggested that the odds of quitting are reduced by 50% among smokers with depressive symptoms at the time of a quit attempt, even when they receive gold-standard treatment combining pharmacotherapy with intensive smoking cessation counseling [23]. Furthermore, a majority of treatment-seeking smokers express concern about the impact of mood on their likelihood of quitting. Illustrating the pervasiveness of this concern among users of mHealth interventions, data from the first 1100 users of our SmartQuit smoking cessation app indicated that 83% of the users endorsed mood difficulties as an anticipated barrier to quitting [24]. A problem with the current standard treatment approach, as outlined in the US Clinical Practice Guidelines (USCPG) [25], is that it does not address depressive symptoms as a mechanism that maintains smoking.

2.1.2. Solution: A readily accessible mHealth app for smoking cessation grounded in evidence-based behavioral activation therapy for depression (BAT-D).

2.1.2.a. mHealth apps for cessation are readily accessible and can be effective. Currently, 77% of US adults own smartphones [26], and ownership rates among smokers mirror those of the general population [27]. The proportion of smartphone owners using mHealth applications is steadily increasing [27], broadening potential reach of mHealth apps for smoking cessation. From 2012-2014, smoking cessation apps were downloaded to smartphones in the US over 3.2 million times [28, 29], which is substantially greater than enrollment in text messaging programs for smoking cessation (i.e., 140,000 subscriptions/year [30]). In a 2014 survey, 15% of US smokers said that had previously downloaded an app for smoking cessation, and 43% indicated an intent to use a cessation app in the future [31]. Given the fast pace at which uptake of technology and technology-delivered interventions occurs, it is likely that these 2014 data underestimate current use of and interest in mHealth apps for smoking cessation.

mHealth apps could make cessation treatment more accessible at the population level, particularly to low-income, uninsured smokers. Even at the lowest level of income ($0-$14,999/year), almost half (45%) of US smokers own smartphones [27], and evidence suggests that similar proportions of smokers across the socioeconomic spectrum use smartphone apps for smoking cessation [32]. Additionally, smartphone ownership is not associated with race or ethnicity either in the broader US population [26] or among cigarette smokers [27] and, as such, does not perpetuate racial/ethnic disparities in access to interventions delivered in this new modality (as opposed to healthcare settings, where there are racial ethnic disparities in access to care). An increasing number of Americans—particularly racial/ethnic minorities and low-income adults—are now relying exclusively on smartphones for Internet access (~20% of each group) [26], meaning that traditional web-based interventions for smoking cessation that are not optimized for small screens or repackaged as mHealth apps will become virtually unusable for large segments of the population. As such, mHealth apps may have greater potential reach—including reach into tobacco-related health disparities groups—than both text message and web-based interventions as smartphones become an increasingly ubiquitous technology.

Although a fully-powered effectiveness trial has yet to be completed, mHealth apps for smoking cessation have been evaluated in a number of pilot studies, demonstrating promising results for acceptability and quit rates as high as 45% [10, 33-38]. However, the literature base to support apps for smoking cessation is still emerging and currently includes only two randomized, controlled trials [10, 34]—both of which are pilot trials with wide confidence intervals for the point estimates of cessation and, as expected for a pilot study, lack of a statistically significant difference between treatment groups, even where differences in quit rates would be clinically meaningful if replicated in a larger trial [10]. While the early results are promising, published pilot studies of mHealth apps for smoking cessation have a number of methodological limitations including lack of biochemical verification, few studies with active control groups, and no assessment of long-term outcome data. In the design of the proposed project, we address all of these methodological limitations of prior app studies.

Although the literature on mHealth apps for smoking cessation are still in nascent stage, there is ample evidence from the broader literature on mHealth interventions for behavior change that apps can be effective for supporting improved health behaviors. Results of the most comprehensive review to date of mHealth interventions for health behavior change showed that the majority (17 of 23 studies meeting inclusion criteria) showed statistically significant effects of the mHealth app on the targeted health behavior [39].

2.1.2.b. BAT-D is an efficacious, theory-based treatment for depression. Content analyses of mHealth apps that are currently available for a variety of conditions (including over 400 for smoking cessation) have been repeatedly shown to adhere poorly to behavioral theory and evidence-based behavior change techniques [40-43]. BAT-D is based on a well-supported behavioral conceptualization of depression as resulting from inadequate positive reinforcement obtained from one's environment for non-depressed behaviors [44, 45]. The primary goal of BAT-D is to increase engagement in positively

reinforcing activities consistent with one's values. These, in turn, are expected to increase positive affect and to reduce negative moods and avoidance behaviors [45]. Behavioral activation (BA) is a component of cognitive behavioral therapy (CBT), demonstrated in a seminal dismantling study by Jacobson and colleagues to have similar efficacy to the full CBT package for treating depression [46]. Given that BA is less complex than CBT, it is more disseminable at the population level. BAT-D's disseminability is even greater given that it is a briefer form of the treatment that, like BA [47], has demonstrated effectiveness as a treatment for depression [48, 49].

2.1.2.c. Application of BA to smoking cessation improves quit rates. Although the origins of BA are as a treatment for depression, this approach has particular relevance for cigarette smoking and its co- occurrence with depressive symptomatology. In accordance with reinforcement theory, maintenance of smoking as well as depressed behaviors results in part from a lack of reinforcement for healthy, alternative behaviors [44]. In support of the theory, preliminary outcomes from an adult smoking cessation trial of combined counseling and pharmacotherapy indicated that participants who were abstinent at the end of an eight-week treatment demonstrated an increase in the level of alternative, smoke-free, rewarding activities during the course of treatment and evidenced a reduction in depressive symptoms [50].

Evidence to date suggests that the integration of BA principles more broadly, and BAT-D specifically, into standard cessation counseling can significantly improve quit rates for (1) the general population of smokers (of whom an estimated 40-55% will have depressive symptoms) [51], (2) smokers with depression [52], and, (3) smokers at high risk of either having or developing depression [53]. Evidence from a fully- powered, randomized, controlled trial [51] of a face-to-face, BA-based cessation intervention (n=110) compared with standard cessation (n=109) and a waitlist control group (n=56) for general population smokers (of which 40% had a history of depression treatment) provides evidence to support integrating BA with standard cessation treatments for improved cessation. In this trial, recently completed by our consultant, Dr. Becoňa and colleagues, the two active treatment groups received 8 weeks of hour-long group counseling. At end of treatment, biochemically-confirmed quit rates were superior in the BA condition (64.7%) relative to the standard counseling condition (45.9%, p=.008) and the waitlist control condition (5.4%. p=.001). The higher quit rates in the BA condition relative to standard counseling persisted across the 3-month (38.2% vs. 22.9%, p=.045), 6-month (30% vs. 18.3%, p=.273), and 12-month follow-ups (30.0% vs. 18.3%, p=.302), albeit with some attenuation of the effect over time. A limitation of this study was that it was underpowered to detect smaller but still clinically meaningful effects (e.g., absolute difference of 12 percentage points between two behavioral interventions at long-term follow-up could readily be considered a meaningful difference [54]).

In a proof-of-concept study conducted by our consultant, Dr. MacPherson, smokers with depressive symptoms were assigned to receive either the BAT-D-based Behavioral Activation Treatment for Smoking (BATS; n= 35) or standard cessation treatment (ST; n=33), and both groups received nicotine patches. Participants were assessed at baseline, throughout treatment, and at 4, 16, and 26-week follow-ups for depressive symptoms and carbon-monoxide (CO)-verified 7-day point prevalence abstinence. At the end of treatment, BATS participants were 2.1 times more likely to be abstinent ($p< 0.05$) than ST participants (17.1% vs. 9.1%). As expected, abstinence rates declined over time in both groups, yet there remained a significant effect of BATS treatment at the 26-week follow-up (14.3% vs. 0.0%; $p < 0.05$). Participants receiving BATS also evidenced greater improvements in depressive symptoms across the 26-week follow-up period.

Another pilot study [53] showed promising results of a BATS-based cessation treatment for smokers recently hospitalized with acute coronary syndrome (CS)—a population with a high prevalence of depression. Participants received either the BATS-CS intervention (n=28) or an intervention using standard cessation counseling content (standard of care, or SC; n=31). Results of this feasibility trial

indicated that BATS-CS was highly acceptable to participants and also produced greater improvements in positive affect, negative affect, and stress than SC at 24-week follow-up. Additionally, the effect size for BATS-CS on smoking cessation was promising: OR=1.27 (95% CI=0.41-3.93) for 7-day point prevalence abstinence at 24 weeks. The study was not powered to detect statistically significant effects, but cessation and mood outcomes were all in the hypothesized direction, favoring BATS-CS over SC.

2.1.2.d. Evidence that BAT-D is efficacious as a treatment for non-nicotine substance use disorders. The first fully-powered trial of BAT-D for non-nicotine substance use disorders was published in 2018, adding further support for the scientific premise of the proposed study. In a large, methodologically rigorous trial, our consultant, Dr. Daughters, and colleagues found that the BAT-D in-person intervention resulted in superior biochemically-verified abstinence rates at 3- (42% vs. 25%, OR=2.2, 95% CI=1.3-3.7), 6- (27% vs. 12%, OR=2.6, 95% CI=1.3-5.0), and 12-month (20% vs. 8%, OR=2.9, 95% CI=1.3-6.1) follow-ups relative to a contact-matched control condition [55]. While not necessarily generalizable to smoking cessation, these findings suggest that BAT-D can be an effective treatment for substance use disorders that share common causal and maintenance factors with nicotine dependence, including lack of reinforcement of alternative behaviors to substance use.

2.1.3. Summary of significance. Symptoms of depression, which are common among smokers, decrease the odds of quitting by 50%. This study addresses the important public health problem of low quit rates and resultant tobacco-related health disparities among smokers experiencing mood dysregulation. The proposed project builds off of a growing body of literature supporting the value of behavioral activation as a component of cessation counseling. Behavioral activation is a promising treatment approach for an mHealth cessation intervention because: (1) it has demonstrated long-term efficacy for promoting abstinence from tobacco and other substance use and shown promise for smoking cessation in the face-to-face format [52, 53, 55], (2) its rationale, principles, and components are well-suited to translation into an app (e.g., scheduling valued activities and tracking their completion), and, (3) it is theory-based [44]. A BAT-D-based treatment accessed through smartphones–where there have been steady increases in ownership rates among adults–represents a new opportunity for increasing the accessibility of evidence-based smoking cessation interventions. This work fits with NIDA Behavioral & Integrative Treatment research priorities: developing interventions that are designed for dissemination, guided by theory-based mechanisms of change, and with a focus on co-occurring psychiatric symptoms and disorders. At present, randomized controlled trials of BAT-D-based cessation interventions have relied on face-to-face treatment, which would reach only 4-6% of the 42 million smokers in the US based on current utilization of the traditional treatment modalities of individual and group counseling [1, 4, 56]. To extend the reach of this promising new intervention to the estimated 32 million smokers with smartphones [1, 57, 58], the vast majority of whom will not seek formal treatment, we propose to develop a BAT-D app for smoking cessation to provide smokers with an effective method of addressing depressive symptoms as a barrier to quitting.

2.2 Clinical Data to Date

2.2.1. Development of the Actify app. With the support of a pilot grant from the Fred Hutchinson Cancer Research Center (PI: Heffner), we developed a working prototype of a smartphone app, Actify, that delivers BAT-D as part of a smoking cessation intervention. The app was created following user-centered design processes, including competitive analysis, focus groups, and usability testing of early and late prototypes, followed by a single-arm pilot trial.

2.2.1.a. Competitive analysis. We first reviewed depression apps currently on the market to generate (via personal experience) and assess (via user comments in app stores) user sentiment toward them in relation to their design and functionality. Such information is useful for understanding desirable features for a new app as well as "pain points" that a user may experience if Actify contained similar features. Example desirable features included a user interface that is easy to navigate, personalized, and with clear presentation of accessible community or national resources for assistance with depression. Example pain points included multi-screen data input, incoherent gamification, and unclear indication of progress.

2.2.1.b. Focus groups. Two focus groups were conducted in October 2016 to assess potential users' previous experience using depression apps (e.g., likes/dislikes); to develop user personas, the embodiment of a "typical" user or users, which is a common user-centered design strategy; to elicit ideas for valued activities in several life domains (e.g., relationships, health, leisure) that the app could suggest to the user; and to understand users' associations between emotions and colors that might appear in the app. Participants expressed a desire for a flexible, customizable program that took into account the uncertainties of daily life and provided relevant mood-related suggestions, tracking of no more than 5-10 basic emotions, and feedback on progress. Participants described mood apps they used previously as "boring" and noted that addition of some humor or excitement would help keep them engaged, as would a light color palette that had positive, uplifting associations. Two distinct user personas were developed (one primary, one secondary) to guide design decisions, and lists of common values and valued activities were generated for inclusion in the app.

2.2.1.c. Late prototype usability testing. Based on users' reactions to early prototypes, the study team decided to continue developing Prototype B, the first version of Actify. The user experience (UX) design team, consisting of a UX researcher and two UX design interns, developed several iterations of Actify features revised on the basis of early prototype testing. The revised version underwent three rounds of user testing between Jan 2017 and March 2017. In each round, users were given 4-5 tasks to complete to test their ability to navigate the major app components of onboarding, values identification, activity scheduling, activity tracking, calendar, progress, and resources as well as to assess user expectations and desires for app functionality. The programmed version of the app was completed by the study team's long-time partner, 2Morrow, in July 2017. For evaluation purposes, Actify was developed as a native app for Apple's iOS.

2.2.1.d. Single-arm trial of a limited Actify app. Between November 2017 and June 2018 we conducted a single-arm pilot trial of an Actify app with functionality limited to the BAT-D component. Because the planned notifications and other components to support smoking cessation were not included in this early development phase due to budgetary constraints, participants used NCI's SmokefreeTXT text messaging program alongside Actify to provide content similar to what would be included in the final app. Primary aims were to (1) obtain preliminary data on user engagement and satisfaction, and (2) evaluate effects on the target behavior of increased engagement in valued activities as well as smoking cessation and improved mood. To achieve these aims, we used a 6-week evaluation period to evaluate both engagement and short-term efficacy.

Major inclusion criteria were: (1) age 18 or older, (2) current smoker, averaging at least 5 cigarettes/day for the last 30 days, (3) interested in quitting smoking in the next 30 days, (4) own an iPhone version 5 or higher, which is necessary to run the current version of the Actify app without technical problems, (5) experience downloading and using one or more apps on their iPhone, (6) screens positive for mild to moderate current depressive symptoms (PHQ-9 score 5-19). Exclusion criteria were: (1) currently receiving other treatment for depression, including psychotherapy or medication, (2)

current use of another depression app, (3) severe depression (PHQ-9 ≥ 20) (3) current suicidal ideation (PHQ-9 item 9 score > 1), (4) receiving other treatment for smoking cessation, and (5) previous use of the SmokefreeTXT program.

