Study Protocol

Title: Randomized Trial of an Innovative Smartphone Intervention for Smoking Cessation
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PROJECT SUMMARY/ABSTRACT (DESCRIPTION)

There is tremendous need for smoking cessation intervention technologies with strong potential population-level impact at the lowest possible cost. That potential can be found in the newest technological innovation in quit smoking interventions: smartphone-based smoking cessation software applications ("apps"). There are over 400 smoking cessation apps, which were downloaded in the United States 3.2 million times during the two-year period 2012 to 2013. No trials of any app's effectiveness for general adult cessation have been published and no NIH-funded cessation intervention trials are in progress—despite the fact this is a high priority NIH funding topic. The enormous usage of smoking cessation apps contrasted with their unknown effectiveness creates a serious scientific gap that could stifle their population-level impact.

Research on US Clinical Practice Guidelines (USCPG) apps begins to address that research gap. But only following the USCPG has had limitations in other modalities of delivery. An approach, called Acceptance & Commitment Therapy (ACT), addresses these limitations with both innovative intervention content and highly promising results from six published trials. ACT's innovation is its dual focus on increasing willingness to experience physical cravings, emotions, and thoughts that cue smoking while making values-guided committed behavior changes. We recently developed the first ACT app for smoking cessation, called "SmartQuit," and tested it in a pilot randomized controlled trial (N = 196), comparing it with an app that follows USCPG (National Cancer Institute's "QuitGuide"). Results showed that SmartQuit had: (1) higher participant engagement and satisfaction than QuitGuide, (3) higher levels of acceptance of cravings than QuitGuide, and (3) descriptively higher quit rates (albeit non-significant) than QuitGuide at the two-month follow-up.

Building on these promising results, we propose a fully-powered, randomized controlled trial (n = 1250 per arm) that compares a refined version of SmartQuit, called iCanQuit to QuitGuide, which follows the USCPG, to definitively determine whether an ACT app is more efficacious than a USCPG app.

As millions of people are choosing smartphone apps to help them quit smoking, this innovative study shows exciting promise for improving the success rates of quit smoking apps and thereby lowering healthcare costs and reducing premature tobacco-related deaths.

SIGNIFICANCE & SPECIFIC AIMS

States' funding for population-level smoking cessation programs remains far below their CDC-recommended levels. Consequently, there is tremendous need for intervention technologies with strong potential population-level impact at the lowest possible cost [1]. That potential can be found in the newest technological innovation in quit smoking interventions: smartphone-based smoking cessation software applications (aka, "apps") [2-4]. There are over 400 smoking cessation apps [2] which were downloaded in the United States 3.2 million times during 2012 to 2013 [5]. No trials of any app's efficacy for general adult cessation have been published and no NIH-funded randomized trials on apps for cessation are in progress —despite the fact this is a high priority NIH funding topic [7, 8]. The enormous usage of smoking cessation apps contrasted with their unknown efficacy creates a serious scientific gap that could stifle their population-level impact.

Randomized trials on apps that follow the US Clinical Practice Guidelines (USCPG) begin to address that research gap. But only following the USCPG has had limitations in other modalities of delivery [9-15]. An approach, called Acceptance & Commitment Therapy (ACT), addresses these limitations with both innovative intervention content and highly promising results from six published trials [16-21]. ACT's innovation is its dual focus on increasing willingness to experience physical cravings, emotions, and thoughts that cue smoking while making values-guided committed behavior changes [22]. We recently developed the first ACT app for smoking cessation, called "SmartQuit," and tested it in a pilot randomized controlled trial (N = 196), comparing it with an app that follows USCPG (National Cancer Institute's "QuitGuide"). The trial design was proven feasible, with successful national recruitment (N = 196 recruited in 10 weeks) and strong outcome survey completion rate (84%). Results showed that SmartQuit had: (1) higher participant engagement and satisfaction than QuitGuide, (2) higher levels of acceptance of cravings than QuitGuide, and (3) descriptively higher quit rates (albeit non-significant) than QuitGuide at the two-month follow-up [21]. Building on these promising results, we propose a fully-powered, randomized controlled trial that compares a refined version of SmartQuit, called iCanQuit to QuitGuide, which follows the USCPG, to definitively determine whether an ACT app is more efficacious than a USCPG app. Thus we propose the following Specific Aims:

Aim 1. Determine whether iCanQuit produces significantly higher abstinence than QuitGuide. **Primary endpoint:** 30-day point prevalence abstinence at 12 months post-randomization. Importance of this aim: will determine the quit rates with precision and whether iCanQuit provides more robust quit rates than QuitGuide.

Aim 2. Determine whether the iCanQuit (but not the QuitGuide) smoking cessation outcomes are mediated by these psychological processes central to the theoretical model underlying ACT: commitment to quitting and acceptance of internal (a) sensations, (b) emotions, and (c) thoughts that cue smoking. Importance of this aim: will identify ACT processes needing further targeting, and determine whether iCanQuit, but not QuitGuide, operates through ACT-specific theoretical processes.

Aim 3. Determine whether iCanQuit is significantly more cost-effective than QuitGuide, as measured by cost per additional quitter, incremental cost-effectiveness ratio (ICER), and incremental cost per quality-adjusted life year (QALY). Importance of

this aim: will provide payers (e.g., insurance companies) and policymakers results needed to decide whether to adopt iCanQuit.

