Study Protocol and Statistical Analysis Plan (SAP)

A PROOF-OF-CONCEPT RCT OF VERSION 3.0 OF THE SMOKING CESSATION SMARTPHONE APP "SMILING INSTEAD OF SMOKING" (SIS)

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I. BACKGROUND AND SIGNIFICANCE

1. Why Nondaily Smoking Matters

Cigarette smoking continues to be the leading cause of preventable disease and death in the United States, accounting for more than 480,000 deaths every year.[1] While the prevalence of smoking has steadily declined over a number of years,[2] an increasingly prevalent pattern of smoking is nondaily smoking. Currently, 24.3% of all adult smokers are nondaily smokers, which constitutes a 27% increase in prevalence in the last decade.[3]

Nondaily smoking poses substantial health risks,[4,5] and is a recognized public health issue.[6] It poses significant carcinogenic exposure (i.e., 40-50% of that seen in daily smokers)[7] and has been linked to total and cardiovascular mortality among men.[8] Indeed, the risk for cardiovascular disease has been found to be nearly equal to that of daily smoking, given a highly non-linear dose-response relationship between tobacco exposure and cardiovascular mortality.[9]

Untreated nondaily smoking contributes to persisting health disparities in smoking prevalence. Nondaily smoking is disproportionally represented in ethnic minority groups,[10-14] and increasingly prevalent in adults with a mental health or substance use problem.[15] Both of these groups have substantially higher smoking prevalence rates (e.g., 31.8% in American Indian/Alaska Natives,[2] 35.8% in adults with serious psychological distress,[2] 65% to 87% in individuals with substance use disorders[16]) compared to the general population (15.5%).[2] Thus, a failure to provide smoking cessation support for nondaily smokers disproportionally impacts populations already systematically missed by current public health efforts.

2. The Need for Smoking Cessation Support for Nondaily Smokers

Nondaily smokers are motivated to quit smoking. Indeed, epidemiological evidence demonstrates that compared to daily smokers, nondaily smokers have greater current intentions to quit smoking,[11,17,18] and more recent and planned cessation efforts [18-21] than daily smokers. The fact that nondaily smokers regularly abstain from smoking from day-to-day suggests that they should have relatively little trouble quitting, but recent evidence demonstrates that most nondaily smokers (up to 82%) fail in their quit attempts.[22] Together, the high motivation to quit coupled with a high failure rate demonstrate the need for smoking cessation support for nondaily smokers.

3. Why Traditional Smoking Cessation Interventions Fail Nondaily Smokers

Engaging nondaily smokers in treatment has been largely unsuccessful. Despite being motivated to quit, nondaily smokers are less likely than heavier smokers to seek or receive treatment, leaving cessation efforts among nondaily smokers largely unaided.[18,23] Treatment engagement is made difficult by nondaily smokers' resistance to being thought of as smokers: nondaily smokers feel less addicted than daily smokers,[24] do not consider themselves to be smokers,[25,26] and will deny their smoking habit when asked by family, friends, and healthcare providers.[27] In line with these self-perceptions are data from cross-sectional, naturalistic and laboratory studies that shown that nondaily smokers differ from daily smokers on important dimensions related to smoking cessation, including lower levels of dependence,[28,29] higher levels of self-control,[30,31] superior smoking-related error processing on neurocognitive tasks,[32] and lower sensation-seeking impulses.[33]

One reason traditional smoking cessation treatments fail to appeal to nondaily smokers may be that they are simply not applicable. Existing treatments for smoking cessation are based on studies of daily smokers,[34] and theoretical models of cigarette smoking assume daily smoking.[35]

Such models posit that smoking is primarily driven by nicotine dependence, such that smokers smoke in order to maintain nicotine levels above a certain level, thereby preventing the occurrence of withdrawal symptoms.[36] Nondaily smokers, however, do not smoke continuously. Rather, they smoke on average 4 days per week, and 4 cigarettes per smoking day,[37] and thus are not maintaining a specific level of nicotine. Their reasons for smoking also tend to be different, when compared to daily smokers. Nondaily smokers tend to smoke for social enhancement rather than to cope with negative affect,[24,25] and tend to be driven by acute, situational motives (e.g., cue exposure, positive reinforcement) rather than nicotine dependence (e.g., tolerance, withdrawal symptoms).[38-40] These data suggest that **treatments emphasizing withdrawal and dependence are likely inappropriate for nondaily smokers**.

4. Smiling Instead of Smoking

We developed a smartphone app that specifically addresses the characteristics of nondaily smoking. To support smoking cessation, we use a positive psychology approach. Positive affect enhancement is an empirically sound treatment target: positive affect is psychometrically and neurologically distinct from negative affect, and plays an important role in the days leading up to and following a quit attempt. Enhancing positive affect with brief, self-administered exercises is entirely feasible: in recent years, a large number of positive psychology exercises have been developed that have consistently led to improvements in happiness, reductions in depression, and improvements in overall well-being. Our smartphone app, "Smiling instead of Smoking" administers such positive psychology exercises to enhance and/or maintain positive affect, which is hypothesized to stimulate nondaily smokers to enact healthier alternatives to smoking by broadening their thought-action repertoire, increasing confidence, and decreasing craving and defensiveness about smoking-related health information (Figure 1).