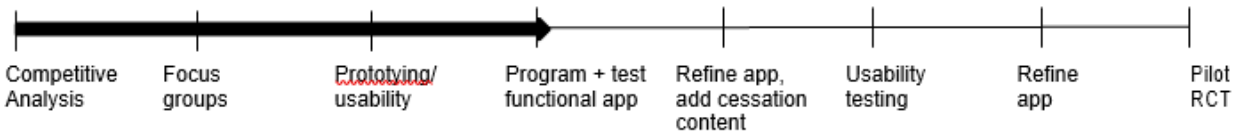
Participants were recruited from the Seattle area primarily via no-cost Craigslist ads (59% of sample) and paid Facebook advertisements (41% of sample). We screened 72 individuals to enroll 17 participants in the single-arm trial, of whom 16 (94%) completed the in-person, 6-week follow-up visit and are included in the subsequent complete-case results. These participants were 56% men, 38% racial minority, and 25% Hispanic, with mean age of 36 (SD=10). There was strong engagement with the app: average number of logins per participant was 20 (SD=16). Average change in depression on the PHQ-9 was a 5-point decrease from baseline (SD=6), which was a statistically significant improvement in symptoms (p=.009). Average change in Behavioral Activation for Depression Scale (BADS) overall scale scores and activation subscale scores (Bat-D's theory-based change mechanism) were not statistically significant but were in the hypothesized direction: BADS total scores increased by 14 points, on average (SD=32; p=.09) and activation subscale scores increased by 4 points (SD=10; p=.17). The 7-day point prevalence abstinence rate at follow-up was 31% (5/16), and the 30-day PPA was 19% (3/16).

Collectively, these results demonstrate (1) our ability to recruit and retain participants, (2) high engagement with the app, and (3) a promising signal for impact on theory-based change processes and cessation outcomes, which were descriptively higher for Actify than for our ACT SmartQuit app among the subgroup of depressed smokers (31% vs. 23% for complete-case 7-day PPA and 19% vs. 6% for 30-day PPA at short-term follow-up) and better than published quit rates of 7% for SmokefreeTXT alone [60]. Engagement was also higher for Actify than SmartQuit (average of 20 logins over 6 weeks for Actify vs. 12 logins over 2 months for SmartQuit). Preliminary quit rates also compare favorably to the previous trial of face-to-face BAT-D for depressed smokers (i.e., CO-confirmed, 7-day PPA rate of 17% at end of treatment vs. 31% for Actify) conducted by our consultant, Dr. MacPherson [52]. These promising findings warrant completing development of the Actify app, modifying it to improve usability, and evaluating the complete product in a controlled pilot trial.

2.2.2. Next steps.

Following our extensive development work to translate BAT-D into an engaging mHealth app format, the next step is to complete the development of Actify by incorporating the smoking cessation content into the established structure of the app. After completion of this next stage of work, the fully developed Actify app will be ready for pilot randomized trial to obtain a preliminary estimate of its acceptability, efficacy, and effects on behavioral activation and depressive symptoms as the theory-based mechanisms of change for smoking cessation (see Figure 1 for development timeline). This plan is consistent with Stage Ia and Ib of the NIDA Behavioral Therapies Development Model [61] and with the aims of the NIDA R34 mechanism to support behavioral and integrative treatment development.

Figure 1. Progress to date toward development of a complete version of the Actify app and launch of a pilot trial.



2.2.3. Preliminary studies of mHealth apps for smoking cessation.

Our research team developed the first mHealth app for smoking cessation based on ACT—called SmartQuit—in 2013 (PI: Bricker, Fred Hutchinson Cancer Research Center Hartwell Innovation Fund). We then conducted the first RCT comparing two smartphone apps for smoking cessation—SmartQuit vs. NCI's QuitGuide. Based on previously successful methods for national recruitment in our trial of web-based ACT [62], we recruited via Facebook ads, Google ads, and a press release developed by the FHCRC communications department. These efforts yielded 738 participants screened, 400 eligible, 340 consented, and 196 randomized (98 per arm). The recruitment sources were: 39% from Facebook ads, 38% from press-release generated media, and 23% from other sources. To maximize outcome data survey completion, we followed a protocol that sequentially timed the administration of separate survey modalities until the survey was completed: first via the web, then by telephone, and then by mail. Participants were compensated $25 for completing the survey. The achieved outcome survey completion rate of 84%, much higher than the 54% typically obtained in web- based cessation trials [63-68], provided confidence in the effectiveness of our follow-up survey methods for maximizing data retention. Retention did not differ between arms. SmartQuit participants had higher engagement with their assigned app ($p < .0001$) and a descriptively higher quit rate than the QuitGuide app at 2 months post-randomization:13% (95% CI: 6%-22%) in SmartQuit vs. 8% (95% CI: 3%-16%) in QuitGuide.

We developed the second version of the app (SmartQuit 2.0) in 2014 (PI: Bricker, Washington State Life Sciences Development Fund). Using data from the trial of SmartQuit 1.0, we evaluated which features of the app were most used and how feature usage was associated with quitting. Based on that analysis [69], the app was restructured to funnel users to the features that showed the strongest relationships with quitting. This method yielded an 8-exercise program with a core feature that prompted users to track when they let an urge pass—a major focus of the ACT exercises and a strong correlate of quitting in the SmartQuit 1.0 trial [69]. Relative to SmartQuit 1.0, we found that SmartQuit 2.0 had better user satisfaction (84% vs. 59%), although the estimated quit rate was similar (11% vs.13% achieved 30-day PPA at 2 months).

In 2016, we completed a major redesign of SmartQuit, now called iCanQuit, which is currently being evaluated in a large (n=2500) RCT (PI: Bricker, R01CA192849). Development of iCanQuit incorporated lessons learned from building SmartQuit 1.0 and 2.0, with additional user research conducted to understand how to best incorporate game elements into the app. With the guidance of our design vendor Ayogo Health, which specializes in patient engagement in digital health interventions, the app now incorporates a level system and badges to increase engagement with the ACT content. Recently, our team developed and began pilot testing a targeted version of iCanQuit for cancer patients who smoke (PI: Bricker, CVS Moonshot Award).

This preliminary work demonstrates that (1) we have acquired considerable experience developing apps for smoking cessation over the past six years, including formative research to understand user needs and desires and on methods to increase engagement (e.g., gamification), (2) our iterative development process has proven effective for improving user satisfaction across app versions, and (3) our methods for conducting nationally-recruiting mHealth trials yield strong recruitment and retention outcomes.

2.3 Risks/Benefits

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

> **Therapeutic risks include**: (1) physical and psychological consequences of smoking abstinence, including nicotine withdrawal, and (2) the possibility that the intervention may not help the

participant manage depressive symptoms and/or quit smoking. Participants will be informed of the discomfort associated with nicotine withdrawal, including common withdrawal symptoms, and that nicotine withdrawal may exacerbate some psychiatric symptoms (e.g., depressive symptoms).

Research-related risks: (1) the possibility that answering some questions may be emotionally upsetting, and (2) the possibility of breach of confidentiality. It is possible that some of the questions asked of participants may cause some emotional discomfort. For example, assessment of symptoms of depression may result in feelings of shame due to the stigma associated with mental health conditions. There is also a small risk of breach of confidentiality if participant data, either in electronic or hard copy form, were to be accessed by an unauthorized person.

Potential Benefits of the Proposed Research to the Subjects and Others
Subjects will be provided with information regarding potential benefits of participation in the study, including: 1) the possibility that the study interventions might help them to quit smoking and manage their depressive symptoms, 2) access to a smoking cessation smartphone application at no cost.

Importance of the Knowledge to be Gained
This study involves pilot testing of an intervention that, if found to be effective in a larger trial that would be informed by this pilot trial, could have an enduring, positive impact on the low quit rates among smokers experiencing depressive symptoms. As such, the minimal risks associated with participation in the proposed study are exceeded by the potential benefits of completing this research.

3.0 PRE-TRIAL INTERVENTION USABILITY TESTING

3.1 Objectives:

3.1.1 Add smoking cessation content to Actify, refine app structure, and conduct a ~9-day diary study to assess user satisfaction with the updated app and its components as well as program utilization (n=10).

3.2 Study Population:

We will recruit 10 adult smokers, age 18 or older with two levels of depressive symptom severity based on PHQ-8 score--none/minimal symptoms of depression (scores of 0-4: n=5) and mild/moderate symptoms of depression (scores of 5-19; n=5)--who are interested in quitting smoking. Participants will be recruited nationally via one or more recruitment strategies used successfully in our previous studies: targeted Facebook ads, Craigslist ads in states with a high prevalence of smoking or racial/ethnic minority residence (to achieve the target 25% racial/ethnic minority representation in the sample), other free methods of advertising on the Internet (e.g., Reddit, Twitter), ResearchMatch.org, and earned media generated by press releases from the Fred Hutch media team.

3.3 Study Design:

When a prototype of the complete Actify app is ready, we will conduct a diary study as a field-based evaluation of its usability. Usability is the extent to which an app can be easily navigated and understood by the user. Usability is a critical outcome of the Stage I intervention development process, as low usability can undermine engagement with the intervention [70] as well as its potential efficacy for smoking cessation [71].

3.3.1 Primary Objective: Completed development of an smartphone application for smoking cessation based on BAT-D. The Actify! app will be easily navigated and understood by the user and free from any technical difficulties.

3.4 Estimated Accrual:

We estimate that our recruitment efforts will lead to 120 screened, 40 eligible and 10 enrolled. We estimate recruitment to take 3 weeks.

3.5 Eligibility:

3.5.1 Inclusion Criteria

- age 18 or older
- current smoker, averaging at least 5 cigarettes/day for the last 30 days
- interested in quitting smoking in the next 30 days
- experience downloading and using one or more apps on their smartphone
- either screens negative (PHQ-8 score 0-4) for depression (n=5) or screens positive for mild to moderate current depressive symptoms (PHQ-8 score 5-19; n=5)
- willing and able to complete all study activities and to receive compensation by mail
- comfortable reading and writing in English
- have a mobile data plan and/or access to WiFi to support the use of the Actify app
- reside in the US

3.5.2 Exclusion Criteria

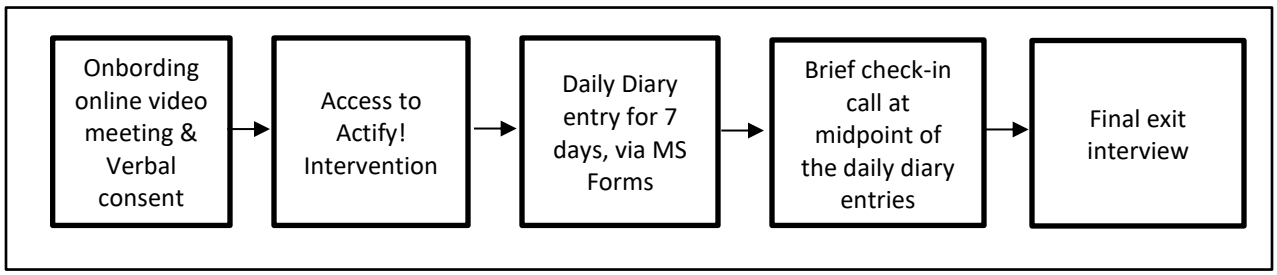
- severe depression (PHQ-8 ≥ 20)
- receiving other treatment for smoking cessation
- employees/family of investigator or study center
- member of the same household as another participant
- woman who is pregnant or breastfeeding, or planning to become pregnant
- having a Google voice number as their primary phone number (due to association with fraudulent study entry attempts in our previous work)
- currently incarcerated
- participated in earlier studies to develop the Actify app

3.6 Registration

Potential participants will be recruited via Craigslist, Facebook, Twitter, and Reddit. Initial screening for participation will be conducted via web-based survey in MS Forms. Individuals deemed eligible will be contacted by phone to ensure eligibility and discuss study procedures; individuals remaining eligible and interested will be invited to attend an online, video-based onboarding visit.

3.7 Usability Testing Overview

Figure 1. Usability Testing Study Flow Chart



During the online, video-based onboarding visit, participants will be provided with information about the study and provide verbal informed consent to participate. During that visit, study staff will assist enrolled participants in downloading Actify to their personal phone. Participants will be instructed to use Actify for one week and to keep a daily diary to report on their usage of and satisfaction with the program. Daily diaries will follow a semi-structured format, including assessments of when they used the app, what prompted them to open it, what features they accessed, and what their overall experience was like. They will also be asked about any technical difficulties encountered and about ease of navigation. Following completion of the diary entries, they will be asked to attend a final debriefing session which will include a semi-structured exit interview to assess (a) usage and satisfaction with the app, and (b) the impact of Actify on their smoking, mood, and engagement in valued activities. Participants will also complete the 10-item System Usability Scale [72], a common method of evaluating the usability of software. The User Experience (UX) researcher will be responsible for conducting the diary study. Full length of study participation will be ~9 days.

These procedures are consistent with best practices and usability testing of government funded cessation programs [73] and have been successfully implemented previously in our treatment development work. After the diary study, the UX Researcher and the UX Designer will work with the PI (Heffner) and consultants (Becoňa, McClure, and Daughters) to use data gleaned from the diary study to inform any needed changes to Actify's content and structure as well as to address any technical difficulties experienced by the users. Based on prior work, the types of changes needed at this stage of development are typically smaller adjustments such as changes to increase readability of text on different devices (e.g., font size, color), changes to the wording of specific messages, or de-bugging new features (e.g., inactive buttons). The Moby Inc. programming team will then make changes needed to improve the usability and/or content of the app. The final version of Actify, which will be developed after the diary study, and will be used in the pilot RCT.

3.8 Participant Compensation

Participants will receive up to $150. Compensation will be pro-rated and dispersed as follows:

- $10 for the baseline visit
- $10 for mid-point check in
- $40 for the final debriefing visit
- $10 for each daily diary entry, up to $70 (for 7 days)
- $20 bonus for completing all 7 diary entries

3.9 Enrollment Procedures

Participants will be recruited nationally through online services (e.g., Facebook, Twitter, Craigslist and Reddit advertisements). Recruitment materials will direct potential participants to a web-based screening survey on Microsoft Forms. The survey provides basic information about the study to allow individuals to choose whether or not to proceed, then assess basic eligibility criteria. Individuals who do not meet eligibility criteria will be provided with the following quit-smoking resources via e-mail; the QuitGuide app and the 800-QUIT-NOW phone number to reach their state's quitline.

Phone screening & informed consent. Study staff will call individuals who are deemed potentially eligible based on the initial online screening. During this call, the purpose and procedures of the study will be

explained in further detail and key eligibility criteria will be re-assessed to ensure consistency of answers. Those who remain eligible will be invited to participate in the diary study. Individuals who remain interested will be scheduled for their onboarding meeting and study staff will email the study information sheet to the individual to review before the onboarding meeting.

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

3.10 Assessments/Evaluations

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

Daily diary entry (Days 2-8): Participants will be instructed to use Actify for one week and to submit a daily diary to report on their usage of and satisfaction with the program. Daily diaries will follow a semi-structured format, including assessments of when they used the app, what prompted them to open it, what features they accessed, and what their overall experience was like. They will also be asked about the specific device and operating system they used to access the app, any technical difficulties encountered and about ease of navigation.