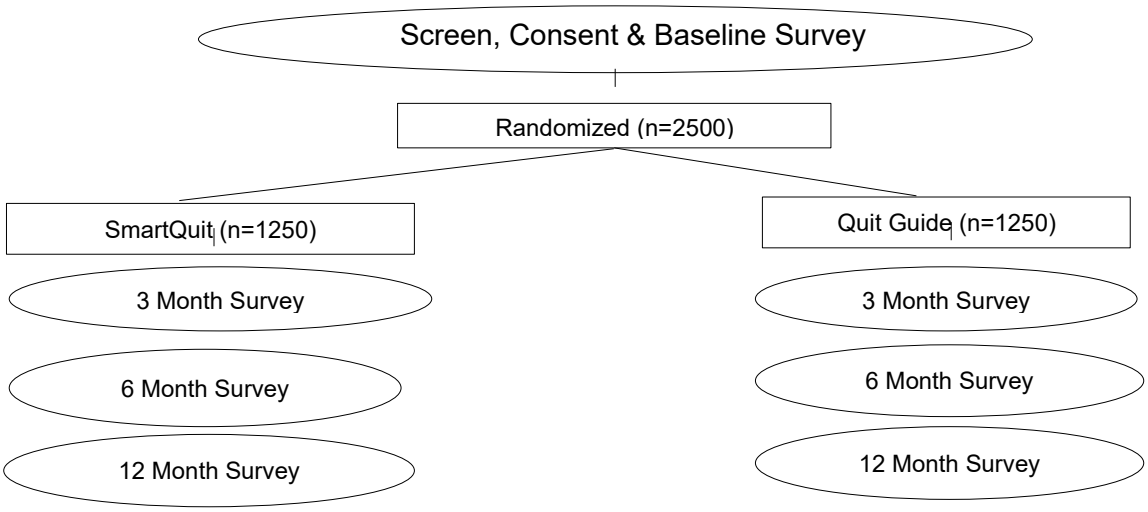
Exploratory Aim: Explore whether iCanQuit, as compared to QuitGuide, has higher quit rates for those with these baseline factors: (a) low acceptance of sensations, emotions, and thoughts that cue smoking, (b) heavy smoking (≥ 20 cigarettes/day), (c) current mental health symptoms, and (d) being racial/ethnic minority. Importance of this aim: will potentially identify key subgroups that benefit most from iCanQuit, and thereby aid in reducing tobacco-related health disparities.

Innovations. (1) ACT's innovative features augment the US Clinical Practice Guidelines; (2) ACT follows an innovative theory: Relational Frame Theory; (3) ACT on the smartphone is novel; (4) First randomized trial of a smartphone app for adult smoking cessation; (5) The first time that the following have been tested for **any** behavior outcome: (a) ACT delivered via smartphone, (b) mediation of the effects of a smartphone app, (c) cost-effectiveness of a smartphone app, and (d) exploration of subgroups who benefit most from a smartphone app. While there are thousands of apps and hundreds for smoking [2], testing an app's efficacy is scientifically innovative. That's a critical gap this application fills.

Approach

Randomized trial experimental design. We will conduct a fully-powered two-arm randomized controlled trial that compares iCanQuit to QuitGuide, which follows the USCPG. To balance baseline variables between the two conditions, we will stratify randomization by daily smoking frequency (≤20 vs. ≥ 21), education (≤ high school vs. ≥ some college), race/ethnicity (minority race/ethnicity vs. non-Hispanic White) and depression screen (CES-D score ≤ 15 vs. ≥ 16). Moderators will be measured at baseline. Mediators will be measured at baseline and three months post randomization. Consistent with cessation trial designs [60], cessation and cost-effectiveness outcomes will be measured at 3, 6, and 12 months post randomization.

Figure 1. Experimental Design



Eligibility: age ≥18 years; smoked ≥ 5 cigarettes a day for the past year; want to quit smoking within the next 30 days; if concurrently using any other tobacco products (e.g., e-cigarettes), wants to quit using them within the next 30 days; interested in learning skills to quit smoking; willing to be randomly assigned to either condition; resides in the United States; has daily access to their own iPhone or Android smartphone; knows how to download smartphone applications; willing and able to read in English; never used QuitGuide and not currently using other cessation treatment; never participated in our prior studies; no household members already enrolled; willing to complete outcome surveys, and provided contact information for themselves and two relatives. Participants not eligible for or interested in enrolling will be given the smokefree.gov website and the 800-QUIT-NOW phone number to reach their state's quitline.

Recruitment. We will use a recruitment process modeled after our the smartphone-delivered ACT pilot [21] as well as our web-delivered ACT pilot trial [20]). The study team will design our participant recruitment website which will provide basic information about the study, a FAQ, a brief video describing the study, information about the study team and Fred Hutch, and a portal to the informed consent form, screening, and baseline surveys. The team will also work with the Fred Hutch communications department to design of a series of press releases and Facebook advertisements to be distributed over the course of the recruitment period.

We have extensive experience in designing recruitment materials for increasing racial/ethnic minority enrollment. Specifically, we will further adapt our approach to recruit at least 30% minority and 30% men: (1) the study team will design and distribute several culturally-relevant press releases; (2) develop effective strategies for using the media and the Internet to target minority smokers, including reaching out to minority-specific media newswire services and including on our ads and enrollment website photos from target minority groups; (3), Partner with Fred Hutch's Diversity Council staff design and disseminate minority-specific recruitment materials that will be disseminated to minority media (e.g., PR Newswire Multicultural Markets Newsline); (4) enrollment will be limited to no more than 70% White participants and no more than 70% women, to ensure racial/ethnic minority and male representation.

Based on our ACT smartphone pilot RCT experience of 78 randomized per month, we estimate recruitment will take 17 months.

Enrollment. We will use the identical enrollment method proven successful in our ACT smartphone pilot RCT. 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 smokefree.gov website and the 800-QUIT-NOW phone number to reach their state's quitline. Those randomized will be emailed a secured link to download their app (either iCanQuit or QuitGuide). All participants will be emailed identical once weekly reminders to use their assigned intervention.

Research Plan and Methods

ACT Intervention. We will use the iCanQuit intervention, which is based on ACT.

Table 3 contrasts ACT intervention strategies with the USCPG intervention strategies—which are based on traditional cognitive behavioral therapy [62].

Table 3. Differences between ACT and US Clinical Practice Guidelines.