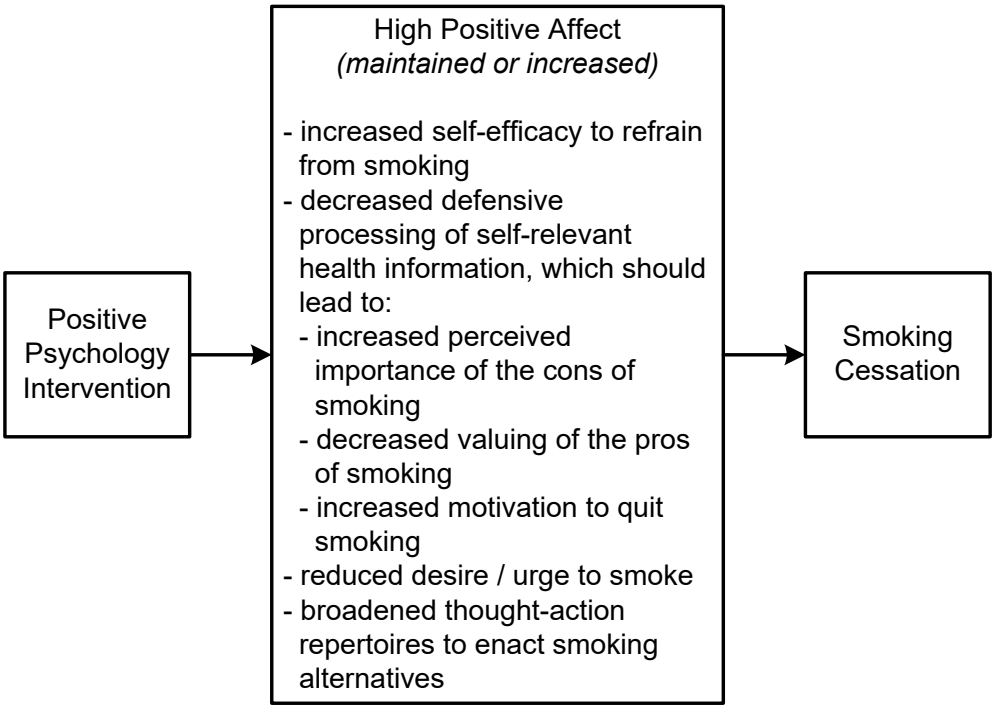


Figure 1. Theorized Mechanisms of Behavior Change

The focus on happiness will help overcome treatment resistance, as the pursuit of happiness is generally appealing and non-stigmatizing. To this end, we have worked closely with nondaily

smokers in Study 1 (#2017P001106)[41] and Study 2 (#2018P002699) to develop Version 3.0 of our "Smiling Instead of Smoking" app. In the current study (i.e., Study 3 in a series of 3 studies funded by the American Cancer Society (130323-RSG-17-021-01-CPPB)), we will conduct a proof-of-concept RCT of Version 3.0 of this app.

II. SPECIFIC AIMS

This is the third study in a series of 3 studies to develop a smartphone app to support nondaily smokers in quitting smoking, as funded by the American Cancer Society grant #RSG CPPB – 130323 (project dates: 07/01/2017 – 6/30/2021). Study 1 (2017P001106) demonstrated feasibility and acceptability when smokers were onboarded in person[41]. Study 2 (2018P002699) demonstrated feasibility and acceptability when smokers were onboarded remotely, nationwide. The present study is Study 3. It is a 3-group proof-of-concept RCT, in which we seek to test if our app (i.e., Version 3 of our developed smartphone app, called 'Smiling instead of Smoking' (SiS)) is superior to treatment as usual (i.e., TAU; no treatment for nondaily smokers) and superior to a control app (i.e., the National Cancer Institute's smartphone app "QuitGuide" (QG). Specifically, our aims are to:

1. Test for differences between randomized groups on the primary outcome of this proof-of-concept RCT, as measured at end of treatment (i.e., Week 6 post-quit): Self-efficacy to remain abstinent, as measured via the Smoking Self-Efficacy Questionnaire (SEQ)[42]: two-dimensional 12-item self-report scale measuring a person's confidence in his or her ability to abstain from smoking when facing internal stimuli [e.g. feeling depressed] and external stimuli [e.g. being with smokers]. Participants rate each item on a sliding scale from 0 [not at all confident] to 100 [extremely confident]. Two subscale scores are created by averaging items assessing internal vs. external stimuli, respectively. We hypothesize that SiS > QG > TAU.

2. Test for differences between randomized groups on secondary outcomes:
    a. Self-reported 30-day point-prevalence abstinence 6, 12 and 24 weeks post quit. We hypothesize that SiS > QG > TAU.
    b. Self-reported past week cigarette reduction at 2, 6, 12, and 24 weeks post quit, compared to baseline. We hypothesize that SiS > QG > TAU.
    c. Satisfaction with smoking cessation support, as self-rated on the Client Satisfaction Questionnaire (CSQ-8)[43] at end of treatment. We hypothesize that SiS > QG > TAU.
    d. Time spent applying content brought up by the apps/"Clearing the Air" at end of treatment ("During this past week, how much time did you spend applying or contemplating the content of the SiS app/QG app/"Clearing the Air"?" [in minutes]). We hypothesize that SiS > QG > TAU.
    e. Use of smoking cessation strategies, as assessed at end of treatment. We hypothesize that SiS > QG > TAU.
    f. Perceived impact of the provided materials on quitting (e.g., "reminded me to stay on track"), as assessed at end of treatment. We hypothesize that SiS > QG > TAU.
    g. Appreciation, as measured via the Appreciation Scale[44] at end of treatment. The Appreciation Scale is an 18-item scale which assesses the degree to which one is appreciative. This is an important process outcome for this study, as the SiS app,