Mid-study check in call (Day 4-5): the UX Researcher will connect briefly with each participant for a 10–15-minute check in about their experience and engagement with the Actify! app. Qualitative research notes will be taken during this call.

Final exit interview (Day 9-10): Following completion of the diary study, participants will be asked to attend an online video meeting for a final debriefing session which will include a semi-structured exit interview to assess (a) usage and satisfaction with the app, and (b) the impact of Actify on their smoking, mood, and engagement in valued activities. As part of the final exit interview, participants will complete the 10-item System Usability Scale [72], a common method of evaluating the usability of software. Participants will also be asked to report any technical difficulties they may have experienced.

3.11 Analytical methods

Qualitative data from diary entries and exit interviews will be coded and analyzed using inductive content analysis to extract themes. Usability data from the SUS will be reported using descriptive statistics and compared against the benchmark score of 68, which represents average usability.

3.12 Objective

The Acitfy! App will be developed that can be easily navigated and understood by the user.

4.0 OVERVIEW OF CLINICAL TRIAL

4.1 Study Objectives

4.1.1 **Primary Objectives:** Assess and compare treatment acceptability across treatment arms.

4.1.2 **Secondary Objectives:** Preliminarily assess efficacy and mechanism of change for the behavioral activation app (Actify) vs. the USCPG app (QuitGuide) for smoking cessation.

4.1.3 **Tertiary Objectives:** Determine whether there is evidence of differential efficacy in smokers with vs. without pre-quit depressive symptoms

4.2 Study Population:

We will recruit 240 adult smokers, both with (PHQ=8 score 5-19; n=120) and without (PHQ-8 score 0-4; n=120) depressive symptoms, who are interested in quitting smoking. Participants will be recruited nationally via recruitment strategies used successfully in our previous studies: targeted Facebook ads, Craigslist ads in states with a high prevalence of smoking or racial/ethnic minority residence (to achieve the target 25% racial/ethnic minority representation in the sample), other free methods of advertising on the Internet (e.g., Reddit, Twitter), ResearchMatch.org, and earned media generated by press releases from the Fred Hutch media team.

Inclusion of Women & Minorities.

Our previous trials suggest that, without intervention to diversify the sample, the vast majority of participants would be Caucasian and female. To attain adequate representation of racial/ethnic minorities and men, we will cap enrollment of Caucasians and women at 75% of the sample via our online screening and enrollment process for the pilot trial. We anticipate that these caps will be necessary and that the resulting sample will be 25% male and 25% racial/ethnic minority. If needed, we will use targeted Facebook and Twitter campaigns specifically to recruit men and/or people with racial/ethnic minority affiliations (the ad platform's proxy for race/ethnicity). Based on demographic data from our recent trial of a technology-delivered cessation intervention using similar recruitment procedures [8], we expect the following percentages of racial minority participants: African American (10%), Native American or Alaska Native (2%), Native Hawaiian or Pacific Islander, Asian (2%), or other/multiple races (5%). In terms of ethnicity, we expect 8% to identify as Hispanic or Latino.

4.3 Study Design

This is a pilot, randomized controlled trial (n=240) to test the primary outcome of treatment acceptability and secondary outcomes of efficacy and mechanism of change for the Actify app vs. the active control app (the National Cancer Institute's QuitGuide app). We will test the interventions using an 8-week treatment period, and, consistent with the evaluation period in our previous cessation app pilot study, our primary outcomes will be assessed at the 8-week end-of-treatment mark. We will also collect 6-month follow-up data to assess long-term outcomes.

4.3.1 **Primary Endpoints:** Treatment acceptability as indicated by user satisfaction with assigned treatment (user satisfaction ratings of the assigned app at 8 weeks post-

randomization) and app utilization (total number of app server-recorded openings of the assigned intervention)

4.3.2 Secondary Endpoints: Treatment efficacy (smoking cessation) and changes to theory-based mechanisms of change (behavioral activation).

- Treatment efficacy:
  - Self-reported 30-day point prevalence abstinence (PPA) from smoking at 8 weeks post-randomization
  - Self-reported 30-day PPA from smoking at 6 months post-randomization; Biochemically-confirmed 30-day PPA from smoking at 8 weeks and 6 months post-randomization; Self-reported and biochemically confirmed 7-day PPA from smoking at 8 weeks and 6 months post-randomization; Self-reported and biochemically confirmed 30-day PPA from cigarettes and other non-medicinal nicotine/tobacco products at 8 weeks and 6 months, including e-cigarettes
- Mechanisms of change:
  - Change in behavioral activation from baseline to 8 weeks post-randomization
  - Change in depressive symptoms from baseline to 8 weeks post-randomization

4.3.3 Exploratory Endpoints: Differences in treatment effects by pre-quit depression (depressed vs. not depressed)

4.4 Estimated Accrual:
We estimate that our recruitments efforts will yield 904 screened, 490 eligible, 416 consented, and 240 randomized into the trial (120 per arm). We conservatively allotted 9 months for recruitment (26 enrolled/month).

4.5 Name of Sponsor/Funding Source:
National Institute on Drug Abuse, Grant Number: 1R34DA050967

5.0 SUBJECT ELIGIBLITY

5.1 Inclusion Criteria

- age 18 or older
- current smoker, averaging at least 5 cigarettes/day for the last 30 days
- interested in quitting smoking in the next 30 days
- experience downloading and using one or more apps on their smartphone
- either screens negative (PHQ-8 score 0-4) for depression (n=120) or screens positive for mild to moderate current depressive symptoms (PHQ-8 score 5-19; n=120)
- willing and able to complete all study activities including willing to receive study compensation by mail
- comfortable reading and writing in English
- have a mobile data plan and/or access to WiFi to support the use of the Actify app
- reside in the US

- have a smartphone either an iPhone (running iOS version 11 or higher) or an Android phone (running version 5.0 or higher)

5.2 Exclusion Criteria

- currently receiving behavioral treatment for depression (e.g., psychotherapy)
- current use of a depression app
- severe depression (PHQ-8 ≥ 20)
- receiving other treatment for smoking cessation
- previous use of the QuitGuide program
- current or recent (within the past year) enrollment in a Fred Hutch smoking cessation study
- employees/family of investigator or study center
- member of the same household as another participant
- woman who is pregnant or breastfeeding, or planning to become pregnant
- currently incarcerated
- Is ineligible per fraud prevention protocol

6.0 SUBJECT REGISTRATION

Recruitment materials will direct potential participants to a recruitment website, which provides basic information about the study and a portal to the informed consent form, screening, and baseline surveys.

For participants who screen eligible on the recruitment website and provide their email address, we will instantly send them an email (and two reminders over a 14-day period) inviting them to complete a secured online survey to provide informed consent and complete the baseline assessment. Those not consenting and completing the online enrollment process within 14 days will be sent an email notifying them that they were not enrolled and providing both the QuitGuide app and the 1-800-QUIT-NOW phone number to reach their state's quitline. Both arms will be described as smartphone apps designed to assist with quitting and containing tools to improve mood.

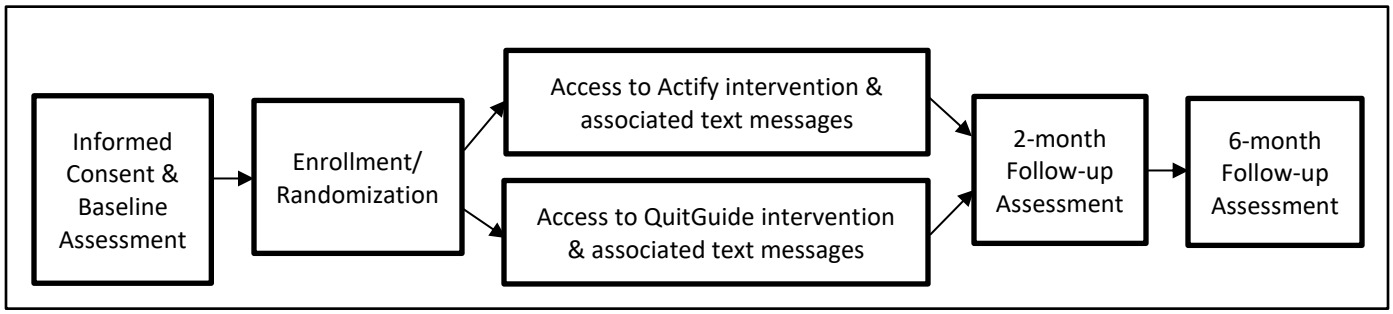
To address potential fraudulent responses to web-based screening surveys with compensation for participation, we will use the same methods used in our previous studies: CAPTCHA verification, ineligibility if the IP address was previously used or suspicious, and telephone contact by research staff if any aspect of automated data collection revealed suspicious activity (e.g., very brief survey completion times or unusual patterns in email addresses). To further deter fraudulent attempts to enter the study, no compensation will be provided for completion of the screening and baseline surveys.

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

7.0 TREATMENT PLAN

7.1 Treatment Plan Overview

Figure 2. Study Flow Chart



7.2 Description of the interventions

QuitGuide app. QuitGuide was created by the NCI's Smokefree team. It contains brief quit advice; a tool for tracking smokefree days and a statistics menu for viewing progress; a tool for tracking cravings and receiving a brief, related tip in response; a "Learn to Quit" feature with information on steps to prepare, cravings, withdrawal, slips, and staying smokefree. QuitGuide also has a "Manage My Mood" feature on the main page that gives it credibility as an intervention for smokers with depression, but with minimal expected efficacy due to the limited nature of the feature—i.e., recording a mood state and having the option to journal, call a friend, view photos and notes, or view a tip or distraction for handling difficult mood states. An example tip offered for handling negative affective states: "Distract. Do a crossword puzzle, play a game, or start a book that's been gathering dust."

Actify. Consistent with the BAT-D treatment model, the core functions of the current version of Actify are: (1) introducing the user to the program by describing the rationale for behavioral activation as an intervention for both depressive symptoms and smoking cessation, (2) helping the user to identify personal values, important life areas and meaningful activities associated with their values that will replace smoking habits (e.g., reading to my children), (3) prompting the user to schedule meaningful activities and providing reminders to complete them and, (4) visualizing overall progress toward meeting activity goals as well as the relationship between activities completed and mood. The app also contains tailored messages for smoking status and activity completion and resource sections with guidance for starting and maintaining a smoke free life. To increase engagement, the user receives daily tips, personalized feedback on money saved by cutting down/quitting smoking, feedback on activities completed, inspirational messages, user stories and quotes of ex-smokers overcoming challenges, noticing the benefits of quitting and how behavioral activation helped them to improve their mood and quit smoking. User stories illustrating how values can be translated into actions were associated with cessation in our prior work [69]. To acknowledge and motivate continued progress, the user is able to earn badges for smoke free streaks, usage of the app, and activity completion.

In-app notifications will be used to provide reminders to use the program, to track daily smoking and activity completion, and to remind users of upcoming scheduled activities. We added a Quit Guide section to the app, similar to QuitGuide's "Learn to Quit" menu, that it is available for reference if users need on-demand assistance. Portions of the QuitGuide are also presented as suggested reading on the users' dashboard. Content for the new Quit Guide feature supports users with setting and preparing for a quit date, learning about medications to assist with quitting, managing cravings and other withdrawal symptoms, handling high-risk situations, staying motivated, and recovering from lapses. The addition of the Quit Guide section matches Actify to the NCI QuitGuide app on the cessation content, allowing for stronger inferences about the specific effects of Actify's BAT-D components

Comparison of Actify and QuitGuide.		
	Actify	**QuitGuide**
Treatment approach	Behavioral activation + USCPG	USCPG
Cessation content description	Static quit guide, push notifications with reminders to track activities and smoking	Static quit guide, push notifications with tips for quitting
Targeting (mood management)	In-depth, personalized based on user input into the in app tracking system; core function of app	Superficial, "manage my mood" feature
Interactive tracking/progress features	Mood, activities, smoking level	Mood, craving
Game elements for engagement	Badges (trophies) for progress	Badges (trophies) for progress

7.3 Concomitant Medication

Use of concomitant treatments for both tobacco cessation and depression will be assessed at each time point. Individuals who report using self-report any other quit smoking treatment, including FDA-approved quit smoking medications (e.g., nicotine patch, nicotine gum, Zyban), during the screening phase will not be eligible to participate in the study. At the 2 and 6-month follow-up assessment, participants will be asked about their use of FDA-approved quit-smoking and pharmacotherapy for depression. Initiating use of FDA-approved quit-smoking medications during the study is allowed.

7.4 2 and 6-Month Follow-up Data Collection

At baseline, we will collect email, phone, and mailing address information as well as optional contact information on up to two collateral contacts. At each follow-up, we will send reminder letters. The data collection protocol is as follows: Day -14: mail a $2 pre-incentive letter (non-contingent incentives increase retention [86]) two weeks before the first online survey invitation; Day 0: First email invitation with link to online version of survey, with offer of $10 bonus for completing the survey within 24 hours; Day 7: Second email invitation with link to online version of the survey; Days 10 to 18: Eight attempts to complete telephone version of survey (one call per day); Day 19: Send mailed version of the survey. Based on our WebQuit RCT trial experience (n=2,637), we estimate that this protocol will yield 89% data retention, and that 92% of respondents will complete the web-based version of the survey (68% within 24 hours and 32% after 24 hours).

7.5 Participant Compensation

Participants will receive up to $124 for participating in this study. Specifically, at 2- and 6-month follow-ups, participants will receive compensation based on the following structure:

- $2 in a pre-incentive letter for each follow-up (for a total of $4)
- $25 for each follow-up survey completed in any modality (for a total of up to $50)
- $10 bonus for completing the follow-survey within 24 hours of the initial email invitation (for a total of up to $20)
- $25 for completing saliva cotinine and smartphone application-based carbon monoxide testing, if asked, after the 2-month and the 6-month follow-up study survey (for a total of up to $50)

Participants whose data are flagged for potential deception related to study eligibility criteria (e.g., age, US residence) will be contacted prior to compensation being provided in order to confirm eligibility. If eligibility cannot be confirmed, participants will not be compensated.

8.0 SUBJECT EVALUATION

8.1 Data Collection Overview

Table 1. Phase II Pilot Study Data Collection Overview

Measure	Screening	Baseline	8-week follow-up	6-month follow-up	Purpose
PHQ-8 *(8 items)*	X	X	X	X	Eligibility, mechanism of change
Other eligibility criteria *(~11 items)*	X				Eligibility
Demographics *(~10 items)*		X			Sample Description
FTND *(6 items)*		X			Sample Description
Treatment satisfaction *(~8 items)*			X		Acceptability
Treatment preferences *(~5 items)*		X			
Tobacco/Nicotine use *(~12 items)*		X	X	X	Efficacy
Behavioral Activation for Depression Scale *(25 items)*		X	X	X	Mechanism of change
Concomitant treatment *(2 items)*	*X*	*X*	*X*	*X*	*Stratification, sensitivity analysis*
Total number of items	*36 items*	*70 items*	*53 items*	*45 items*	
Estimated duration	*~5-8 min*	*~10-15 min*	*~15-20min*	*~10-15 min*	

8.2 Enrollment Procedures.

The study recruitment website provides basic information about the study, FAQ, information about the study team and Fred Hutchinson Cancer Research Center (FHCRC), and a portal to the informed consent form, screening, and baseline surveys.