Conceptual Level	ACT	US Clinical Practice Guidelines
Philosophical Basis	**Functional Contextualism:** One's current and historical context influence all of the one's external (e.g., walking) and internal (e.g., urges, thinking) behavior. The standard for determining whether a behavior needs to be changed is whether it is functional: pragmatic, useful, or helps one obtain a goal [70].	**Critical Rationalism:** Knowledge has an objective truth. Knowledge can only be gained by attempting to validate beliefs that are derived from theories. (While not based on a specific philosophy, Critical Rationalism is arguably consistent with USCPG skills training) [71].
Theoretical Basis	**Relational Frame Theory:** Overt environmental , cognitive, physiological, & emotional stimuli can be related to one another—and thereby take on each other's qualities & functions—in every imaginable way: (Example: seeing an actual cigarette←→ thought "urge" ←→ physical urge←→ smoking a cigarette). Trying to control these processes just adds new relations and interferes with behavior change (Example: distraction from an urge ←→ more urges). In contrast, increasing willingness to experience (and not change) these processes increases value-guided behavior change [63].	**Information Processing Theories:** The mind processes information through the application of mental rules/strategies that guide behavior. Applying Illogical rules/strategies leads to dysfunctional behavior. (Example: Applying the illogical belief that "smoking controls stress" will lead one to smoke.) In contrast, applying logical rules/strategies leads to more effective information processing and functional behavior [72].
Clinical Level	**ACT**	**US Clinical Practice Guidelines**
General approach to intervening on urges, emotions, and thoughts that cue smoking	**Acceptance**: Openness to experience urges, emotions, and thoughts as they are and without any intent that they change (e.g., **no** desire that urge reduces). Example: Asking: "How willing are you to have, and not try to change, your urges to smoke?" [16, 73]	**Avoidance:** Actively trying not to experience urges, emotions, & thoughts with the intent that that they change (e.g., desire for urge to reduce). Example: Asking: "How can you avoid or control your urges to smoke?" ([62] pg. 74)
Specific approach to intervening on urges and emotions that cue smoking	**Being Present**: Being fully aware of the present moment with openness, interest, and receptiveness. Observation and non-judgmental description of experiences in the present moment. Example: while holding an unlit cigarette, take one minute to describe out loud its color, length, texture, smell. Next, describe in the present tense what urges and emotions come up [16, 73].	**Urge/Emotion Coping Skills**: A broad set of strategies designed to manage or control urges and emotions that cue smoking. Examples: avoiding places where you often smoke; engaging in a distracting activity (e.g., crossword puzzle); keeping hands active (e.g., gripping a stress ball); sucking on a hard candy ([62] pg. 81).
Specific approach to intervening on	**Cognitive Defusion**: Stepping back from the process of thinking.	**Cognitive Restructuring:** A method of changing the content of one's

thoughts that cue smoking	Recognizing thoughts, self-judgments, and memories as just words and pictures. Allowing them to come and go without trying to control or avoid them. Example: For a thought that often cues smoking (e.g., "I want to smoke."), reduce it to one key word (e.g. "smoke") and then say the word out loud repeatedly for 30 seconds [16, 73].	unrealistic/irrational beliefs and/or replacing them with realistic/rational beliefs. Example: Change the thought "Smoking is how I cope with things" with this response: "Smoking does nothing to help a smoker cope, other than relieving withdrawal" ([62] pg. 41).
Specific approach to increase motivation to quit smoking	**Values:** Chosen life directions that guide actions. Values require no reasoning. Valuing is a process, not a life goal achieved or an outcome. Examples: "What really really matters to you?; How could quitting smoking be driven by the things that matter to you?" [16, 73].	**Reasons to Change:** The specific expectations one would have for when a behavior has changed. Examining the advantages and disadvantages of a behavior change. Examples: Listing expected benefits of quitting smoking; Listing all of the reasons for quitting and for not quitting smoking ([62] pg. 49-58).

Comparison app. To address the question of whether iCanQuit is more efficacious than an app following USCPG, we chose QuitGuide as the ideal comparison intervention for four key reasons. First, it is one of the few apps (of the 400 available) that follow the USCPG [2]. Second, its content and structure are directly based on Smokefree.gov, the most accessed cessation website in the world. Third, QuitGuide's content is non-proprietary and free to the public, thereby providing maximal transparency, accessibility, and replicability. Finally, because of our pilot RCT, QuitGuide is now the only app following USCPG with adult quit rate estimates that are based on a clinical trial [21].

We also considered pharmacotherapy comparisons. But many participants would be ineligible for use (e.g., medical condition) and, if disseminated, many people would face access barriers (e.g., medication affordability). Some medications (e.g., varenicline) require a physician visit and prescription. For Nicotine Replacement Therapy (NRT), adequately addressing side effects for a nationally-recruited sample who will have had no prior personal contact with the study would be problematic [74, 75].

Table 4. Participant surveys and time points when they will be administered. (All participants)

Measure	Screening	Baseline	3-month	6-month	12-month	Purpose
Eligibility & Enrollment (24 items)	x					Eligibility, Enrollment, & Stratification
Demographics (19 items)		x				Stratification & Exploratory
Nicotine Dependence (6 items)		x	x	x	x	Stratification & Aim 1
Smoking/Tobacco History (4 items)		x				Exploratory Aim
Tobacco Use (6 items)		x	x	x	x	Aim 1

Acceptance of cues (27 items)	x	x			Aim 2 & Exploratory
Quality of Life (8 items)	x	x			Exploratory Aim
Quality of Life (6 items)			x	x	Exploratory Aim
Panic Symptoms (5 items)	x	x	x	x	Exploratory Aim
PTSD Symptoms (6 items)	x	x	x	x	Exploratory Aim
Generalized Anxiety Symptoms (7 items)	x	x	x	x	Exploratory Aim
Social Anxiety Symptoms (17 items)	x	x	x	x	Exploratory Aim
Depression Symptoms (20 items)	x	x	x	x	Exploratory Aim
Distress Tolerance (6 items)	x	x			Exploratory Aim
Values (10 items)	x	x			Aim 2
Growth Mindset (6 items)	x	x			Exploratory Aim
Quitting Self-Efficacy (1 item)	x				Stratification
Alcohol Use (4 items)	x	x	x	x	Exploratory Aim
Mobile Device Use (8 items)	X				Exploratory Aim
Receptivity/utilization (14 items)		x			Acceptance/Adherence
Receptivity/utilization (2 items)			x	x	Acceptance/Adherence
Cessation & Extra Aids (5 items)		x	x	x	Aim 1 and Exploratory
Willingness to discuss (1 item)				x	Follow-up