unlike the QG app or TAU, emphasizes the experience of positive emotions in order to support smoking cessation. Ten of the items assess frequency of action (e.g., "I do things to remind myself to be thankful" 7-point Likert: 1 = More than once a day, 2 = About once a day, 3 = About once a week, 4 = About once a month, 5 = About once a year, 6 = A few times in my life, 7 = Never). The remaining eight of the items assess level of agreement with appreciative statements (e.g., "I feel that it is a miracle to be alive" 7-point Likert: 1 = Strongly agree, 2 = Agree, 3 = Agree somewhat, 4 = Neither agree nor disagree, 5= Disagree somewhat, 6 = Disagree, 7 = Strongly disagree). We hypothesize that SiS > QG > TAU.

h. *(SiS and QG only)* Actual app usage – number of days participants used the assigned app during the prescribed period of app use (i.e., 7 weeks for both apps). Please note that we have a partnership agreement in place with the National Cancer Institute (see attached email) to obtain usage data of the NCI QuitGuide app for our research participants (using de-identified ID numbers), with participants' explicit permission, as explained in the study facts sheet. We hypothesize that SiS > QG.

i. *(SiS and QG only)* Self-reported app usage – number of days used app, asked per week; if used, how many minutes per typical day used app

j. *(SiS and QG only)* Likability rating of the app as measured at end of treatment (i.e., "How much did you like using the smoking cessation app we asked you to use?" 5-point Likert: 1 = I strongly disliked using the app, 2 = I somewhat disliked using the app, 3 = I neither liked nor disliked using the app; 4 = I somewhat liked using the app, and 5 = I strongly liked using the app). We hypothesize that SiS > QG.

k. *(SiS and QG only)* Satisfaction rating of the smoking cessation support provided by the app (i.e., "How satisfied are you with the smoking cessation support this app provided you with?" 5-point Likert: 1 = very unsatisfied, 2 = somewhat dissatisfied, 3 = neither satisfied nor dissatisfied, 4 = somewhat satisfied, 5 = very satisfied). We hypothesize that SiS > QG.

l. *(SiS and QG only)* App usability ratings, as assessed via the System Usability Scale (SUS)[45], a simple, ten-item attitude scale giving a global view of subjective assessments of usability, adapted to include language specific to the smoking app (e.g., "I found the smoking app unnecessarily complex" 5-point Likert: 1 = strongly disagree, 5 = strongly agree). We hypothesize that SiS > QG.

3. (exploratory) To test, via mediational modeling, how treatment via the proposed app conferred benefit, or, if not effective, if failure is due to the treatment failing to impact hypothesized mechanisms of change, or because these mechanisms fail to impact outcome. The outcome of interest in these mediational models is self-reported 30-day abstinence at the final follow-up, 6 months post quit. The mediators to be tested, are:

   a. Self-efficacy as measured via the Smoking Self-Efficacy Questionnaire (SEQ); this is also our primary outcome variable, as described above.

   b. Emotional well-being

      i. Positive and negative affect, as measured via the positive affect subscale of the Positive And Negative Affect Schedule (PANAS)[46]: For each subscale, both positive and negative, 10 mood adjectives are displayed. Participants rate to what extent they have felt each emotion on a 5-point scale [1 = very slightly or not at all, 5 = extremely]. In this study, the timeframe of reference is the past week.

ii. Happiness, as measured via two single-item measures, both rated on a 0-100 slider, anchored at 0=not at all, 100=extremely: "In the PAST WEEK, how happy have you felt?"; "How happy are you feeling RIGHT NOW?"
iii. Satisfaction with life, as measured via the Satisfaction with Life Scale (SWLS)[47]: 5 items rated on a 7-point Likert scale [e.g., "In most ways my life is close to my ideal]).
iv. Subjective happiness, as measured via the Subjective Happiness Scale (SHS)[48]; 4 items rated on a 7-point Likert scale [e.g., "Some people are generally very happy. They enjoy life regardless of what is going on, getting the most out of everything. To what extent does this characterization describe you?"]).
v. Stress and Coping, as measured via the stress and coping subscales of the Perceived Stress Scale (PSS10)[49]: 10-item self-report scale that measures the degree to which situations in one's life are appraised as stressful. Items are worded both negatively (e.g., "In the last month, how often have you been upset because of something that happened unexpectedly?" and positively (e.g., "In the last month, how often have you felt that you were on top of things?" Traditionally, for a total score, positively worded items are reverse-scored, then sum-scored with the negatively worded items. More recently, the PSS-10 has been conceptualized as assessing two sub-scales, perceived stress vs. perceived ability to cope with stressors,[53] which is how we will score this scale for this study.