We will use the identical enrollment method proven successful in our previous, remotely-conducted RCTs. Specifically, for participants who screen eligible on the recruitment website and provide their email address, we will instantly send them an email (and two reminders over a 14-day period) inviting them to complete a secured online survey to provide informed consent and complete the baseline assessment. Those not consenting and completing the online enrollment process within 14 days will be sent an email notifying them that they were not enrolled and provide both the QuitGuide app and the 800-QUIT-NOW phone number to reach their state's quitline.

To address potential fraudulent responses to web-based screening surveys, we will use the same methods used in our previous studies: CAPTCHA verification, ineligibility if the IP address was previously used or suspicious, and telephone contact by research staff if any aspect of automated data collection revealed suspicious activity (e.g., very brief survey completion times or unusual patterns in email addresses). To further deter fraudulent attempts to enter the study, no compensation will be provided for completion of the screening and baseline surveys.

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

Baseline Assessment. The baseline survey assesses demographics, smoking history and current smoking behaviors the use electronic cigarettes, mechanisms of change, and potential treatment moderators. More details below in section 7.3. The baseline survey data will be collected and stored in a research database behind FHCRC firewall.

After completing the baseline assessment, and first log-in, the participants will be randomized to receive either Actify or QuitGuide intervention. Randomization will be stratified based on sex assigned at birth, level of smoking and the presence of pre-treatment depressive symptoms.

Following the completion of the baseline and contact information survey the participant will receive a text message with a link to their phone. Once this link is clicked the study team will send an email and a text message indicating that they are enrolled in the study. This email and text message will provide them with a link to the randomly assigned intervention and login credentials. If in 3 days the participant has not opened the app, they will receive a text message reminder. If in 3 more days the participant has still not opened the app, study staff will reach out by phone and offer technical assistance.

8.3 Assessments/On-Study Clinical Evaluations

A complete schedule of assessments is provided in the table 1 above. All data from these assessments will be collected via web- based, telephone, or mailed surveys.

Eligibility and sample description. Demographic items assessed at baseline will include age, gender, sex assigned at birth, education, employment, income, and marital status. The 6-item Fagerström Test for Nicotine Dependence (FTND) [75] will be administered to assess degree of physical dependence on nicotine. Living with a smoker and quit attempts in the last 12 months will also be assessed. The Patient Health Questionnaire-8 (PHQ-8) is a widely-used assessment of depressive symptoms that has demonstrated ability to detect symptom changes over time as a result of treatment [91]. The scale scores range from 1 to 24, with severity thresholds as follows: 5-9=mild, 10-14=moderate, 15-19=moderately severe, 20-24=severe. A score of 10 has 88% sensitivity and 88% specificity for a diagnosis of major depression [6]. We elected to use the PHQ-8 rather than the PHQ-9 because (a) the suicidal ideation item on the PHQ-9, which is omitted from the PHQ-8, does not have a significant impact on the evaluation of depression severity, as the cut-off scores are the same for both versions, (b) because it would be impractical to conduct follow-up suicidality assessments and referrals for all screening completers who endorse any suicidal thoughts, and (c) because there is no reason to believe that behavioral interventions for tobacco cessation would increase the risk of suicidality and therefore require ongoing monitoring of suicidality as a safety assessment.

Treatment acceptability will be assessed at the 8-week end-of-treatment follow-up using measures of treatment utilization and satisfaction. *Treatment utilization* will include number of logins to the assigned application, determined objectively using custom web site analytics data. Consistent with our prior studies, *treatment satisfaction* will be assessed with 8 items on the 8-week outcome survey. Example

items include, “Overall, how satisfied are you with your assigned program?”; and “How useful was your assigned program?” Follow-up questions will probe satisfaction with specific components of the program (e.g. app content, app organization, push notification content, push notification frequency). These data are critical for making iterative improvements of the content and functionality of the app as it progresses through the development cycle.

Efficacy for smoking cessation will be self-reported 30-day point prevalence abstinence (PPA) at 8 weeks post-randomization (“Have you smoked at all, even a puff, in the last 30 days?”), consistent our previous RCT of SmartQuit vs. QuitGuide for smoking cessation [10]. Secondary efficacy endpoints include: (1) 30-day PPA at 6-months post-randomization, (2) 7-day PPA at 8 weeks and 6 months, and (3) no use of cigarettes and other non-medicinal nicotine/tobacco products at 8 weeks and 6 months, including e-cigarettes. Use of these products will be measured at baseline and at 8-week and 6-month follow-up. Generally, biochemical verification of smoking abstinence is considered unnecessary in population-level interventions with no face-to-face contact [77]. However, we will confirm self-reported abstinence among those who report 30-day PPA at 8 weeks and at 6 months using saliva cotinine and expired carbon monoxide. Based on the just-published expert recommendations on biochemical confirmation of tobacco use and abstinence [90], our biochemical verification procedures will include both saliva cotinine testing as well as remote carbon monoxide (CO) monitoring using iCO Smokerlyzers. Both the cotinine tests and the Smokerlyzers will be sent to participants by mail. Participants will complete the CO testing on their smartphones using the iCO app and send results to the study team via email, using a function available within the app. We will also ask them to take a photo of the cotinine test results and return it via email. Aside from analysis of minor tobacco alkaloids (anabasine/anatabine, which require a urine sample and laboratory testing that would not be feasible in a remotely-conducted trial), this combination of methods is the best available approach that is feasible in a trial of this nature for differentiating distinct forms of nicotine and tobacco use. In order to meet the definition of biochemically-confirmed smoking abstinence, only the CO testing must be negative (<6 ppm for CO[1]). For analysis of abstinence from all forms of nicotine and tobacco, the CO test must be negative and the saliva cotinine must be negative for all abstainers who do not report recent (past 72 hours) use of nicotine replacement therapies. For those who report recent use of NRT, there is no feasible method of differentiating therapeutic use of nicotine from other forms of nicotine intake in this trial. We will report both self-reported abstinence and biochemically confirmed abstinence in all reports of study outcomes.

Mechanisms of change will be assessed using the PHQ-8 for depression and the 25-item Behavioral Activation for Depression Scale (BADS) [82], which was designed to assess activation as a treatment process targeted by BAT-D. Example items from the BADS scale include “I did something that was hard to do but it was worth it,” and “I made good decisions about what type of activities and/or situations I put myself in.”

Other assessments. Use of concomitant treatments for both tobacco cessation and depression will be assessed at each time point. Treatment preferences will be assessed with a single question and alcohol (AUDIT-C) will be assessed at baseline.

9.0 SUBJECT DISCONTINUATION OF ACTIVE TREATMENT

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

10.0 CONCOMITANT MEDICATIONS

Use of concomitant treatments for both tobacco cessation and depression will be assessed at each time point. Individuals who report using self-report any other quit smoking treatment, including FDA-approved quit smoking medications (e.g., nicotine patch, nicotine gum, Zyban), during the screening phase will not be eligible to participate in the study. At the 2 and 6-month follow-up assessment, participants will be asked about their use of FDA-approved quit-smoking and pharmacotherapy for depression. Initiating use of FDA-approved quit-smoking medications during the study is allowed.

11.0 ADVERSE EVENTS

11.1 Adverse Events

This is a low-risk study with no intervention agent/drug. Because this is a smoking cessation intervention, some participants may quit smoking cigarettes and may experience the physical and psychological consequences of smoking abstinence, such as nicotine withdrawal symptoms. As part of the informed consent procedures, participants will be informed about potential nicotine withdrawal symptoms and effects of abstinence. The intervention provides strategies designed to cope more effectively with symptoms of nicotine withdrawal. Finally, participants will be given information on pharmacotherapy for smoking cessation (e.g., nicotine patch) and how to obtain these medications.

11.2 Collection and reporting of AEs and SAEs

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

Monitoring.

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

Reporting.

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

Reporting SAEs. For AEs meeting the criteria for an SAE, regardless of attribution, the study coordinator will inform the Fred Hutch IRB per their reporting guidelines and will complete and submit a NIDA SAE report form within 72 hours of the reported event. Should additional information become available after the initial report, a revised report will be submitted as soon as possible**.**

Reporting AEs that do not meet the criteria for SAE. All reported AEs will be collected and reported via the study's electronic database. AEs that are expected will be summarized at the time of continuation review.

Reporting UEs that do not meet the criteria for AEs. The study team will report any UEs to the Fred Hutch IRB per their reporting guidelines. Fred Hutch will report the UE to the sponsor in accordance with the protocol.

Definitions

In general, unexpected events (UEs) include any event, adverse or otherwise, that was not described as part of the study risks. For this trial, an example of an unexpected event that is not adverse is a participant who has become very unhappy with trial procedures. Adverse events (AEs) are any untoward occurrence with a trial participant whether or not it can be considered to be related to their smoking cessation intervention. Examples of adverse events in this trial could include development or worsening of depression symptoms. Serious adverse events (SAEs) include any AE that results in death, a real risk of dying, inpatient hospitalization, persistent or significant disability/incapacity, or AEs that require intervention to prevent permanent impairment or damage. In this trial, an example of a serious adverse event would be a suicide attempt.

Management of SAEs or other study risks

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

Attribution

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

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

12.0 DATA AND SAFETY MONITORING PLAN

This study is a low-risk, single-site, randomized 2-arm pilot trial of a behavioral intervention for smoking cessation, monitoring of participant safety and data quality will be overseen by the PI, who will have weekly meetings with the study team to discuss study progress, including recruitment and retention, adverse events, and protocol adherence. Detailed DSMP in included in Appendix A.

13.0 DATA MANAGEMENT/CONFIDENTIALITY

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

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

Any data included in manuscripts or publications stemming from this study will be presented as aggregate data only, and in a way that no individual could be identified. At the end of the study, after all manuscripts are published, all identifiable files and crosswalks will be destroyed in accordance with Fred

Hutch IRB policy (7 years after the end of the study). Electronic media used to store all data will be cleaned or destroyed so the data is not retrievable. As a result of these measures, we do not expect any invasion of privacy or breach of confidentiality.

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

Online Surveys. The study database will be designed and maintained by Datatope, kept behind FHCRC firewall. Only key study staff will have access to the study database system. All staff have received Human Subject Research and HIPAA training. All data will be stored in a secure password protected computer folder, which only authorized research staff will have access to.
Mailed Surveys. Numerous safeguards will keep hard copy data secure. All hard copy data will be kept in a locked file cabinet accessible only by authorized research staff.

Actify and QuitGuide app-based Intervention. Numerous safeguards will keep electronic data secure. A secure password is required to access computers at our site, and computer networks are on secured servers that meet or exceed federal confidentiality standards. Each participant will have access to their website protected with a login. All connections to this website will be made using the secure sockets layer (SSL). Participant data are maintained on a server in a locked server room at Fred Hutch. Full access to the server is restricted to two staff members of the Fred Hutch Public Health Sciences Information Technology (PHS-IT) group and the two staff members of Datatope Inc. Participants access their intervention app by providing login credentials on the app, which is hosted on a secure server. The Login server has no access to the study database. It can send login credentials and, upon successful login, it can receive the participant's responses provided in the intervention app to questions related to smoking and values. No potentially identifying information is entered into the app by the participant. All communication with the Actify and the QuitGuide app occurs over Secure Sockets Layer (SSL). The intervention app stores participant usage data. The only participant identifier that will be transmitted to this database server will be their login id. The site only stores data related to site usage.

14.0 STATISTICAL CONSIDERATIONS

14.1 Study Design

Randomized controlled 2-arm pilot trial

14.2 Primary/Secondary Endpoints/Hypotheses and Analytical Methods

Data analyses will be conducted using the intent-to-treat approach, except where otherwise indicated.

Aim 1. Conduct a pilot, randomized controlled trial (n=240) to test the primary outcome of treatment acceptability and secondary outcomes of efficacy and mechanism of change for the two treatment groups: Actify vs. QuitGuide.

ENDPOINTS

- The primary acceptability endpoints are number of app openings and overall satisfaction ratings.

- For smoking cessation:
    - The primary endpoint is the 30-day point prevalence abstinence (PPA) at 8 weeks post-randomization, which is comparable to the primary endpoints of the two extant trials of smartphone apps for smoking cessation [10, 34].
    - The secondary endpoints are 7- and 30-day PPA at 6 months, 7-day PPA at 8 weeks, and biochemically-confirmed abstinence from any nicotine/tobacco product (other than FDA-approved cessation medications) between baseline and 8-week and 6-month follow-ups.

- For mechanism of change,
    - The primary endpoint is the change in BADS scores between baseline and the 8-week follow-up
    - The secondary endpoint is the change in depressive symptoms over the same time period.

ANALYTICAL METHODS

Linear regression will be used to evaluate treatment effects between the two arms for continuous endpoints. This model will adjust for any demographic or other variables that differ between study arms at baseline and are related to outcome as well as the stratification factors (depression severity, sex assigned at birth, and level of smoking). To compare binary endpoints between two arms (e.g. smoking abstinence), a logistic regression model will be conducted with control for potential confounding variables and the stratification variable. Sensitivity analyses excluding participants using concomitant treatment for smoking cessation and/or depression will also be conducted.

Additional exploratory analyses will be conducted. To explore differential treatment effects by pre-quit depression, we will preliminarily test the interaction of treatment group assignment and pre-quit depression and present descriptive data on quit rates for the four subgroups (Actify, depressed; Actify non-depressed; QuitGuide, depressed; QuitGuide non-depressed). To evaluate the theory underlying BAT-D for smoking cessation, we will examine change in BADS scores between baseline and 8-week follow-up as a predictor of 30-day PPA at 6-month follow-up using a logistic regression model. To generate empirical evidence to set usage benchmarks for the Actify app, we will evaluate the relationship between app "dosage" and cessation outcomes by regressing 30-day PPA at 8 weeks on objective measures of app utilization (e.g., number of app logins, total duration of use) using logistic regression. Similar to our feature analysis of SmartQuit that guided future app development [69], we will also regress 30-day PPA at 8 weeks on utilization of specific app components (e.g., scheduling, mood tracking) to determine "active ingredients." To evaluate the relationship between user characteristics and treatment utilization and outcomes, we will use logistic (for cessation outcomes) or negative binomial (for login count data) models and baseline data as predictors. To examine sex as a biological variable, we will preliminarily test for sex differences in treatment response by descriptively examining results separately by sex.

Missing data: Consistent with prevailing standards for smoking cessation trials [88], participants with missing smoking data will be considered non-abstinent in the primary analysis. As a sensitivity analysis, we will also report abstinence rates from complete case analyses and multiple imputation. Treatment acceptability and mechanism of change (i.e., behavioral activation [BADS] and depression [PHQ-8] scores) will be analyzed using complete case analysis.