Primary assessments. **Aim 1: Tobacco outcomes**. Primary endpoint: 30-day point prevalence abstinence at 12-months post randomization, as readily comparable to other smoking cessation trials [60] and our ongoing web-based ACT intervention trial (R01CA166646). A 12-month main endpoint accounts for the relapse rates observed between 2 and 12 month follow-up [60, 76, 77]. Moreover, a 12-month endpoint directly addresses the overall need for technology-delivered cessation trials to show longer term benefit (e.g., 12 months) [9-15]. Secondary endpoints: prolonged abstinence (i.e., no smoking since three months after randomization, as consistent with ACT's approach of allowing participants a grace period of several lapses as opportunities to practice ACT skills) and 7-day point prevalence [78]. All endpoints will also be examined at 3 and 6 months post randomization. The secondary definition of cessation will include abstinence from cigarettes **and** these non-cigarette nicotine/tobacco products: e-cigarettes, snus, chewing and smokeless tobacco, hookahs, cigars, cigarillos, tobacco

pipes, and kreteks (clove/tobacco cigarettes). Use of nicotine and tobacco products will be measured at baseline and all follow-up endpoints. We considered continuous monitoring of tobacco but elected not to because (1) it lowers response rates—a confound [30], and (2) effect sizes are similar to point prevalence [31].

We also considered biochemical validation but self-reported smoking is a standard method for assessing technology-based interventions. Evidence suggests false reporting is minimal for low-intensity interventions with no face-to-face contact [79, 80]. Due to cost and low demand characteristics for false reporting, the SRNT Subcommittee on Biochemical Verification recommends biochemical confirmation has low response rates [69] and is unnecessary in population-based studies with limited face-to-face contact and studies where the optimal data collection methods are through the mail or telephone [81].

Aim 2: ACT Mediators. Acceptance of internal cues to smoke: Measured using the Avoidance and Inflexibility Scale (AIS; α = .93; [16, 20], which assesses one's willingness to experience sensations (9 items), emotions (9 items), and thoughts (9 items) that cue smoking. A sample item for the sensations scale is: "To what degree did you allow yourself to have urges to smoke?" Commitment to quitting. Commitment to quitting despite internal (e.g., cravings, anxiety) and external (e.g., smoking in the social environment) cues to smoke will be measured using the Commitment to Quitting Scale (CQS; α = .93; [59]). Sample item: "No matter how many people around me smoke, I won't let myself smoke once I quit." Regarding assessment timing, three months post randomization is when we expect acceptance and commitment to increase the most, as consistent with past ACT smoking cessation studies [16, 17, 20, 82], and would allow testing of our hypothesized model of increases in acceptance and commitment at three months mediating the impact of the intervention on smoking cessation by twelve months.

Aim 3: Costs of delivery, for cost-effectiveness analyses. Costs associated with each app's delivery include the cost to: (1) host the servers and databases, (2) conduct software updates to accommodate ongoing changes in operating systems, (3) have programming staff to answer technical questions, and (4) cost of facilities and equipment needed to maintain each (e.g., office space for personnel, computers). NCI, the host of QuitGuide, has agreed to provide these costs for QuitGuide [32]. Research-related costs will not be included.

Exploratory aim: Moderators of treatment outcome. Hypothesized moderators of treatment effectiveness will be heaviness of smoking (smoking at least 20 cigarettes per day vs. less than 20 at baseline), acceptance of cravings to smoke (AIS scores below vs. above the median), mental health symptoms (positive vs. negative screen for depression, anxiety, or heavy alcohol use), and racial/ethnic minority status (Caucasian vs. minority). Mental health symptoms will be assessed as follows: (1) depression screening via the 10-item Center for Epidemiologic Studies Depression Scale (CES-D; cutoff ≥ 10) [83, 84]; (2) anxiety screening via the Generalized Anxiety Disorder Scale; (GAD-7; cutoff ≥ 10, [85]); (3) alcohol screening via the Alcohol Use Disorders Identification Test—Consumption items (AUDIT-C; cutoffs ≥4 drinks/day for women, ≥5 drinks/day for men or 7 drinks/week for women, 14 drinks/week for men [86, 87]).

Treatment acceptability/adherence: Treatment satisfaction and utilization. Measured with the 8-item Treatment Satisfaction/Utilization Scale used in our pilot. Sample satisfaction item: "Overall, how satisfied are you with your assigned app?" Sample utilization items: "Overall, about how many times per week did you use the strategies taught in your assigned app?" and "How useful was your assigned app's quit plan?"

Cessation pharmacotherapy usage: Measures number of days per week, number of total weeks, and start/end dates, that participants on their own elected to use (1) nicotine replacement therapy (i.e., patch, gum, lozenge, inhaler, nasal spray), (2)

varenicline, (3) bupropion, and (4) other (fill in).

Follow-up survey methods. For trial integrity, the follow-up data will be collected by our survey research unit that will be (1) blind to random assignment and (2) collecting cessation outcome data outside of the intervention apps. At each follow-up, we will send reminder letters. Each follow-up survey and Internet tracking will collect address information. The **online-telephone-mailed sequence** data collection protocol is as follows: 1) Three email attempts to complete the online version of the survey; 2) Eight attempts to complete a **telephone** version of survey (one call per day from a trained surveyor); 3) Send a paper version of the survey via US **mail.** Based on our ACT smartphone pilot RCT experience, we conservatively estimate this protocol will yield 84% retention. And to further boost retention, we will make the following protocol enhancements at all follow-up points: (1) mail a $2 pre-incentive letter (noncontingent incentives increase retention [88]) 2 weeks before the first online survey invitation (i.e., Day -14); (2) provide a $10 incentive for completing the online survey within 24 hours [89]; and (3) send a postcard with two questions about smoking status.