c. Desire to smoke, as measured via the Brief Questionnaire of Smoking Urges (QSU)[50]: a 10-item self-report measure of craving. Sample items include: "I have an urge for a cigarette" and "I would do almost anything for a cigarette now" and are rated on 7-point Likert scale [1 = strongly disagree, 7 = strongly agree]).
d. Breadth of thought-action-repertoire, as measured via the Modified Twenty Statements Test (MTST)[51]: participants list any and all "actions" they can think of while experiencing a specific emotion. We have modified Fredrickson's scale to make it smoking-specific [e.g., at baseline, it states "Name the strongest emotion you feel when thinking about your upcoming quit attempt. Take a moment to experience that emotion. Concentrate on it and live it as vividly and as deeply as possible. Now recall the most recent cigarettes you have smoked. Given the feeling you just named ([piped]), please list all the things you could have done instead of smoking at those times. You can list as many or as few things as come to mind in the lines below").
e. Processing of self-relevant health information
    i. Perceiving effects of smoking, as measured via the Attitudes Towards Smoking Scale (ATS)[52]: an 18-item self-report measure assessing to what degree participants perceive adverse effects of smoking, psychoactive benefits of smoking, and pleasure of smoking.
    ii. Importance of the pros and cons of smoking, as measured via the Decisional Balance Inventory – short form (DCB)[53] for Smoking: a 6-item scale which rates the perceived importance of pros and cons of smoking.
    iii. Single item pros (rated on a 0-10 slider scale [0 = not at all, 10 = extremely important]; "Think about all the things you LIKE/LOVE about quitting/being smoke-free; taken together, how important are those things to you RIGHT NOW?")

iv. Single item cons (rated on a 0-10 slider scale [0 = not at all, 10 = extremely important]; "Think about all the things you DISLIKE/HATE about quitting/being smoke-free; taken together, how important are those things to you RIGHT NOW?")
v. Commitment to Quitting Smoking, as measured via the Commitment to Quitting Smoking scale (CQSS),[54] an 8-item self-report measure capturing the extent to which persons feel personally obligated to persist in quitting smoking despite difficulties, craving and discomfort.
vi. Single item how motivated (rated on a 0-10 slider scale [0 = not at all, 10 = extremely motivated]; "How MOTIVATED are you to quit smoking/ stay quit?")

III. SUBJECT SELECTION

Eligibility criteria includes the following: (a) 18+ years of age, (b) smartphone ownership (Android or iPhone only), (c) current nondaily smoker, who smokes at least weekly, and no more than 25 out of the past 30 days, and (d) lifetime history of having smoked 100+ cigarettes, and (e) is willing to make a smoking quit attempt as part of this study (f) currently residing in the United States of America. We will use both grass-root efforts (e.g., PI's Harvard Scholar website, Craigslist, quit smoking forums) and commercial advertising (e.g., Facebook).
In addition to the aforementioned recruitment methods, we will also recruit through the RPDR (Research Patient Data Registry) at Partners Healthcare. The Research Patient Data Registry (RPDR) is supported by the dedicated team of nearly a dozen developers and support personnel. RPDR is the centralized clinical data registry/warehouse directed by Research IS & Computing's Director, Shawn Murphy, M.D. PhD. The RPDR gathers data from hospital systems and stores it in one place, bringing clinical information to a researcher's fingertips and ensuring the security of patient information. We will run bi-weekly queries for current nondaily cigarette smokers seen at Partners Healthcare primary care sites, and subsequently submit the appropriate data requests to receive the following identifiable information: MRN (medical record number), contact information (email address, phone number, and mailing address), and RODY answer (yes/no). We will only contact patients who are designated "yes" in the Epic system, for the column "okay to contact." Under the new MGB opt-out system, this column designates "whether it is okay to contact the patient about research recruitment. This may be based on the patient's explicit preference, system default, or an override rule. The information displays in Yes/No format.

In addition to the above mentioned recruitment efforts, research staff will use EPIC to assist in recruitment. To this end, we have worked with the Partners eCare Research Core (PeRC) to set up the necessary steps. PeRC leverages the Epic EHR to assist researchers in identifying and recruiting patients for their research studies conducted at Partners HealthCare. PeRC will put together a report through EPIC based on a list of predetermined variables (please see attached list of variables to be extracted – this list includes contact information and smoking status). After Epic training, and hands-on guidance from the PeRC team, study staff will run this automated report within Epic to identify patients who are smokers and recently completed a primary care visit at MGH. For those who have RODY status = "yes", study staff will send an opt-out email via Patient Gateway (please see attached letter). (A RODY "yes" designation in Epic means as shown in the report that the patient "okay to contact the patient about research recruitment. This may be based on the patient's explicit preference, system default, or an override rule.")For those who do not opt out of hearing about the study, study staff will follow-up by phone to ask about their interest in participating in the study, and, if interested, will phone screen them.

We will use stratified enrollment to ensure that our final sample will (a) be equally balanced between men and women, and (b) reflect national prevalence rates of nondaily smoking in terms of ethnicity and race, where we will enroll no more than 54% non-Hispanic White participants, as per the 2014 National Health Interview Survey (http://www.cdc.gov/nchs/nhis/nhis_2014_data_release.htm), which shows that 54% of nondaily smokers are non-Hispanic White.

IV. SUBJECT ENROLLMENT

This is a nation-wide proof-of-concept randomized controlled trial conducted entirely remotely. We will enroll 225 nondaily smokers based on the following eligibility criteria: (a) 18+ years of age, (b) smartphone ownership (Android or iPhone only) (c) current nondaily smoker, who smokes at least weekly, and no more than 25 out of the past 30 days, and (d) lifetime history of having smoked 100+ cigarettes, and (e) is willing to make a smoking quit attempt as part of this study.