Modified intent-to-treat approach. Because treatment acceptability is the primary outcome of this pilot trial, and because a valid assessment of acceptability is not possible in cases where there is pre-intervention attrition (i.e., never downloading or opening the assigned app), we will use a modified intent-to-treat approach in which only those participants who open their assigned app at least once will be included in the outcome analyses.

14.3 Sample Size and Power

As a pilot treatment development project, this study is not powered to detect statistically significant differences by treatment group. However, we plan to compare the outcomes of the two interventions to obtain a preliminary estimate of effect size. We will use these pilot data to optimize the treatment and study design and to prepare for a rigorous test of the efficacy of Actify in a subsequent R01. We plan to accrue a total of 240 patients in the pilot RCT for a balanced design. The NIDA Stage Model of behavioral treatment development suggests that pilot treatment development trials should include approximately 15-30 participants per arm to test feasibility [61]. However, as demonstrated in a recent simulation focused on sample size for pilot studies [87], binary outcomes (e.g., smoking abstinence) require higher sample sizes for reasonable precision of the effect size estimate than do continuous outcomes. To be conservative, and in consideration of the higher recruitment capacity in remotely conducted studies involving standalone mHealth interventions, we chose to include 60 subjects per arm within each stratum (depressed vs. non-depressed), as a sample size of 60 is a point of diminishing returns in terms of precision of effect size estimates for binary outcomes [87]. Thus, each arm will have 120 participants, of which 60 will meet criteria for mild to moderate depression.

14.4 Randomization

Following completion of the baseline survey, the web-based program will randomize participants to receive either Actify or QuitGuide with a 1:1 allocation ratio. The randomization algorithm will be developed by the study biostatistician, with stratification by presence of mild to moderate depressive symptoms (PHQ-8 < 5 or PHQ-8 ≥ 5), sex assigned at birth (2 levels: male or female) and level of smoking (2 levels: 20 or more cigarettes per day vs. < 20). Randomized participants will be emailed a secured link to download their assigned app. All participants will be emailed identical once-weekly reminders to use their assigned intervention. Although we project, based on recent data from our trial of web-based interventions [8], that the vast majority (92%) of outcome assessments will be completed via web-based survey, any outcome evaluator who has direct contact with participants will be blinded to treatment group assignment.

14.5 Ethnic and Gender Distribution Chart: Projected Target Accrual

Planned

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native		2	0	0	6
Asian	4	2	0	0	6

Native Hawaiian or Other Pacific Islander	2	0	0	0	2
Black or African American	17	8	2	0	27
White	139	47	12	4	202
More than One Race	10	2	0	0	12
Total	176	61	14	4	255

15.0 INVESTIGATOR OBLIGATIONS

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

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

16.0 REFERENCES

1. US Department of Health and Human Services. The health consequences of smoking--50 years of progress. A report of the Surgeon General. US Department of Health and Human Services CfDCaP, National Center for Chronic Disease Control and Prevention, Office on Smoking and Health., editor. Atlanta, GA.2014.
2. Centers for Disease Control and Prevention. Alcohol and public health: Alcohol-related disease impact (ARDI). Average for United States 2006-2010 alcohol-attributable deaths due to excessive alcohol use. [cited 2017 September 30]. Available from: https://nccd.cdc.gov/DPH_ARDI/Default/Report.aspx?T=AAM&P=f6d7eda7-036e-4553-9968-9b17ffad620e&R=d7a9b303-48e9-4440-bf47-070a4827e1fd&M=8E1C5233-5640-4EE8-9247-1ECA7DA325B9&F=&D.
3. Rudd RA, Seth P, David F, Scholl L. Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015. MMWR Morb Mortal Wkly Rep. 2016;65(5051):1445-52. Epub 2016/12/30. doi: 10.15585/mmwr.mm655051e1. PubMed PMID: 28033313.
4. Centers for Disease Control and Prevention. Quitting smoking among adults--United States, 2001- 2010. MMWR Morb Mortal Wkly Rep. 2011;60(44):1513-9. Epub 2011/11/11. PubMed PMID: 22071589.
5. Weinberger AH, Gbedemah M, Wall MM, Hasin DS, Zvolensky MJ, Chaiton M, et al. Depression Among Non-Daily Smokers Compared to Daily Smokers and Never-Smokers in the United States: An Emerging Problem. Nicotine Tob Res. 2017. Epub 2017/03/25. doi: 10.1093/ntr/ntx009. PubMed PMID: 28339571.

6. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606-13. Epub 2001/09/15. PubMed PMID: 11556941; PubMed Central PMCID: PMCPMC1495268.
7. Hebert KK, Cummins SE, Hernandez S, Tedeschi GJ, Zhu SH. Current major depression among smokers using a state quitline. Am J Prev Med. 2011;40(1):47-53. Epub 2010/12/15. doi: 10.1016/j.amepre.2010.09.030. PubMed PMID: 21146767; PubMed Central PMCID: PMCPMC3006168.
8. Bricker JB, Mull KE, McClure JB, Watson NL, Heffner JL. Improving quit rates of web-delivered interventions for smoking cessation: full-scale randomized trial of WebQuit.org versus Smokefree.gov. Addiction. 2018;113(5):914-23. Epub 2017/12/14. doi: 10.1111/add.14127. PubMed PMID: 29235186.
9. Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. Applied Psychological Measurement. 1977;1:385-401.
10. Bricker JB, Mull KE, Kientz JA, Vilardaga R, Mercer LD, Akioka KJ, et al. Randomized, controlled pilot trial of a smartphone app for smoking cessation using acceptance and commitment therapy. Drug Alcohol Depend. 2014. Epub 2014/08/03. doi: 10.1016/j.drugalcdep.2014.07.006. PubMed PMID: 25085225.
11. Weinberger AH, Kashan RS, Shpigel DM, Esan H, Taha F, Lee CJ, et al. Depression and cigarette smoking behavior: A critical review of population-based studies. Am J Drug Alcohol Abuse. 2017;43(4):416-31. Epub 2016/06/11. doi: 10.3109/00952990.2016.1171327. PubMed PMID: 27286288.
12. Cooper J, Borland R, McKee SA, Yong HH, Dugue PA. Depression motivates quit attempts but predicts relapse: differential findings for gender from the International Tobacco Control Study. Addiction. 2016;111(8):1438-47. Epub 2016/02/19. doi: 10.1111/add.13290. PubMed PMID: 26888199; PubMed Central PMCID: PMCPMC4940212.
13. Stepankova L, Kralikova E, Zvolska K, Pankova A, Ovesna P, Blaha M, et al. Depression and Smoking Cessation: Evidence from a Smoking Cessation Clinic with 1-Year Follow-Up. Ann Behav Med. 2017;51(3):454-63. Epub 2016/12/31. doi: 10.1007/s12160-016-9869-6. PubMed PMID: 28035641; PubMed Central PMCID: PMCPMC5440483.
14. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: A population-based prevalence study. JAMA. 2000;284(20):2606-10. Epub 2000/11/22. PubMed PMID: 11086367.
15. Himelhoch S, Daumit G. To whom do psychiatrists offer smoking-cessation counseling? Am J Psychiatry. 2003;160(12):2228-30. Epub 2003/11/26. PubMed PMID: 14638595.
16. Heffner JL, Strawn JR, DelBello MP, Strakowski SM, Anthenelli RM. The co-occurrence of cigarette smoking and bipolar disorder: phenomenology and treatment considerations. Bipolar Disord. 2011;13(5-6):439- 53. Epub 2011/10/25. doi: 10.1111/j.1399-5618.2011.00943.x. PubMed PMID: 22017214.
17. Hitsman B, Papandonatos GD, McChargue DE, DeMott A, Herrera MJ, Spring B, et al. Past major depression and smoking cessation outcome: a systematic review and meta-analysis update. Addiction.

2013;108(2):294-306. Epub 2012/10/18. doi: 10.1111/add.12009. PubMed PMID: 23072580; PubMed Central PMCID: PMCPMC3593055.

18. Berlin I, Covey LS. Pre-cessation depressive mood predicts failure to quit smoking: the role of coping and personality traits. Addiction. 2006;101(12):1814-21. Epub 2006/12/13. doi: 10.1111/j.1360- 0443.2006.01616.x. PubMed PMID: 17156181.
19. Cook J, Spring B, McChargue D, Doran N. Effects of anhedonia on days to relapse among smokers with a history of depression: a brief report. Nicotine Tob Res. 2010;12(9):978-82. Epub 2010/08/17. doi: 10.1093/ntr/ntq118. PubMed PMID: 20709727; PubMed Central PMCID: PMCPMC2948830.
20. Leventhal AM, Ramsey SE, Brown RA, LaChance HR, Kahler CW. Dimensions of depressive symptoms and smoking cessation. Nicotine Tob Res. 2008;10(3):507-17. Epub 2008/03/08. doi: 10.1080/14622200801901971. PubMed PMID: 18324570; PubMed Central PMCID: PMCPMC2650807.
21. Leventhal AM, Piper ME, Japuntich SJ, Baker TB, Cook JW. Anhedonia, depressed mood, and smoking cessation outcome. J Consult Clin Psychol. 2014;82(1):122-9. Epub 2013/11/14. doi: 10.1037/a0035046. PubMed PMID: 24219183; PubMed Central PMCID: PMCPMC3934823.
22. Kenford SL, Smith SS, Wetter DW, Jorenby DE, Fiore MC, Baker TB. Predicting relapse back to smoking: contrasting affective and physical models of dependence. J Consult Clin Psychol. 2002;70(1):216-27. Epub 2002/02/28. PubMed PMID: 11860048.
23. Heffner JL, Mull KE, McClure JB, Bricker JB. Positive affect as a predictor of smoking cessation and relapse: Does it offer unique predictive value among depressive symptom domains? Subst Use Misuse. Accepted.
24. Heffner JL. Smoking cessation app users' motivations, concerns, and plans: profile of the first 1100 users of SmartQuit. Society for Research on Nicotine and Tobacco Florence, Italy2017.
25. Fiore MC, Jaén CR, Baker TB, Bailey WC, Benowitz NL, Curry SJ, et al. Treating tobacco use and dependence: 2008 update. Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service; 2008.
26. Mobile fact sheet [Fact sheet]. Pew Research Center; 2017 [cited 2017 April 14]. January 12, 2017:[Available from: http://www.pewinternet.org/fact-sheet/mobile/.
27. Heffner JL, Mull KE. Smartphone Ownership Among US Adult Cigarette Smokers: 2014 Health Information National Trends Survey (HINTS) Data. J Med Internet Res. 2017;19(8):e305. Epub 2017/09/02. doi: 10.2196/jmir.7953. PubMed PMID: 28860108; PubMed Central PMCID: PMCPMC5599728.
28. Estimated US downloads of smoking cessation apps since 2012 [updated March 24, 2014]. Available from: xyo.net.
29. Fast growth of apps user base.: Portico Research; [updated March 26, 2014]. Available from: http://www.portioresearch.com/en/blog/2013/fast-growth-of-apps-user-base-in-booming-asia-pacific- market.aspx.
30. Augustson E. Personal communication on estimated total number of US smoking cessation text messaging program subscribers since 2012. March 4, 2014.
31. Borrelli B, Bartlett YK, Tooley E, Armitage CJ, Wearden A. Prevalence and Frequency of mHealth and eHealth Use Among US and UK Smokers and Differences by Motivation to Quit. J Med

Internet Res. 2015;17(7):e164. Epub 2015/07/08. doi: 10.2196/jmir.4420. PubMed PMID: 26149323; PubMed Central PMCID: PMCPMC4526978.

32. Ubhi HK, Kotz D, Michie S, van Schayck OCP, West R. A comparison of the characteristics of iOS and Android users of a smoking cessation app. Transl Behav Med. 2017;7(2):166-71. Epub 2017/02/09. doi: 10.1007/s13142-016-0455-z. PubMed PMID: 28168609; PubMed Central PMCID: PMCPMC5526810.
33. Bricker JB, Copeland W, Mull KE, Zeng EY, Watson NL, Akioka KJ, et al. Single-arm trial of the second version of an acceptance & commitment therapy smartphone application for smoking cessation. Drug Alcohol Depend. 2017;170:37-42. Epub 2016/11/22. doi: 10.1016/j.drugalcdep.2016.10.029. PubMed PMID: 27870987; PubMed Central PMCID: PMCPMC5183543.
34. Buller DB, Borland R, Bettinghaus EP, Shane JH, Zimmerman DE. Randomized Trial of a Smartphone Mobile Application Compared to Text Messaging to Support Smoking Cessation. Telemed J E Health. 2013. Epub 2013/12/20. doi: 10.1089/tmj.2013.0169. PubMed PMID: 24350804.
35. Ubhi HK, Michie S, Kotz D, Wong WC, West R. A mobile app to aid smoking cessation: preliminary evaluation of SmokeFree28. J Med Internet Res. 2015;17(1):e17. Epub 2015/01/18. doi: 10.2196/jmir.3479. PubMed PMID: 25596170; PubMed Central PMCID: PMCPMC4319069.
36. Iacoviello BM, Steinerman JR, Klein DB, Silver TL, Berger AG, Luo SX, et al. Clickotine, A Personalized Smartphone App for Smoking Cessation: Initial Evaluation. JMIR Mhealth Uhealth. 2017;5(4):e56. Epub 2017/04/27. doi: 10.2196/mhealth.7226. PubMed PMID: 28442453; PubMed Central PMCID: PMCPMC5424127.
37. Gordon JS, Armin J, M DH, Giacobbi P, Jr., Cunningham JK, Johnson T, et al. Development and evaluation of the See Me Smoke-Free multi-behavioral mHealth app for women smokers. Transl Behav Med. 2017;7(2):172-84. Epub 2017/02/06. doi: 10.1007/s13142-017-0463-7. PubMed PMID: 28155107; PubMed Central PMCID: PMCPMC5526811.
38. Businelle MS, Ma P, Kendzor DE, Frank SG, Vidrine DJ, Wetter DW. An Ecological Momentary Intervention for Smoking Cessation: Evaluation of Feasibility and Effectiveness. J Med Internet Res. 2016;18(12):e321. Epub 2016/12/14. doi: 10.2196/jmir.6058. PubMed PMID: 27956375; PubMed Central PMCID: PMCPMC5187451.
39. Zhao J, Freeman B, Li M. Can Mobile Phone Apps Influence People's Health Behavior Change? An Evidence Review. J Med Internet Res. 2016;18(11):e287. Epub 2016/11/04. doi: 10.2196/jmir.5692. PubMed PMID: 27806926; PubMed Central PMCID: PMCPMC5295827.
40. Abroms LC, Lee Westmaas J, Bontemps-Jones J, Ramani R, Mellerson J. A content analysis of popular smartphone apps for smoking cessation. Am J Prev Med. 2013;45(6):732-6. Epub 2013/11/19. doi: 10.1016/j.amepre.2013.07.008. PubMed PMID: 24237915; PubMed Central PMCID: PMCPMC3836190.
41. Abroms LC, Padmanabhan N, Thaweethai L, Phillips T. iPhone apps for smoking cessation: a content analysis. Am J Prev Med. 2011;40(3):279-85. Epub 2011/02/22. doi: 10.1016/j.amepre.2010.10.032. PubMed PMID: 21335258; PubMed Central PMCID: PMCPMC3395318.