Table 5. Schedule of key activities.

Year of study	1				2				3				4				5				06 NCE			
Quarter	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
1. Refinement & Usability	xxx	xxx	xxx	xxx	xxx	xxx																		
2. Set up[a]	xxx	xxx			xxx	xxx	xxx																	
3. Recruitment							xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xx									
4. Interventions							xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx						
5. Outcome Surveys[b]								xx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx				
6. Data Entry & QC[c]								xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xx			
7. Analyses								xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
8. Dissemination																						xxx	xxx	xxx

[a] Set up study procedures, survey instruments, recruitment materials and advertising; IRB application.[b]3,6,&12 month outcome survey administration protocol (29 days long) timed to participant randomization date.[c]Telephone & mailed versions of each survey are data entered by a trained surveyor. A 20% random sample of entries are checked against audio-recorded telephone surveys and mailed hard copies. Errors over 1% trigger 100% batch re-entry and surveyor performance remediation.

Analyses. Aim 1. Our primary outcome hypothesis is that iCanQuit will have significantly higher 30-day point prevalence abstinence at 12 months post-randomization than QuitGuide. **Analyses:** For each comparison of the arms on the primary and all secondary endpoints, we will use a logistic regression model with complete case smoking cessation outcome [9-14]. The model will adjust for all stratification factors as well as baseline factors that might be imbalanced after randomization. In addition, we will conduct these analyses: (1) multiple imputation of missing outcomes [90-92], (2) missing equals smoking outcomes [9-14], (3) using a secondary cessation outcome of no use of cigarettes **and** other nicotine or tobacco products except FDA-approved nicotine replacement therapies. Finally, we will compare the two arms on utilization of their assigned app.

Aim 2. We hypothesize that the iCanQuit arm's (but not the QuitGuide arm's) smoking cessation outcomes will be strongly mediated by these psychological measures that are central to the theoretical model underlying ACT: commitment to quitting and acceptance of internal (a) sensations, (b) emotions, and (c) thoughts that cue smoking. This hypothesis is consistent the ACT model and prior ACT for smoking cessation intervention studies [16, 17, 20, 82]. **Analyses:** For each mediator, the model is expressed as three regression equations that relate the main independent variable X

(ACT intervention), the mediator M (change from baseline to 3-months post randomization in the acceptance variable, and/or commitment to quitting smoking despite internal cues), and the binary endpoint Y at 12-months post-randomization (e.g., 30-day abstinence). The first regression describes the total intervention effect (X) on the outcome (Y): logit (Y) = $\gamma_1 + \tau X$, where the parameter τ measures the total intervention effect. The second regression describes the impact of the intervention (X) on the mediator (M): $M = \gamma_2 + \alpha X$. The third regression describes the simultaneous impacts of the intervention (X) and mediator (M) on the outcome (Y): logit (Y) = $\gamma_3 + \tau' X + \beta M$. Since the endpoint is binary, the mediation effect is the product term $\alpha\beta$, whose empirical distribution will be estimated via 5000 bootstrapped samples. Bootstrapping is a resampling method which provides a powerful test of mediation that does not rely on normality assumptions [93-95]. Randomization should remove potential confounding effects [92, 93], and if needed, we will adjust each model by covariates that differ at baseline or predict outcome. Following VanderWeele and Preacher methods [94, 95], we will also explore any interactions between mediators and treatment arm. And we will explore whether utilization of assigned app and usage of cessation pharmacotherapy mediates cessation outcomes.

Aim 3. We hypothesize that iCanQuit will be more cost-effective than QuitGuide, as measured by cost per quitter, incremental cost-effectiveness ratio (ICER), and incremental cost per quality-adjusted life year (QALY). We will use current good practices of estimating cost-effectiveness, which were articulated by [96], as applied to smoking cessation interventions [77, 97]. First, to examine whether iCanQuit costs less than QuitGuide to help a person quit, we will estimate the incremental cost-per-quitter: difference in total cost of delivering the two interventions [98] divided by the difference in the number of 30-day abstinent participants at 12-months ($\text{Total Cost}_{\text{iCanQuit}} - \text{Total Cost}_{\text{QuitGuide}}$/$\#\text{ Abstinent}_{\text{iCanQuit}} - \#\text{ Abstinent}_{\text{QuitGuide}}$). Total delivery cost assessments are described in Section 3.3.11. Second, to estimate whether iCanQuit costs less than QuitGuide per life year added [77], we will calculate standard Incremental Cost-Effectiveness Ratios (ICER): $\text{Total Cost}_{\text{iCanQuit}} - \text{Total Cost}_{\text{QuitGuide}}$/$\#\text{ Life Years Added}_{\text{iCanQuit}} - \#\text{ Life Years Added}_{\text{QuitGuide}}$). Life years added attributable to each intervention's 12-month primary endpoint effect size will be derived from the life years estimates, reported in Stapleton & West [77], that conservatively account for gender, age, discounting, relapse, and unaided cessation. Third, to examine whether iCanQuit costs less than QuitGuide to add greater quality to each life year added [93], a separate ICER quality of life analysis called incremental cost-per-QALY will be conducted ($\text{Total Cost}_{\text{iCanQuit}} - \text{Total Cost}_{\text{QuitGuide}}$)/($\text{QALY}_{\text{iCanQuit}} - \text{QALY}_{\text{QuitGuide}}$). This analysis will be calculated by adding a Generalized Linear Model-based weighted quality of life parameter derived from the standard EQ-5D quality of life measure [99] taken at the 12-month endpoint. Finally, we will conduct multi-way sensitivity analyses of these results using 1000 Markov Chain Monte Carlo simulations that will derive a cost-effectiveness plane (and 95% CI ellipse) across a range of total costs and effect sizes. In all estimates, we will adjust future costs to a standard reference year and discount future costs and benefits incurred after one year at 3% per annum as is recommended by the USPSTF on cost-effectiveness in health and medicine [100].