Participants will participate in screening, consisting of (1) a phone screen, (2) an online screening survey, which will contain check-questions to verify that respondents are truly reading items (100% accuracy required; If less than 100% accuracy, participant is screened out unless there is a compelling reason to justify missed check items. This would only happen upon review with the PI and after a phone conversation with the study participant has taken place to review the missed item(s) and explain the situation. Examples would include survey glitch, otherwise thoughtful write-in answer indicating survey attention, careful review of other survey answers and length of time spent on survey); (3) provision of contact information for two collaterals who can assist research staff in locating participants; collaterals will be told that the participant is participating in a study tracking health behaviors; and (4) provision of their social security number to enable remuneration by check, as required by MGH. We expect that 1/3 of participants who start the online survey will enroll in the study.

During the phone screen, research staff will provide an overview of the study, and will answer any questions participants may have about the study. If found eligible during the phone-screen (see attached phone screen script), staff will email a pdf of the study fact sheet to the potential participant, using SEND SECURE or not, based on the potential participant's preference, as indicated during the phone screen. The study fact sheet provides an outline of the nature of the study, risks and benefits to participation, details on remuneration for participation, and how to contact with PI or IRB staff in case they have any concerns (see attached study fact sheet). The same email will contain a person-specific link to the online survey and a general resource sheet. Participants are encouraged to ask questions about the study and anything they have read in the study fact sheet prior to clicking on the survey link. When the participant starts the survey, they will be presented with the same study fact sheet in REDCap that they have received via email. They must click "I agree to participate in this screening survey" in order to proceed to the survey. The study fact sheet reminds participants that, at this point, they are agreeing to participating in the online survey: "Once we have reviewed your survey responses, we will contact you to proceed with the remaining parts of the screening test. If you are eligible to enroll in this study, and you decide you would like to participate in this study, we will ask you for your verbal consent to participate in the study during a phone call with study staff."

Staff will receive an automatic email from REDCap once the screening participant has completed the survey. If the screening participant incorrectly responded to the check items

(please see attached for the specific check items), staff will inform the screening participant that they are ineligible for the study. If the survey is complete and valid, staff will collect (via email, phone, and/or REDCap form) the contact information for collaterals the participant would like to specify for this study. Social security number (to enable payment by check) and a mailing address to which Accounts Payable can mail the check containing remuneration will be collected via phone, and only after participants have been enrolled in the study. For screen participants who do not enroll in the study (i.e., because they are ineligible or because they decide against the study) study staff will ask for verbal consent (via phone) to allow us to collect their SSN (during the same phone call) and send them a check for completing the screening survey.

At the end of this phone call, study staff will ask the screening participant to indicate the date on which they would like to quit smoking. The enrollment call is then scheduled to occur 8 days before that date. If the chosen quit date falls on a Monday or Sunday, meaning that the enrollment call should be on a Saturday or a Sunday, the enrollment call will be adjusted to fall on a weekday.

During the enrollment call, staff will review the study fact sheet with the participant, and will invite the participant to ask any questions they may have about the study and all its procedures. Once all questions have been answered, study staff will ask the participant to give verbal consent to enroll in this study. The date and time of this verbal consent will be documented by study staff in our REDCap dataset.

After providing verbal consent, the participant is randomized. This is an unblinded study. Randomization will occur via a randomization sheet, as generated using the PROC PLAN procedure in the statistical software package SAS. Randomization will be in a 1:1:1 ratio (SiS3 vs. QG vs. TAU), with a block size of 4. Study staff will use the randomization sheet to determine the participant's treatment group, document this randomized assignment in our REDCap dataset, and will then onboard the participant to the smoking cessation support they have been randomized to receive (i.e., our smartphone app SiS or NCI's app QuitGuide or TAU, which consists of NCI's written materials, "Clearing the Air"), using a time-matched, ~15 minute script.

We will stop enrollment when n=225 participants have been successfully onboarded to their randomized condition. Based on our experience in Study 1 (#2017P001106) and Study 2 (#2018P002699), we expect that 1/3 of participants who start the screening survey will enroll in the study. Thus, we are estimating that n=675 will be necessary to start the screening survey in order for n=225 to be successfully enrolled to their randomized treatment condition.

V. STUDY PRODECURES

This is a single site study. Participation will last 6 months (see Figure 2), and entails:

- Completing a scripted onboarding call (approximately 30-45 minutes)
- Making a quit attempt
- Engaging with smoking cessation support (randomized) over the course of seven weeks, one week prior and 6 weeks following the originally chosen quit day

- Completing five online, REDCap-administered surveys, administered prior to the quit day (online, as part of a screening test), and at 2-week, 6-week, 3-month, and 6-month follow-ups of the participant's chosen quit day