42. Azar KM, Lesser LI, Laing BY, Stephens J, Aurora MS, Burke LE, et al. Mobile applications for weight management: theory-based content analysis. Am J Prev Med. 2013;45(5):583-9. Epub 2013/10/22. doi: 10.1016/j.amepre.2013.07.005. PubMed PMID: 24139771.
43. Davis SF, Ellsworth MA, Payne HE, Hall SM, West JH, Nordhagen AL. Health Behavior Theory in Popular Calorie Counting Apps: A Content Analysis. JMIR Mhealth Uhealth. 2016;4(1):e19. Epub 2016/03/05. doi: 10.2196/mhealth.4177. PubMed PMID: 26935898; PubMed Central PMCID: PMCPMC4795330.
44. Hopko DR, Lejuez CW, Ruggiero KJ, Eifert GH. Contemporary behavioral activation treatments for depression: procedures, principles, and progress. Clin Psychol Rev. 2003;23(5):699-717. Epub 2003/09/16. PubMed PMID: 12971906.
45. Lejuez CW, Hopko DR, Acierno R, Daughters SB, Pagoto SL. Ten year revision of the brief behavioral activation treatment for depression: revised treatment manual. Behav Modif. 2011;35(2):111-61. Epub 2011/02/18. doi: 10.1177/0145445510390929. PubMed PMID: 21324944.
46. Jacobson NS, Dobson KS, Truax PA, Addis ME, Koerner K, Gollan JK, et al. A component analysis of cognitive-behavioral treatment for depression. J Consult Clin Psychol. 1996;64(2):295-304. Epub 1996/04/01. PubMed PMID: 8871414.
47. Ekers D, Webster L, Van Straten A, Cuijpers P, Richards D, Gilbody S. Behavioural activation for depression; an update of meta-analysis of effectiveness and sub group analysis. PLoS One. 2014;9(6):e100100. Epub 2014/06/18. doi: 10.1371/journal.pone.0100100. PubMed PMID: 24936656; PubMed Central PMCID: PMCPMC4061095.
48. Dimidjian S, Hollon SD, Dobson KS, Schmaling KB, Kohlenberg RJ, Addis ME, et al. Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the acute treatment of adults with major depression. J Consult Clin Psychol. 2006;74(4):658-70. Epub 2006/08/03. doi: 10.1037/0022- 006x.74.4.658. PubMed PMID: 16881773.
49. Hopko DR, Lejuez CW, LePage JP, Hopko SD, McNeil DW. A brief behavioral activation treatment for depression. A randomized pilot trial within an inpatient psychiatric hospital. Behav Modif. 2003;27(4):458-69. Epub 2003/09/16. doi: 10.1177/0145445503255489. PubMed PMID: 12971122.
50. Goelz PM, Audrain-McGovern JE, Hitsman B, Leone FT, Veluz-Wilkins A, Jepson C, et al. The association between changes in alternative reinforcers and short-term smoking cessation. Drug Alcohol Depend. 2014;138:67-74. Epub 2014/03/07. doi: 10.1016/j.drugalcdep.2014.02.007. PubMed PMID: 24598122; PubMed Central PMCID: PMCPMC4030632.
51. Martinez-Vispo C, Rodriguez-Cano R, Lopez-Duran A, Senra C, Fernandez Del Rio E, Becona E. Cognitive-behavioral treatment with behavioral activation for smoking cessation: Randomized controlled trial. PLoS One. 2019;14(4):e0214252. Epub 2019/04/09. doi: 10.1371/journal.pone.0214252. PubMed PMID: 30958831; PubMed Central PMCID: PMCPMC6453447.
52. MacPherson L, Tull MT, Matusiewicz AK, Rodman S, Strong DR, Kahler CW, et al. Randomized controlled trial of behavioral activation smoking cessation treatment for smokers with elevated depressive symptoms. J Consult Clin Psychol. 2010;78(1):55-61. Epub 2010/01/27. doi: 10.1037/a0017939. PubMed PMID: 20099950; PubMed Central PMCID: PMCPMC3108050.

53. Busch AM, Tooley EM, Dunsiger S, Chattillion EA, Srour JF, Pagoto SL, et al. Behavioral activation for smoking cessation and mood management following a cardiac event: results of a pilot randomized controlled trial. BMC Public Health. 2017;17:323. doi: 10.1186/s12889-017-4250-7. PubMed PMID: PMC5392972.
54. West R. The clinical significance of "small" effects of smoking cessation treatments. Addiction. 2007;102(4):506-9. Epub 2007/03/17. doi: 10.1111/j.1360-0443.2007.01750.x. PubMed PMID: 17362283.
55. Daughters SB, Magidson JF, Anand D, Seitz-Brown CJ, Chen Y, Baker S. The effect of a behavioral activation treatment for substance use on post-treatment abstinence: a randomized controlled trial. Addiction. 2018;113(3):535-44. Epub 2017/10/01. doi: 10.1111/add.14049. PubMed PMID: 28963853; PubMed Central PMCID: PMCPMC5807178.
56. Shiffman S, Brockwell SE, Pillitteri JL, Gitchell JG. Use of smoking-cessation treatments in the United States. American Journal of Preventive Medicine. 2008;34(2):102-11. Epub 2008/01/19. doi: 10.1016/j.amepre.2007.09.033. PubMed PMID: 18201639.
57. Pew Internet Research Project. Mobile technology fact sheet 2013 [March 7, 2014]. Available from: http://www.pewinternet.org/fact-sheets/mobile-technology-fact-sheet.
58. Heffner JL, Mull KE, McClure JB, Bricker JB. Positive Affect as a Predictor of Smoking Cessation and Relapse: Does It Offer Unique Predictive Value Among Depressive Symptom Domains? Subst Use Misuse. 2017:1-9. Epub 2017/11/22. doi: 10.1080/10826084.2017.1387569. PubMed PMID: 29161212.
59. Barry MB, Saul J, Bailey LA. U.S. quitlines at a crossroads: utilization, budget, and service trends 2005- 2010. Phoenix, AZ: 2010.
60. Augustson E, Cole-Lewis H, Sanders A, Schwarz M, Geng Y, Coa K, et al. Analysing user-reported data for enhancement of SmokefreeTXT: a national text message smoking cessation intervention. Tob Control. 2017;26(6):683-9. Epub 2016/11/18. doi: 10.1136/tobaccocontrol-2016-052945. PubMed PMID: 27852892.
61. Rounsaville BJ, Carroll KM, Onken LS. A stage model of behavioral therapies research: Getting started and moving on from stage I. Clinical Psychology: Science and Practice. 2001;8(2):133-42. doi: 10.1093/clipsy/8.2.133. PubMed PMID: 2001-17463-001. First Author & Affiliation: Rounsaville, Bruce J.
62. Heffner JL, Wyszynski CM, Comstock B, Mercer LD, Bricker J. Overcoming recruitment challenges of web-based interventions for tobacco use: the case of web-based acceptance and commitment therapy for smoking cessation. Addict Behav. 2013;38(10):2473-6. doi: 10.1016/j.addbeh.2013.05.004. PubMed PMID: 23770645; PubMed Central PMCID: PMC3725211.
63. Berg CJ. Internet-based interventions for smoking cessation show inconsistent effects across trials, with only some trials showing a benefit. Evidence-based Nursing. 2011;14(2):47-8. Epub 2011/03/23. doi: 10.1136/ebn.14.2.47. PubMed PMID: 21421974.
64. Civljak M, Sheikh A, Stead LF, Car J. Internet-based interventions for smoking cessation. Cochrane Database Syst Rev. 2010(9):CD007078. Epub 2010/09/09. doi: 10.1002/14651858.CD007078.pub3. PubMed PMID: 20824856.

65. Graham AL, Cobb NK, Papandonatos GD, Moreno JL, Kang H, Tinkelman DG, et al. A randomized trial of Internet and telephone treatment for smoking cessation. Archives of Internal Medicine. 2011;171(1):46-53. Epub 2011/01/12. doi: 10.1001/archinternmed.2010.451. PubMed PMID: 21220660.
66. Hutton HE, Wilson LM, Apelberg BJ, Tang EA, Odelola O, Bass EB, et al. A systematic review of randomized controlled trials: Web-based interventions for smoking cessation among adolescents, college students, and adults. Nicotine Tob Res. 2011;13(4):227-38. Epub 2011/02/26. doi: 10.1093/ntr/ntq252. PubMed PMID: 21350042.
67. Shahab L, McEwen A. Online support for smoking cessation: a systematic review of the literature. Addiction. 2009;104(11):1792-804. Epub 2009/10/17. doi: 10.1111/j.1360-0443.2009.02710.x. PubMed PMID: 19832783.
68. Webb TL. Commentary on Shahab & McEwen (2009): Understanding and preventing attrition in online smoking cessation interventions: a self-regulatory perspective. Addiction. 2009;104(11):1805-6. Epub 2009/10/17. doi: 10.1111/j.1360-0443.2009.02751.x. PubMed PMID: 19832784.
69. Heffner JL, Vilardaga R, Mercer LD, Kientz JA, Bricker JB. Feature-level analysis of a novel smartphone application for smoking cessation. Am J Drug Alcohol Abuse. 2015;41(1):68-73. Epub 2014/11/15. doi: 10.3109/00952990.2014.977486. PubMed PMID: 25397860; PubMed Central PMCID: PMCPMC4410684.
70. Kalin S. Mazed and Confused 1999 [updated April 1, 1999Retrieved April 1, 1999]. Available from: http://www.cio.com/archive/Webbusiness/040199_use.html.
71. Cheh JA, Ribisl KM, Wildemuth BM. An assessment of the quality and usability of smoking cessation information on the Internet. Health Promot Pract. 2003;4:278-87.
72. Brooke J. SUS: A "quick and dirty" usability scale". In: Jordan PW, Thomas B, Weerdmeester BA, McClelland AL, editors. Usability Evaluation in Industry. London: Taylor and Francis; 1996.
73. Stoddard JL, Augustson EM, Mabry PL. The importance of usability testing in the development of an internet-based smoking cessation treatment resource. Nicotine Tob Res. 2006;Dec;8 Suppl 1:S87-93. PMID: 17491175.
74. Bricker J, Wyszynski C, Comstock B, Heffner JL. Pilot randomized controlled trial of web-based acceptance and commitment therapy for smoking cessation. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2013;15(10):1756-64. Epub 2013/05/25. doi: 10.1093/ntr/ntt056. PubMed PMID: 23703730; PubMed Central PMCID: PMC3768336.
75. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO. The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. British Journal of Addiction. 1991;86(9):1119-27.
76. Titov N, Dear BF, McMillan D, Anderson T, Zou J, Sunderland M. Psychometric comparison of the PHQ-9 and BDI-II for measuring response during treatment of depression. Cognitive Behaviour Therapy. 2011;40(2):126-36. doi: 10.1080/16506073.2010.550059. PubMed PMID: 2011-14818-005. First Author & Affiliation: Titov, Nickolai.

77. SRNT Subcommittee on Biochemical Verification. Biochemical verification of tobacco use and cessation. Nicotine & Tobacco Research. 2002;4(2):149-59. Epub 2002/05/25. doi: 10.1080/14622200210123581. PubMed PMID: 12028847.
78. Benowitz NL, Jacob III P, Ahijevych K, Jarvis MJ, Hall S, LeHouezec J, et al. Biochemical verification of tobacco use and cessation. Nicotine Tob Res. 2002;4(2):149-59.
79. Etter JF, Neidhart E, Bertrand S, Malafosse A, Bertrand D. Collecting saliva by mail for genetic and cotinine analyses in participants recruited through the Internet. Eur J Epidemiol. 2005;20(10):833-8. Epub 2005/11/12. doi: 10.1007/s10654-005-2148-7. PubMed PMID: 16283473.
80. Greeley DA, Valois RF, Bernstein DA. Stability of salivary cotinine sent through the U.S. mail for verification of smoking status. Addict Behav. 1992;17(3):291-6. Epub 1992/01/01. doi: 0306-4603(92)90034-S [pii]. PubMed PMID: 1636476.
81. Jacob P, 3rd, Hatsukami D, Severson H, Hall S, Yu L, Benowitz NL. Anabasine and anatabine as biomarkers for tobacco use during nicotine replacement therapy. Cancer Epidemiol Biomarkers Prev. 2002;11(12):1668-73. Epub 2002/12/24. PubMed PMID: 12496059.
82. Kanter JW, Mulick PS, Busch AM, Berlin KS, Martell CR. The Behavioral Activation for Depression Scale (BADS): Psychometric properties and factor structure. Journal of Psychopathology and Behavioral Assessment. 2007;29(3):191-202. doi: 10.1007/s10862-006-9038-5. PubMed PMID: 2008-02953-007.
83. El-Hilly AA, Iqbal SS, Ahmed M, Sherwani Y, Muntasir M, Siddiqui S, et al. Game On? Smoking Cessation Through the Gamification of mHealth: A Longitudinal Qualitative Study. JMIR Serious Games. 2016;4(2):e18. Epub 2016/10/26. doi: 10.2196/games.5678. PubMed PMID: 27777216; PubMed Central PMCID: PMCPMC5099502.
84. Whittaker R, McRobbie H, Bullen C, Rodgers A, Gu Y. Mobile phone-based interventions for smoking cessation. Cochrane Database Syst Rev. 2016;4:Cd006611. Epub 2016/04/12. doi: 10.1002/14651858.CD006611.pub4. PubMed PMID: 27060875.
85. Whittaker R, McRobbie H, Bullen C, Borland R, Rodgers A, Gu Y. Mobile phone-based interventions for smoking cessation. Cochrane Database Syst Rev. 2012;11:CD006611. Epub 2012/11/16. doi: 10.1002/14651858.CD006611.pub3. PubMed PMID: 23152238.
86. Dillman DA. Mail and Internet Surveys: The Tailored Design Method. 2nd ed. Hoboken, NH: John Wiley & Sons, Inc.; 2007.
87. Teare D, Dimairo M, Hayman A, Shephard N, Whitehead A, Walters S. Sample size requirements for pilot randomised controlled trials with binary outcomes: a simulation study. Trials. 2013;14(S1):O21.
88. West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. Addiction. 2005;100(3):299-303. Epub 2005/03/01. doi: ADD995 [pii] 10.1111/j.1360- 0443.2004.00995.x. PubMed PMID: 15733243.
89. Muñoz RF, Lenert LL, Delucchi K, Stoddard J, Perez JE, Penilla C, et al. Toward evidence-based Internet interventions: A Spanish/English Web site for international smoking cessation trials. Nicotine & Tobacco Research. 2006;8(1):77-87. Epub 2006/02/25. doi: 10.1080/14622200500431940. PubMed PMID: 16497602.

90. Benowitz NL, Bernert JT, Foulds J, Hecht SS, Jacob P, Jarvis MJ, et al. Biochemical Verification of Tobacco Use and Abstinence: 2019 Update. Nicotine Tob Res. 2019. Epub 2019/10/02. doi: 10.1093/ntr/ntz132. PubMed PMID: 31570931.