Exploratory Aim. This aim will explore whether iCanQuit, as compared to QuitGuide, has higher quit rates for those with these baseline factors: (a) those scoring low on acceptance of sensations, emotions, and thoughts that cue smoking, (b) heavy smokers (≥ 20 cigarettes/day), (c) smokers screening positive for mental health symptoms, and (d) being a racial/ethnic minority. **Analyses:** This aim will explore key moderators of ACT treatment outcomes and aid in the critical effort to improve quit rates for these high-risk groups [101-105]. The ACT model suggests that, in addition to being a key mechanism (i.e., mediator) of treatment, baseline acceptance is a moderator of treatment outcome [22]. Specifically, we hypothesize that people who avoid their

triggers to smoke (i.e., low acceptance) will benefit most from ACT because ACT teaches skills to overcome avoidance. We also hypothesize that this focus on acceptance may be especially helpful for heavy smokers and those with mental health symptoms because physical, emotional, and cognitive cues to smoke are stronger for these individuals [106-109]. Finally, testing moderation by race/ethnicity will allow us to generate hypotheses about whether minorities overall respond differently to ACT than non-Hispanic Caucasians. We will explore moderation with separate logistic regression models for each moderator variable, where 30-day abstinence at 12-months post randomization is the outcome (Y). The model will include the moderator (Z), group assignment (X), and an interaction between moderator and group assignment (X*Z). Statistically significant interactions will be assessed with plots showing how the slope of Y on X is dependent on the value of Z. The slopes will be derived from logistic regressions that correspond to the prediction of Y from X at a single value of moderator Z.

Power. We determined sample size with 5,000 iterative simulations aimed at 80% power for Primary Aim 1. We used the following parameters: (1) participants randomized to one of the two arms; (2) two-sided test with α = .05; (3) intent-to-treat analysis where, as standard in smoking cessation trials, all those with missing data are coded as smokers [11, 60]. The calculations do not account for potentially higher effect sizes from the adjustment of stratification factors.

For Primary Aim 1, projected quit rates at 12 month follow-up were conservatively calculated using (1) quit rates at two-month follow-up in our pilot RCT (which used methods similar to this proposed R01) and (2) well-established relapse curves, which provide a data-derived estimate of the rate of decay of 2-month intervention effects by 12 month follow-up [60, 76, 77]. Specifically, the estimates account for a quit rate reduction from the observed two-month 13% quit rate in the pilot to an estimated 11% 12-month quit rate for ACT and from the observed two-month 8% quit rate in the pilot to an estimated 7% 12-month quit rate for QuitGuide. These reduction estimates are consistent with the relapse rates observed by 12 month follow-up [60, 76, 77]. Having 80% two-tailed power to significantly detect a quit rate as low as 11% for iCanQuit (vs. 7% for QuitGuide) required a sample size of 1622. However, we set the target recruitment to 2500 participants for the Exploratory Aim analyses.

For Primary Aim 2, regarding the acceptance mediators, we estimated that they would explain at least 60% of ACT's effect on quitting smoking, as based on prior trials [16, 17, 20, 82]. For the commitment to quitting mediator, we estimated that it would explain at least 25% of ACT's effect on quitting smoking, as based on prior trials [16, 17, 20, 82]. The 5000 iterative simulations showed that a sample size of 811 per arm would provide high power (>99%) to detect the estimated mediation effects for acceptance and commitment.

PROTECTION OF HUMAN SUBJECTS

All procedures for this study will be reviewed by Fred Hutch's IRB prior to human subjects' participation. Based on our prior history with the pilot randomized trial which motivated this proposed trial, we expect no problems obtaining IRB approval.

Experimental design

We will conduct a fully-powered two-arm randomized controlled trial that compares iCanQuit to QuitGuide, which follows the USCPG [67]. To balance baseline variables between the two conditions, we will stratify randomization by daily smoking frequency (≤20 vs. ≥ 21), education (≤ high school vs. ≥ some college), race/ethnicity (minority race/ethnicity vs. non-Hispanic White) and depression screen (CES-D score ≤ 15 vs. ≥ 16). Moderators will be measured at baseline. Mediators will be measured at baseline and three months post randomization. Cessation and cost-effectiveness outcomes will be measured at 3, 6, and 12 months post randomization. Enrollment and baseline data collection will occur via a SSL secured website hosted by Fred Hutch. The ACT intervention will occur on an app platform which will send, via 256-bit SSL encryption, study-ID coded usage data from smartphones to secured Fred Hutch servers. Outcome surveys occur via an online-telephone-mailed sequence conducted by Fred Hutch.

Sources of material

As shown in Table 3 of the Research Plan, these are sources of survey data for the study: (1) screening survey, (2) baseline survey, (3) 3-month follow-up survey, (4) 6-month follow-up survey, and (5) 12-month follow-up survey. We will also collect automated utilization data from both apps. A description of these sources of data follows.

Survey Data

As further outlined in Table 4 and Research Plan, the Baseline Survey, hosted on our secured recruitment website, will collect data on (1) demographics, (2) current smoking status and smoking history, (3) readiness to quit, (4) nicotine dependence, (5) acceptance of internal cues to smoke, (6) commitment to quitting, (7) quality of life, (8) mental health, and (9) contact information needed for the study's follow-up data collection activities – as well as information about whether or not it is acceptable to receive email or voice messages and mail from the study. The Three-Month survey will primarily collect data on cessation processes (e.g., acceptance of cues to smoke), progress (e.g., quit attempts) and outcomes (e.g., 30-day abstinence), and the participant's experiences with their assigned smoking cessation intervention. The Six and Twelve Month surveys will primarily collect data on cessation progress and outcomes.