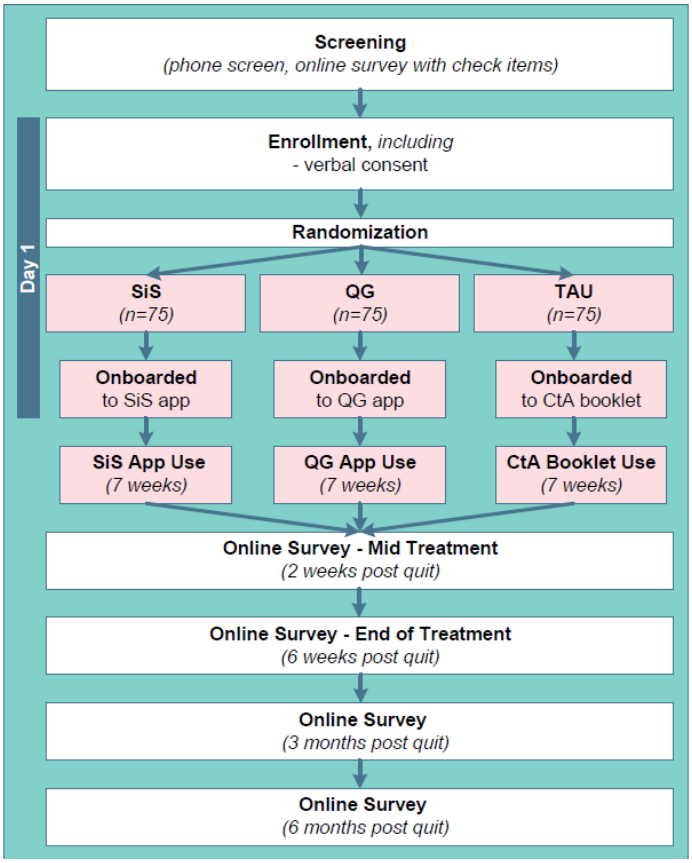
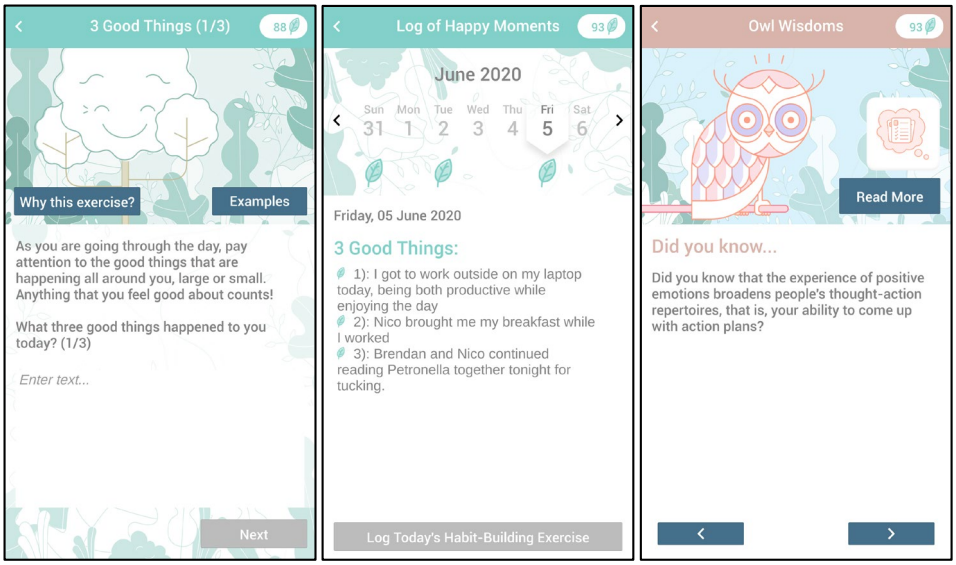


Figure 2. Timeline of study participation

After onboarding, participants will be asked to engage with the smoking cessation materials they receive as part of this study (i.e., smartphone apps or written materials) for a period of seven weeks (1 week before, 6 weeks following the quit attempt). They may choose to continue to use these materials thereafter.

Treatment Condition: "Smiling Instead of Smoking" (SiS) smartphone app

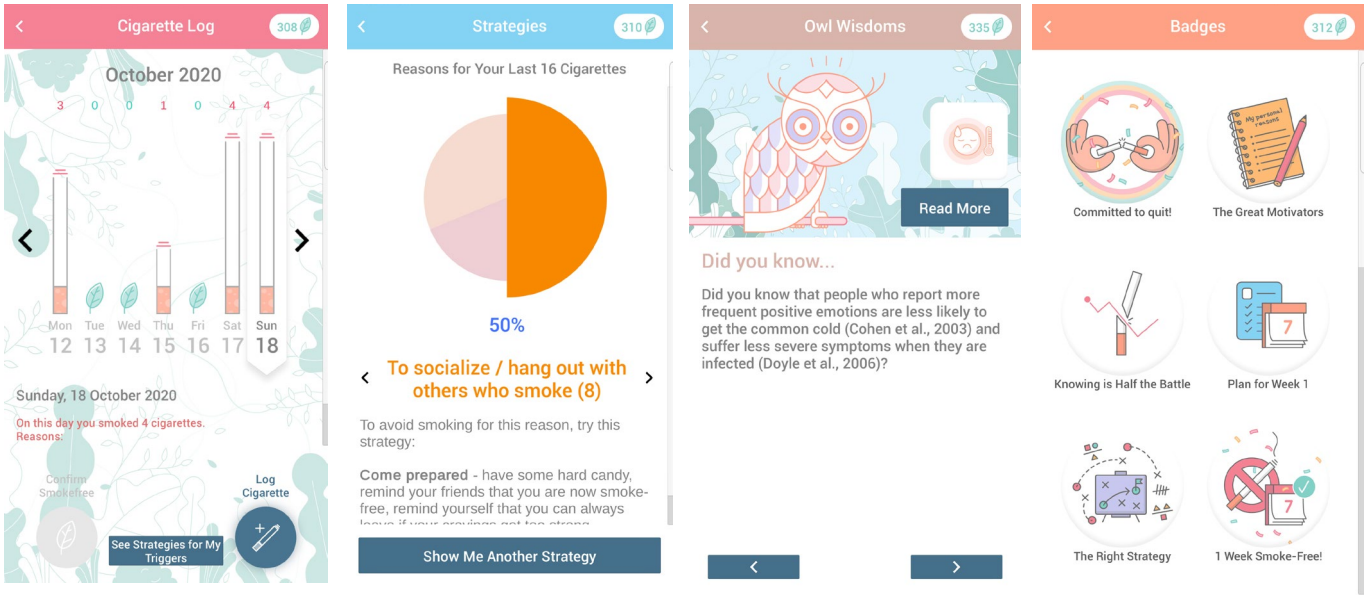
Participants randomized to the treatment condition will be asked to use Version 3 of our "Smiling Instead of Smoking" (SiS) smartphone app for a period of 7 weeks. The SiS app is a smartphone app that engages participants in daily positive psychology habit-building exercises over the course of 7 weeks, as-needed happiness boost activities and 'behavioral challenges' every 2-3 days that are designed to engage participants with *ad libitum* tools offered by the app, which offer tracking functionality (i.e., log of smoked cigarettes), graphical summaries (i.e., pie chart of reason smoked for the past 20 cigarettes), reminders (i.e., a tool to send reminders to stay smoke-free at specific times), note keeping (i.e., personal reasons for quitting), distraction (i.e., a game called "Magma Bear") and information (e.g., benefits of quitting, suggested strategies for specific situations). Along the way, the app also provides participants with information about how positive affect is relevant to quitting smoking and health.