91. Kroenke K, Strine TW, Spitzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord. 2009 Apr;114(1-3):163-73. doi: 10.1016/j.jad.2008.06.026. Epub 2008 Aug 27. PMID: 18752852.

17.0 APPENDICES

Appendix A: Data & Safety Monitoring Plan

Appendix B: Fraud Prevention Protocol for Pilot Trial

*Included in this protocol document for Scientific Review Committee, all other appendices will be provided for IRB submission

Appendix A: Data & Safety Monitoring Plan

Version 2, 1/25/2022

R34 DA050967

"An mHealth mood management tool to improve population-level tobacco cessation"

PI: Heffner, Jaimee L.

DSMP Contents

1 Summary of the protocol

1.1 Brief description of the protocol

This study aims to inform the development of an app (Actify!) for smoking cessation that is grounded in behavioral activation therapy for depression (BAT-D). The primary aims are to (1) complete development of the new app by adding cessation content, improving the app structure, conducting a 1-week diary study to evaluate the app's usability, and refining the app, and (2) conduct a pilot, randomized controlled trial (n=240) to test the primary outcome of treatment acceptability and secondary outcomes of efficacy and mechanism of change for the Actify app vs. the active control app (the National Cancer Insitute's QuitGuide app). We will test the interventions using an 8-week treatment period, and, consistent with the evaluation period in our previous cessation app pilot study, our primary outcomes will be assessed at the 8-week end-of-treatment mark. We will also collect 6-month follow-up data to assess long-term outcomes.

1.2 Primary and secondary outcome measures

Acceptability outcomes:

- Co-primary: User satisfaction ratings of the assigned app at 8 weeks post-randomization
- Co-primary: Total number of log-ins to the assigned app at 8 weeks post-randomization

Smoking abstinence outcomes

- Primary: Self-reported 30-day point prevalence abstinence (PPA) from smoking at 8 weeks post-randomization
- Secondary:
  - Self-reported 30-day PPA from smoking at 6 months post-randomization
  - Biochemically-confirmed 30-day PPA from smoking at 8 weeks and 6 months post-randomization
  - Self-reported and biochemically confirmed 7-day PPA from smoking at 8 weeks and 6 months post-randomization
  - Self-reported and biochemically confirmed 30-day PPA from cigarettes and other non-medicinal nicotine/tobacco products at 8 weeks and 6 months, including e-cigarettes

Mechanisms of change

- Co-primary: Change in behavioral activation from baseline to at 8 weeks post-randomization
- Co-primary: Change in depressive symptoms from baseline to 8 weeks post-randomization

1.3 Inclusion/exclusion criteria

Inclusion criteria:

- age 18 or older
- current smoker, averaging at least 5 cigarettes/day for the last 30 days
- interested in quitting smoking in the next 30 days
- experience downloading and using one or more apps on their smartphone
- either screens negative (PHQ-8 score 0-4) for depression (Phase I n=5, Phase II n=120) or screens positive for mild to moderate current depressive symptoms (PHQ-8 score 5-19; Phase I n=5, Phase II n=120)
- willing and able to complete all study activities and willing to receive study compensation by US mail
- comfortable reading and writing in English
- have a mobile data plan and/or access to WiFi to support the use of the Actify app

- reside in the US
- have a smartphone either an iPhone (running iOS version 11 or higher) or an Android phone (running version 5.0 or higher)

Exclusion criteria:

- currently receiving behavioral treatment for depression (e.g., psychotherapy)
- current use of a depression app
- severe depression (PHQ-8 ≥ 20)
- receiving other treatment for smoking cessation
- previous use of the QuitGuide program
- current or recent (within the past year) enrollment in a Fred Hutch smoking cessation study
- employees/family of investigator or study center
- member of the same household as another participant
- woman who is pregnant or breastfeeding, or planning to become pregnant
- currently incarcerated
- is ineligible per fraud prevention protocol

1.4 Power calculation and sample size

As a pilot treatment development project, this study is not powered to detect statistically significant differences by treatment group. However, we plan to compare the outcomes of the two interventions to obtain a preliminary estimate of effect size. We will use these pilot data to optimize the treatment and study design and to prepare for a rigorous test of the efficacy of Actify in a subsequent R01. We plan to accrue a total of 240 patients in the pilot RCT for a balanced design. The NIDA Stage Model of behavioral treatment development suggests that pilot treatment development trials should include approximately 15-30 participants per arm to test feasibility [1]. However, as demonstrated in a recent simulation focused on sample size for pilot studies [2], binary outcomes (e.g., smoking abstinence) require higher sample sizes for reasonable precision of the effect size estimate than do continuous outcomes. To be conservative, and in consideration of the higher recruitment capacity in remotely conducted studies involving standalone mHealth interventions, we chose to include 60 subjects per arm within each stratum (depressed vs. non-depressed), as a sample size of 60 is a point of diminishing returns in terms of precision of effect size estimates for binary outcomes [2]. Thus, each arm will have 120 participants, of which 60 will meet criteria for mild to moderate depression.

2 Trial management

2.1 List of participating enrolling clinics or data collection centers

Fred Hutchinson Cancer Research Center, Seattle, WA

2.2 Projected timetable for the pilot RCT

Task	Year 1				Year 2				Year 3			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Complete app development												
Diary study												
Pilot RCT preparation[a]												
Recruitment for pilot RCT												
Intervention												
Outcome assessment												
Data entry & quality control												
Data analysis												
Grant & manuscript preparation												

Note: Recruitment rate (~26 randomized/month) is feasible based on prior work and will prevent pilot RCT activities from being delayed.
[a] Finalize survey instruments and recruitment materials; IRB application and approval; build web-based study management system.

2.3 Target population distribution

Broadly, this study targets adult smokers with no more than mild to moderate symptoms of depression. Our previous trials suggest that, without intervention to diversify the sample, the vast majority of participants would be Caucasian and female. To attain adequate representation of racial/ethnic minorities and men, we will cap enrollment of Caucasians and women at 75% of the sample via our online screening and enrollment process for the pilot RCT. We anticipate that these caps will be necessary and that the resulting sample will be 25% male and 25% racial/ethnic minority. Based on demographic data from our recent trial of a technology-delivered cessation intervention, we expect the following percentages of racial minority participants: African American (10%), Native American or Alaska Native (2%), Native Hawaiian or Pacific Islander, Asian (2%), or other/multiple races (5%). In terms of ethnicity, we expect 8% to identify as Hispanic or Latino.

3 Data management and analysis

3.1 Data acquisition and transmission

3.1.1 Consent and enrollment

Participants will be recruited nationally via recruitment strategies used successfully in previous technology-delivered cessation intervention studies conducted by our group. This includes targeted Facebook and Twitter advertisements, Craigslist advertisements in states with a high prevalence of smoking or racial/ethnic minority residence (to achieve the target 25% racial/ethnic minority representation in the sample), other free methods of advertising on the Internet (e.g., Reddit, Twitter), ResearchMatch.org, and earned media generated by press releases from the Fred Hutch media team. If needed, we will use targeted Facebook and Twitter ad campaigns specifically to recruit men and/or people with racial/ethnic minority affiliations (the ad platform's proxy for race/ethnicity).

Our recruitment materials, which have now been used in two nationally-recruiting trials of web- and smartphone-delivered smoking cessation interventions (R01CA166646, R01CA192849), were developed in partnership with the Dana Farber/Harvard University Health Communications Core, which specializes in participant recruitment. They designed our recruitment website, which provides basic information about the study, FAQ, information about the study team and Fred Hutchinson Cancer Research Center (FHCRC), and a portal to the informed consent form, screening, and baseline surveys. They also assisted with the design and optimization of online ads (e.g., Facebook and Twitter ads) for referring potential participants to the recruitment website and worked with the FHCRC communications department on the design of press releases to be distributed over the course of the recruitment period. All of these recruitment procedures and materials will be adapted for this trial. Similar to our other trials, we will program the recruitment website to limit non-minority recruitment to 75% and continue recruitment until the minority recruitment goal of at least 25% is reached.

We will use the identical enrollment method proven successful in our previous, remotely-conducted RCTs. Specifically, for participants who screen eligible on the recruitment website and provide their email address, we will instantly send them an email (and two reminders over a 14-day period) inviting them to complete a secured online survey to provide informed consent and complete the baseline assessment. Those not consenting and completing the online enrollment process within 14 days will be sent an email notifying them that they were not enrolled and provide both the QuitGuide app and the 800-QUIT-NOW phone number to reach their state's quitline.

To address potential fraudulent responses to web-based screening surveys, we will use the same methods used in our previous studies: CAPTCHA verification, ineligibility if the IP address was previously used or suspicious, and telephone contact by research staff if any aspect of automated data collection revealed suspicious activity (e.g., very brief survey completion times or unusual patterns in email addresses). To further deter fraudulent attempts to enter the study, no compensation will be provided for completion of the screening and baseline surveys.

3.1.2 Smartphone app utilization data

Web site analytics data will be used to determine the number of times participants log into their assigned smartphone apps.

3.1.3 Outcome data collection

At baseline, we will collect email, phone, and mailing address information. At each follow-up, we will send reminder letters. The data collection protocol is as follows: Day -14: mail a $2 pre-incentive letter (non-contingent incentives increase retention [3]) two weeks before the first online survey invitation; Day 0: First email invitation with link to online version of survey, with offer of $10 bonus for completing the survey within 24 hours; Day 7: Second email invitation with link to online version of the survey; Days 10 to 18: Eight attempts to complete telephone version of survey (one call per day); Day 19: Send mailed version of the survey. Based on our WebQuit RCT trial experience (n=2,637), we estimate that this protocol will

yield 89% data retention, and that 92% of respondents will complete the web-based version of the survey (68% within 24 hours and 32% after 24 hours). Participants will be compensated $25 for each follow-up survey completed.

3.2 Data entry methods

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

3.3 Data analysis plan

Primary statistical review of the study will be conducted by the study statistician at the end of the study, guided by the Principal Investigator. (See section 7 for detailed analysis plan).

4 Quality assurance plan

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

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

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

4.2 Procedures to guarantee the accuracy and completeness of the data

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

4.2.1 Procedures during data entry

Both participants and site personnel will enter study data into the study database managed by Datatope, Inc. The project manager will monitor completeness of data submitted by participants and staff and accuracy of data entered by staff from phone or mailed surveys. Missing data and data flagged for indication of inaccuracy (e.g., inconsistent dates of birth across surveys) will be reviewed regularly and flagged for follow-up with study participants.

4.2.2 Procedures during data transmission

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

Project staff access the study database via the Study Management (SM) Web site. The SM Web site is only accessible from specific Internet Protocol (IP) addresses used by study staff. All communication with the SM Web site occurs over Secure Sockets Layer (SSL). Both intervention arms will store participant usage data.

4.2.3 Procedures during data analysis

When data collection is complete, the study statistician will lock the database and conduct quality checks. Data quality will be assessed through a number of analytic methods. The study statistician will tabulate categorical variables with frequency counts, and for continuous variables we will examine descriptive statistics (mean, standard deviation, median, interquartile range, minimum, maximum), distributional characteristics (skewness, kurtosis, frequency histograms, normal probability plots), and associations (correlations, scatter plots). Any free text or numeric values will be checked for accuracy, range consistency, and outlying values. We will examine all missing response data to determine whether or not there are predictive characteristics that suggest the values are not missing at random and to determine whether imputation may be needed. Data determined to be invalid based on apparent inaccuracies (e.g, two different dates of birth provided at different survey time points) that cannot be resolved via follow-up with participants will be excluded from the final dataset.

5 Regulatory issues

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

5.1.1 Reporting SAEs

For AEs meeting the criteria for an SAE, regardless of attribution, the study coordinator will inform the Fred Hutch IRB per their reporting guidelines and will complete and submit a NIDA SAE report form within 72 hours of the reported event. Should additional information become available after the initial report, a revised report will be submitted as soon as possible.

5.1.2 Reporting AEs that do not meet the criteria for SAE

All reported AEs will be collected and reported via the study's electronic database. AEs that are expected will be summarized at the time of continuation review.

5.1.3 Reporting UEs that do not meet the criteria for AEs

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

5.2 Reporting mechanisms of IRB actions to NIDA

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

5.3 Report of changes or amendments to the protocol

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

5.4 Trial stopping rules

5.4.1 Complying with trial suspension reporting requirements

Were the IRB or Clinical Trials Office to issue a temporary or permanent suspension of the trial, the trial's Principal Investigators will immediately contact the trial's project officer, Will Aklin, Ph.D., National Institute on Drug Abuse, Division of Clinical Neuroscience & Behavioral Research, Behavioral and Integrative Treatment Branch, 6001 Executive Boulevard, Room 3182 Bethesda, Maryland 20892-9551. Phone: 301-443-4877, Email: aklinwm@mail.nih.gov.

5.5 Disclosure of any conflict of interest

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

6 Trial safety

6.1 Potential risks and benefits for participants

6.1.1 Risks of intervention and mitigation plan

Therapeutic risks include: (1) physical and psychological consequences of smoking abstinence, including nicotine withdrawal, and (2) the possibility that the intervention may not help the participant quit smoking. Participants will be informed of the discomfort associated with nicotine withdrawal, including common withdrawal symptoms, and that nicotine withdrawal may temporarily exacerbate some psychiatric symptoms (e.g., depressive symptoms, which are part of nicotine withdrawal) even though mental health has been extensively demonstrated to either remain unchanged or to improve by end of treatment and follow-up [4].

Physical and psychological consequences of smoking abstinence, including nicotine withdrawal. Participants will be informed about potential nicotine withdrawal symptoms. A rating scale for depression (PHQ-8) will be administered at screening to assess eligibility and follow-up to assess intervention effects. Study staff completing telephone assessments and processing questionnaires returned by mail will be trained to alert the study coordinator immediately if any suicidal ideation is spontaneously reported by participants. All non-eligible individuals who complete the screening survey will receive an email containing other resources for depression assistance (including crisis line numbers) and cessation assistance. Enrolled participants will receive crisis line information as part of their weekly emails with reminders to use their assigned program. Additionally, if a participant reports suicidal ideation at any time point, the participant will be evaluated by the PI using the Suicidal Ideation Action Tree that we have used in previous studies of remotely delivered cessation interventions with national recruitment. Participants will be told, as part of the informed consent process, that study staff will not be monitoring self-report data in real time and that, should they experience suicidal thoughts during the study, they should seek assistance from a healthcare provider or crisis line.

Possibility that the study interventions may not help the participant to quit smoking. Participants will receive information about the availability of alternative treatments to facilitate smoking cessation, including pharmacotherapies such as nicotine replacement, bupropion, or varenicline; and counseling/support through telephone quitlines (1-800-QUIT-NOW) or web sites like Smokefree.gov.