App utilization data and security

Activation of the assigned app on the participant's smartphone will be conducted by entering the login code sent to them in their trial enrollment email. Personal information collected from the apps is limited to a first name and optional email in the ACT version of the app. The apps send, via 256-bit SSL encryption, participant-specific utilization data from smartphones to secured Fred Hutch servers: (1) # of times app was

opened, (2) specific features used, and (3) tracking of smoking and exercise practice (iCanQuit only). These data are identified by alphanumeric IDs only. Fred Hutch Shared Resource programmers will be the only persons with the ability to re-identify study participants based on the alphanumeric IDs. There will be secured backup and half-yearly risk assessment and mitigation.

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Follow-up surveys data collection procedures.

For trial integrity, the follow-up data will be collected by our survey research unit that will be (1) blind to random assignment and (2) collecting cessation outcome data outside of the intervention apps. At each follow-up, we will send reminder letters using an "Address Service Requested" envelope, for automatic forwarding to new mailing addresses. Each follow-up survey and Internet tracking will collect address information. The online-telephone-mailed sequence data collection protocol is as follows: 1) Three email attempts to complete the online version of the survey; 2) Eight attempts to complete a **telephone** version of survey (one call per day from a trained surveyor); 3) Send a paper version of the survey via US **mail.**

Based on our ACT smartphone pilot RCT experience, we conservatively estimate this protocol will yield 84% retention. And to further boost retention, we will make the following protocol enhancements at all follow-up points: (1) mail a $2 pre-incentive letter (noncontingent incentives increase retention [88]) 2 weeks before the first online survey invitation (i.e., Day -14); (2) provide a $10 incentive for completing the online survey within 24 hours [89]; and (3) send a second copy of the **mailed** survey 2 weeks after the first mailing.

Telephone administration of the surveys will be conducted by trained staff. If the staff member gets voicemail, a short and simple message will be given letting the participant know the purpose of the call and encouraging him/her to call the study's toll-free number. Mailed surveys will include a letter inviting participants to complete the survey, a printed survey form, a self-addressed-stamped-return-envelope for the completed survey.

Potential risks to participants

The main risk to participation in this study is a small risk of breach of confidentiality. A breach could possibly occur if, for example, an unauthorized person accesses the study's database records and/or hard copy records, telephone survey conversations are accidentally overheard by someone who does not know the participant smokes or is taking part in a smoking cessation study. Also, some participants might feel emotional upset during their assigned intervention or embarrassment when talking about their smoking during the telephone surveys. Finally, some smokers making quit attempts may experience some short-term discomfort associated with nicotine withdrawal. Participants will be fully apprised of all anticipated risks in the informed consent and other intervention materials.

Protection against risk

All research activities will be reviewed and approved by the IRB at Fred Hutch to ensure that participants are adequately protected against risk. The research aims and activities, as well as risks and benefits, will be explained in detail to all potential participants prior to obtaining informed consent. Steps to protect against risk are described below:

Protection against breach of confidentiality: How survey data are processed and stored in HIPAA compliant server

All survey data records are stored in secured HIPAA compliant servers or in locked file cabinets inside locked (limited access) rooms in our secured building. Completed paper surveys have no identifying information other than the participant's unique Study ID number. Access to paper and electronic study data and records, and to the link between participant names and Study ID numbers, is restricted to a limited number of need-to-know study personnel, and data may not be taken off the premises for any purpose. Users have no access to project computers unless they have a domain (network) account. All users must change passwords every 120 days. The electronic database resides on a server that is in a locked cabinet in a locked server room, with strictly limited, key-card access. The server also lies behind Fred Hutch's firewall, which permits no access to the server at all from outside Fred Hutch, except through the database server port using a secure, encrypted channel. The research group places additional restrictions, through DBMS software, on which data items users may view and the kinds of activities they are permitted. These permissions are based strictly on each staff member's need to see and use the data. No staff member will be able to access the data by default. The Project web server also resides in the same secure room as the database server, and is similarly protected by firewalls, with no user access except through the web server software. The database administrators maintain a rigorous system of daily full tape backups of the database and web servers. The backups include sets of tapes stored at a secure distant site.

Study participants will be recruited using a publicly accessible web site running on the Apache web server on a Linux operating system. The public web server is segregated from the rest of the Fred Hutch network within a DMZ (demilitarized zone). After indicating interest in the study, participants will complete online surveys via the 256-bit secure sockets layer protocol (SSL). Employment of the SSL protocol will prevent anyone from intercepting data passed between the end user's web browser and the web server. Once randomized, each treatment group will have access to their assigned smartphone application protected upon successful download.

Surveys are implemented using a secure, metadata-driven system designed and tested by our software development team, which has been in use for the past five years for other research studies in which participants enter information about themselves. Surveys are hosted on a Web site running on the Apache web server on a Linux operating system. The public web server is segregated from the rest of the Fred Hutch network within a DMZ (demilitarized zone). Study participants who complete these online surveys will only have access to data that they have entered on in-process surveys. Participants may access partially completed surveys via a participant-specific link provided by email and entry of the participant's birthdate. Once surveys are complete, the data are inaccessible from the data collection web site. Participants and others will be prevented from accessing any other data on the Web server by a number of operating system, web server, and application controls. Users will connect to the web site to complete the surveys using the secure sockets layer protocol (SSL). Employment of the SSL protocol will prevent anyone from intercepting data passed between the end user's web browser and the web server.

Protection against emotional upset or embarrassment.

If participants feel uncomfortable answering research questions or participating in their assigned intervention they will be able to skip any assessment items that they are not comfortable answering. Participation during the intervention will also be voluntary. Participants may choose not to participate in any components of their assigned intervention which make them feel uncomfortable. All participants will have the option of contacting via email the PI, Dr. Bricker, a Licensed Clinical Psychologist with the experience and expertise to responding effectively to potential adverse emotional reactions. He will plan to respond within 24 hours. If a referral to treatment is needed, he is acquainted with appropriate referral facilities and processes of identifying treatment available throughout the United States.