Screenshots from SiS Version 3: (1) a habit-building exercise is assigned, (2) its completion is logged, and (3) science findings are shared to reinforce the value of happiness.

Conceptual Model. Our goal in using a positive psychology approach is two-fold: (1) to foster engagement with the app, which delivers tools and information recommended by United States Clinical Practice Guidelines (USCPG) for smoking cessation[34], and (2) to protect against deficits in positive affect occurring during the quit attempt. Based on previous findings on the role of positive affect in smoking cessation regarding desire to smoke[55], smoking relapse[56], self-efficacy[57], and processing of self-relevant health information[58], and based on the broaden-and-build theory[59], we hypothesize that completing the app's happiness exercises should protect against expected decreases in positive affect, and thereby provide smokers with the benefits associated with positive affect, namely, reduced desire to smoke, increased self-efficacy, and greater cognitive readiness to deal with the challenges of smoking cessation.

The SiS app does not collect identifiable information. It asks app users to click buttons to log when they smoke and for what reasons they smoke, and to enter text in text boxes describing their personal reasons for quitting smoking, the circumstances under which they smoke, and to describe their experiences in response to the happiness exercises (e.g., naming three good things they experienced that day; describing something beautiful they saw that day). It uses push notifications to alert app users to new tasks (e.g., new behavioral challenge), remind them of tasks that still need to be completed (e.g., a happiness exercise that still needs to be done), and to notify them of challenging times (i.e., "Smoke Alarms" that app users scheduled for themselves within the app). These push notifications are optional, and can be toggled off. The onboarding script teaches participants how to toggle them on and off.

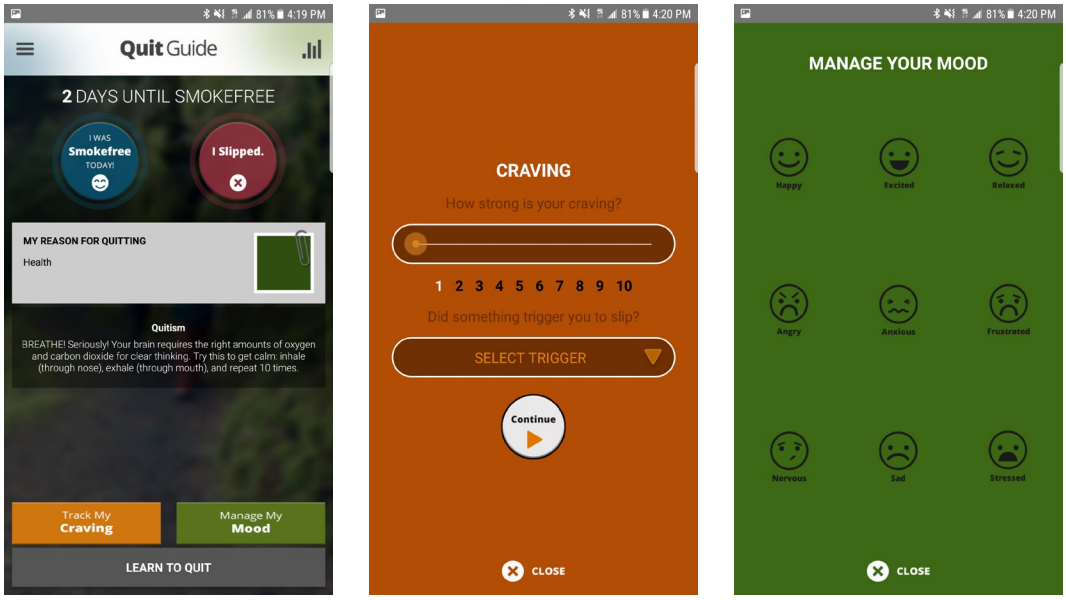


The "Smiling Instead of Smoking" (SiS) smartphone app provides information in graphical format, text, and provides links to outside websites (users need to click "Read More" in the "Owl Wisdoms", and are warned that clicking that link exits the app). App user's progress through quitting is tracked with 'badges'.