6.1.2 Risks related to research procedures and risk mitigation plan

Participants will be informed of the following research-related risks: (1) the possibility that answering some questions may be emotionally upsetting, and (2) the possibility of breach of confidentiality. It is possible that some of the questions asked of participants may cause some emotional discomfort. For example, assessment of symptoms of depression may result in feelings of shame due to the stigma associated with mental health conditions. There is also a small risk of breach of confidentiality if participant data, either in electronic or hard copy form, were to be accessed by an unauthorized person.

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

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

Emotional upset. Prior to administration of study assessments, participants will be reminded that they have the choice to not answer any question that makes them uncomfortable. Participants who report feeling upset as a result of responding to study assessment items will be given the option to speak with the PI. Dr. Heffner is a clinical psychologist who has experience working with smokers with mood disorders in a research context.

Breach of confidentiality. Numerous safeguards will keep electronic and hard copy data secure. Each subject will be assigned a code number so that, should any non-study personnel gain access to the data, they will not know to whom they belong. All hard copy data will be kept in a locked file cabinet accessible only by authorized research staff. A secure password is required to access computers, and computer networks are on secured servers that meet or exceed federal confidentiality standards. Once randomized, each participant will have access to the assigned apps protected with a login. To address the possibility that individuals other than the participant might gain access to the participant's phone, we will suggest that each participant password protect their phone to prevent unauthorized access.

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

6.1.3 Benefits of intervention

It is possible that trial participants could quit smoking as a result of their participation. If so, the benefit to their short and long-term health would be significant.

6.1.4 Benefits of research procedures

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

6.1.5 Other information

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

6.2 Collection and reporting of AEs and SAEs

6.2.1 Monitoring

Throughout the study, the project manager and outcome assessors will monitor participants' progress and responses to surveys for adverse events and protocol compliance. The project manager will complete quarterly reports on participant progress and status, any adverse events, and any protocol deviations. Protocol adherence will be monitored by the Principal Investigator.

6.2.2 Reporting

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

6.2.3 Definitions

In general, unexpected events (UEs) include any event, adverse or otherwise, that was not described as part of the study risks. For this trial, an example of an unexpected event that is not adverse is a participant who has become very unhappy with trial procedures. Adverse events (AEs) are any untoward occurrence with a trial participant whether or not it can be considered to be related to their smoking cessation intervention/NRT therapy. Examples of adverse events in this trial could include development or worsening of depression symptoms. Serious adverse events (SAEs) include any AE that results in death, a real risk of dying, inpatient hospitalization, persistent or significant disability/incapacity, or AEs that require intervention to prevent permanent impairment or damage. In this trial, an example of a serious adverse event would be a suicide attempt.

6.3 Management of SAEs or other study risks

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

6.3.1 Attribution

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

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

7 Trial efficacy

7.1 Plans for interim analysis of efficacy data

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

7.2 Plans for final analysis

Data analyses will be conducted using the intent-to-treat approach, except where otherwise indicated. Analyses will consist of a comparison between two arms on three outcomes: acceptability, efficacy for smoking cessation, and effect on BAT-D theory-based mechanisms of change. The primary acceptability outcomes are number of app openings and overall satisfaction ratings. For smoking cessation, the primary endpoint is self-reported 30-day point prevalence abstinence (PPA) at 8 weeks post-randomization, which is comparable to the primary endpoints of the two extant trials of smartphone apps for smoking cessation [10, 34]. The secondary endpoints are self-reported and biochemically confirmed 7- and 30-day PPA at 6 months, 7-day PPA at 8 weeks, and biochemically-confirmed abstinence from any nicotine/tobacco product (other than FDA-approved cessation medications) between baseline and 8-week and 6-month follow-ups. For mechanism of change, the primary endpoint is the change in BADS scores between baseline and the 8-week follow-up and the secondary endpoint is the change in depressive symptoms over the same time period.

Linear regression will be used to evaluate treatment effects between the two arms for continuous endpoints (e.g, treatment satisfaction ratings). This model will adjust for any demographic or other variables that differ between study arms at baseline and are related to outcome as well as the stratification factors (depression severity, sex assigned at birth, and heaviness of smoking). To compare binary endpoints between two arms (e.g. smoking abstinence), a logistic regression model will be conducted with control for potential confounding variables and the stratification variable. Sensitivity analyses excluding participants using concomitant treatment for smoking cessation and/or depression will also be conducted.

Additional exploratory analyses will be conducted. To explore differential treatment effects by pre-quit depression, we will preliminarily test the interaction of treatment group assignment and pre-quit depression and present descriptive data on quit rates for the four subgroups (Actify, depressed; Actify non-depressed; QuitGuide, depressed; QuitGuide non-depressed). To evaluate the theory underlying BAT-D for smoking cessation, we will examine change in BADS scores between baseline and 8-week follow-up as a predictor of 30-day PPA at 6-month follow-up using a logistic regression model. To generate empirical evidence to set usage benchmarks for the Actify app, we will evaluate the relationship between app “dosage” and cessation outcomes by regressing 30-day PPA at 8 weeks on objective measures of app utilization (e.g., number of app logins, total duration of use) using logistic regression. Similar to our feature analysis of SmartQuit that guided future app development [69], we will also regress 30-day PPA at 8 weeks on utilization of specific app components (e.g., scheduling, mood tracking) to determine “active ingredients.” To evaluate the relationship between user characteristics and treatment utilization and cessation outcomes, we will use logistic (for cessation outcomes) or negative binomial (for login count data) models and baseline data as predictors. To examine sex as a biological variable, we will preliminarily test for sex differences in treatment response by descriptively examining results separately by sex.

Missing data: Consistent with prevailing standards for smoking cessation trials [88], participants with missing smoking data will be considered non-abstinent in the primary analysis. As a sensitivity analysis, we will also report abstinence rates from complete case analyses and multiple imputation. Treatment acceptability and mechanism of change (i.e., behavioral activation [BADS] and depression [PHQ-8] scores) will be analyzed using complete case analysis.

8 DSM plan administration

8.1 Responsibility for data and safety monitoring

Dr. Heffner will be responsible for monitoring the trial.

8.2 Frequency of DSM reviews

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

8.3 Content of DSM report

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

9 DSM Board Plan

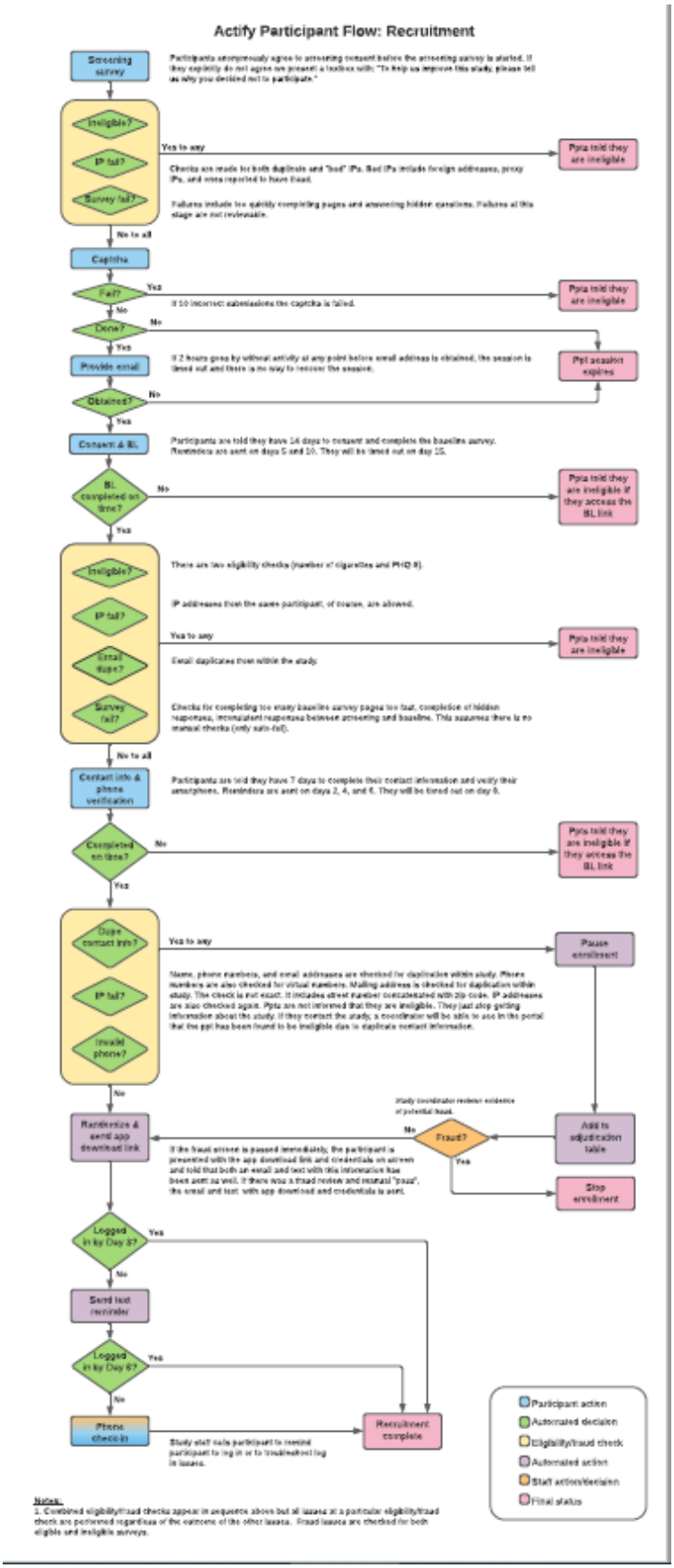
A DSMB is not needed for this low-risk, single-site trial of two behavioral interventions for smoking cessation.

References

1. Rounsaville BJ, Carroll KM, Onken LS. A stage model of behavioral therapies research: Getting started and moving on from stage I. *Clinical Psychology: Science and Practice.* 2001;8(2):133-142.
2. Teare D, Dimairo M, Hayman A, Shephard N, Whitehead A, Walters S. Sample size requirements for pilot randomised controlled trials with binary outcomes: a simulation study. *Trials.* 2013;14(S1):O21.
3. Dillman DA. *Mail and Internet Surveys: The Tailored Design Method.* 2nd ed. Hoboken, NH: John Wiley & Sons, Inc.; 2007.
4. Taylor G, McNeill A, Girling A, Farley A, Lindson-Hawley N, Aveyard P et al. Change in mental health after smoking cessation: systematic review and meta-analysis BMJ 2014; 348 :g1151 doi:10.1136/bmj.g1151

Appendix B: Fraud Prevention Protocol

ANTI-FRAUD PROCEDURES FOR STUDY ENTRY


Actify Participant Flow: Recruitment
Screening survey
Participants anonymously agree to screening consent before the screening survey is started. If they explicitly do not agree we present a textbox with: "To help us improve this study, please tell us why you decided not to participate."
Ineligible?
IP fail?
Survey fail?
Yes to any
Ppts told they are ineligible
Checks are made for both duplicate and "bad" IPs. Bad IPs include foreign addresses, proxy IPs, and ones reported to have fraud.
Failures include too quickly completing pages and answering hidden questions. Failures at this stage are not reviewable.
No to all
Captcha
Fail?
Yes
Ppts told they are ineligible
If 10 incorrect submissions the captcha is failed.
No
Done?
No
Yes
Provide email
If 2 hours goes by without activity at any point before email address is obtained, the session is timed out and there is no way to recover the session.
Ppt session expires
Obtained?
No
Yes
Consent & BL
Participants are told they have 14 days to consent and complete the baseline survey. Reminders are sent on days 5 and 10. They will be timed out on day 15.
BL completed on time?
No
Ppts told they are ineligible if they access the BL link
Yes
Ineligible?
IP fail?
Email dupe?
Survey fail?
There are two eligibility checks (number of cigarettes and PHQ-9).
IP addresses from the same participant, of course, are allowed.
Yes to any
Ppts told they are ineligible
Email duplicates from within the study.
Checks for completing too many baseline survey pages too fast, completion of hidden responses, inconsistent responses between screening and baseline. This assumes there is no manual checks (only auto-fail).
No to all
Contact info & phone verification
Participants are told they have 7 days to complete their contact information and verify their smartphone. Reminders are sent on days 2, 4, and 6. They will be timed out on day 8.
Completed on time?
No
Ppts told they are ineligible if they access the BL link
Yes
Dupe contact info?
IP fail?
Invalid phone?
Yes to any
Pause enrollment
Name, phone numbers, and email addresses are checked for duplication within study. Phone numbers are also checked for virtual numbers. Mailing address is checked for duplication within study. The check is not exact. It includes street number concatenated with zip code. IP addresses are also checked again. Ppts are not informed that they are ineligible. They just stop getting information about the study. If they contact the study, a coordinator will be able to see in the portal that the ppt has been found to be ineligible due to duplicate contact information.
No
Study coordinator reviews evidence of potential fraud.
Randomize & send app download link
No
Fraud?
Yes
Add to adjudication table
Stop enrollment
If the fraud screen is passed immediately, the participant is presented with the app download link and credentials on screen and told that both an email and text with this information has been sent as well. If there was a triad review and marked "pass", the email and text with app download and credentials is sent.
Logged in by Day 8?
Yes
No
Send text reminder
Logged in by Day 8?
Yes
No
Phone check-in
Study staff calls participant to remind participant to log in or to troubleshoot log in issues.
Recruitment complete
Participant action
Automated decision
Eligibility/fraud check
Automated action
Staff action/decision
Final status
Notes:
1. Combined eligibility/fraud checks appear in sequence above but all issues at a particular eligibility/fraud check are performed regardless of the outcome of the other issues. Fraud issues are checked for both eligible and ineligible surveys.

ANTI-FRAUD PROCEDURES FOR POST-ENROLLMENT DATA CLEANING

Procedure for project manager to validate eligibility post-enrollment:

1. Datatope will create post-enrollment flags on data validity, including (a) inconsistency between outcome surveys and screening/baseline surveys in date of birth, (b) multiple IP addresses/non-US IP addresses detected post-enrollment
2. Post-baseline manual checks for address and IP address.
3. Depending on level of evidence for fraud a participant could beflagged and contacted by telephone. Let them know that, before they can be compensated for their participation, we need to verify that some the information that they provided is correct.
4. Ask for full name and address. If different than what they provided previously, ask if they may have provided any other name or address and the reason for the change.
5. Ask for their date of birth, current age, gender, and race and ethnicity. If gender or race/ethnicity are different than what they provided previously, ask if they may have provided any different response on a survey.
6. After completing the call, check information provided against survey data. If there is clear evidence of deception (e.g, different dates of birth provided, non-matching age and DOB, different first and last name provided across surveys, with no explanation), note in their study record that they should be excluded from outcome analyses. Do not mail compensation for survey completion if they can't be reached for verification.
7. After final dataset is received from Datatope, review all records for incoherent responses to open-ended questions on baseline & follow-up surveys. Flag these records for manual review to check for data quality (e.g, evidence of straightlining, unusual responses).
8. In cases where deception is suspected but cannot be confirmed, add participant ID to database of participants whose inclusion will be adjudicated by the study team prior to analyzing outcome data. Include note providing all reasons why deception is suspected, along with any evidence that might indicate that the participant's data are valid.