Protection against discomfort of nicotine withdrawal.

Participants who quit smoking may experience some discomfort associated nicotine withdrawal. Participants will also be fully informed of the symptoms of nicotine withdrawal during the informed consent process. Interventions in all treatment arms provide strategies designed to cope more effectively with symptoms of nicotine withdrawal. Finally, participants in both treatment groups will be given information on pharmacotherapy for smoking cessation (e.g., nicotine patch) and how to obtain these medications.

Reporting breaches and complaints

Taken together, these measures will minimize risks to study participants. However, should a breach/complaint occur, or if a participant is not pleased with any of the surveys, or with the study's procedures, the study's scientific staff will attempt to address the concerns; if unsuccessful, the breach/complaint will be reported to the IRB office, and the participant will be referred to the Fred Hutch IRO Director.

Potential benefits of the proposed research to the subjects and others

Successfully assisting people who smoke to quit would have significant positive benefits to their health. Overall, participants assigned to any of the three interventions have the potential to benefit by quitting smoking and the potential short and long term health benefits of quitting.

Importance of knowledge to be gained

As millions of people are choosing smartphone apps to help them quit smoking, this innovative study shows exciting promise for improving the success rates of quit smoking apps and thereby lowering healthcare costs and reducing premature tobacco-related deaths.

Inclusion of women and minorities

The population for this study will be 2500 adult male and female daily smokers who want to quit smoking. Recruitment and eligibility screening methods are designed to achieve a broad representation of adult smokers, including 70% female and 30% racial/ethnic minority.

Inclusion of children

This is a study of adult smoking cessation; participants will be aged 18 or older. The NIH definition of children includes young adults up to age 21. By the NIH definition, the only "child" participants in this study will be those aged 18-21, over the age of majority and fully capable of participating in informed consent. Therefore, no special protections are required for their inclusion in this research.

Children under the age of 18 will be excluded on the basis of the following: (1) Both interventions used in this trial have not been designed for or tested with adolescent smokers; (2) Youth may respond differently to intervention than do adults. As such, data collected from these individuals may not generalize to the larger adult population; and, (3) Our standardized assessment measures were validated in adult samples and are not applicable to children.

Data safety and monitoring plan

Upon funding, the DSMP will be submitted for review by the Fred Hutch Institutional Review Board. The DSMP includes plans for the following required elements: (1) monitoring the progress of trials and safety of participants, (2) assuring compliance with requirements regarding the reporting of adverse events, (3) assuring that any action resulting in temporary or permanent suspension of the trial is reported to the sponsor, and (4) ensuring data accuracy and protocol compliance. The trial's DSMP will be carried out by the scientific/management team, including the Principal Investigator, at weekly meetings.

Data Management

In addition to and in combination with meeting HIPAA regulations, data collected and managed will be securely handled to prevent unauthorized access or modification. All those in the study staff who have access to data on those screened and/or participating in the study will follow these procedures when handling the data: (1) education about the need for security and confidentiality, (2) signing a confidentiality agreement, (3) using passwords to control access to the electronic databases and regular changing of passwords, (4) keeping paper versions of surveys and any other paper versions of screened/participating individuals' data in a locked room, & (5) servers will be protected by firewalls, McAfee Virus Scan Enterprise anti-virus software, daily full tape backups stored in a locked room, and encryption via the https protocol.

Data Accuracy

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.

Monitoring Data Quality and Integrity

Several procedures will be used to maintain data integrity. All databases will be stored in a centralized location at Fred Hutch on a secure server. Data will be backed up daily and access will be password protected and limited to persons working on the

project. Persons will only have access to specific data required for their project tasks. Identifying information will be stored separately from the assessment data. Data will be audited on an ongoing basis to ensure confidentiality safeguards are being maintained and data integrity is being maintained. Data entry systems will be set-up to allow field checks, range checks for continuous variables, valid value checks for categorical variables, and checks for logical consistency of responses. Queries and data reports will be generated on a routine basis to monitor data quality.

Guidelines for Monitoring and Reporting Unexpected and Adverse Events

Monitoring

Throughout the study, the Principal Investigator, Co-Investigator, and Project Manager will monitor participants for adverse events and protocol compliance. The project manager will complete monthly reports on participant progress and status, any adverse events, and any protocol deviations. Protocol adherence will be monitored by the Principal Investigator.

Reporting

Study staff will be trained, and required, to report all unexpected and adverse events to the Principal Investigator. 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.

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. An example of an adverse event in this trial could include an increase in depressive 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.

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.

Attribution

The Principal Investigator, in consultation with the Co-Investigators, 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 smoking cessation intervention.
- Not Related – AEs that are doubtfully related or clearly not related to the smoking cessation intervention.

Reporting

1. **SAE's:** For AE's meeting the criteria for an SAE, regardless of its attribution, a Fred Hutch SAE Report form will be completed. The SAE Report form will be faxed by the Principal Investigator to the IRO office at 206-667-6831 within 24 hours of the internal report. All available information will be submitted. Should additional information become available after the initial report, a revised report will be submitted within 15 days.
2. **AE's that do not meet the criteria for SAE:** For these events, the Principal Investigator or the Study Coordinator will complete and submit a Fred Hutch Adverse Event Reporting form within ten (10) calendar days of learning of the events.
3. **UE's that do not meet the criteria for AE's**: For these events, the Study Coordinator will complete and submit a Fred Hutch UE Reporting Form within ten (10) calendar days of learning of the events.

Complying with Trial Suspension Reporting Requirements

Were the Fred Hutch's IRB or Clinical Trial's Office to issue a temporary or permanent suspension of the trial, the trial's Principal Investigator will immediately contact the trial's project officer. A Data Safety Monitoring Board will not be required since this is a minimal risk behavioral intervention.

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