<u>Control Condition #1: "QuitGuide" (QG) smartphone app</u>

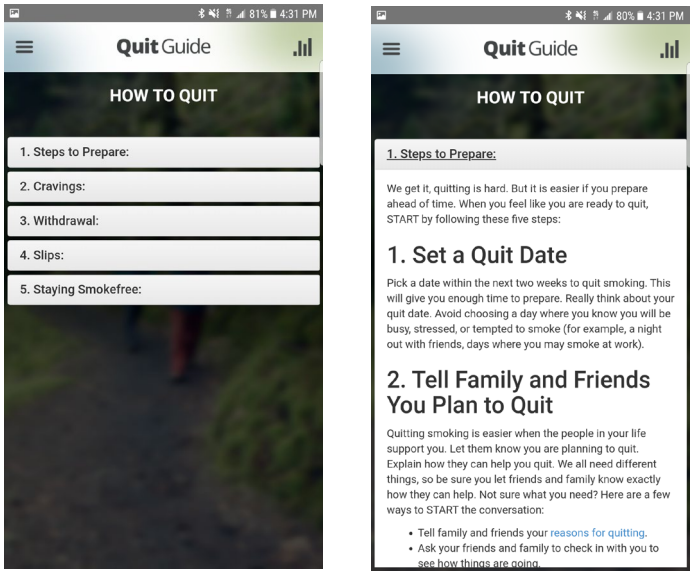
Participants randomized to this control condition will be asked to use the National Cancer Institute's "QuitGuide" (QG) smartphone app for a period of 7 weeks. This smartphone app is one of two smartphone apps the NCI currently has publicly available for use on their smokefree.gov website. Referral to this website is recommended for treating smokers in healthcare settings.[60] QG is frequently used as a comparison app in smartphone app smoking cessation studies.[61-66] While QG was not developed specifically for nondaily smokers, it targets both nondaily and daily smokers (i.e., when downloading the app, users are asked to specify their smoking pattern, which includes both nondaily and daily patterns of smoking). Some SiS features have direct analogs in QG; others do not. The onboarding script leads QG users through the QG content in the same order as for SiS, to the degree possible: setting the quit day (SiS & QG), happiness-promoting activities vs. tracking mood and craving (SiS vs. QG), guidance on quitting (via behavioral challenges in SiS, vs. "Learn to Quit" information in QG), logging cigarettes (SiS & QG), strategies for smoking triggers (pie chart in SiS, various graphs in QG), setting reminders (time-based in SiS, time and location based in QG), and as-needed tools (happiness-boost activities, suggested strategies in SiS vs. tips in response to reporting craving or negative affect in QG).

The QG app does not collect identifiable information. Upon install, the app asks app users to click buttons and to use sliders to describe their smoking (e.g., typically number of cigarettes smoked per day) and craving pattern (e.g., time of day of strongest craving). Going forward, it uses buttons to allow users to describe their craving and mood any time as they are engaging in their quit attempt.



The QuitGuide (QG) smartphone app asks app users to track their craving and mood as they quit smoking. In response to their reports, they receive tips and tricks for dealing with these triggers.

The QG app also contains a "Learn to Quit" guide, which largely mimics the information provided in the NCI's booklet "Clearing the Air".



The QuitGuide (QG) smartphone app provides information in line with the information contained in the NCI booklet "Clearing the Air".

The QG app also allows text entry so participants can name their personal reasons for quitting smoking, and so they can journal in response to craving or mood triggers. The content of these textboxes is saved on the client but not the server side of this app, so that app users can see their typed in text (e.g., personal reason for quitting smoking), but the National Cancer Institute's Smokefree Team does not have a record of this text.

Control Condition #2: Treatment as Usual (TAU)

Participants in the treatment as usual (TAU) condition will be asked to make a naturalistic quit attempt, using any methods they feel might help them. To time-match the onboarding experience of SiS and QG participants, study staff will use an onboarding script to lead TAU participants through the NCI booklet "Clearing the Air",[67] which encourages activities in the same order as implemented in the SiS behavioral challenges (i.e., reflecting on reasons to quit, informing about benefits of quitting, logging smoking and its triggers, formulating strategies for dealing with triggers). Additionally, "Clearing the Air" provides information on smoking cessation support resources, such counseling and pharmacological approaches.

At the end of treatment, participants complete an online survey via REDCap. This is our primary study endpoint (see Specific Aims). Participants complete two more online surveys via REDCap, occurring 12 and 24 weeks post-quit, for secondary aims.

Table 1 specifies which data are collected at which time points. Please see attached for specific descriptions of each of these measures.

Table 1. Data Collection Instruments per Time Point

Type of Measure	**Timing of Assessment**				
Specific Measure	**BL**	**Wk 2**	**Wk 6**	**Wk 12**	**Wk 24**
Primary Outcome					
Smoking Self-Efficacy Questionnaire (SEQ-12)	X	X	X	X	X
Secondary outcomes					
Smoking status	X	X	X	X	X
Recent cigarette use	X	X	X	X	X
Client Satisfaction Questionnaire (CSQ-8)			X		
Time spent applying content			X	X	X
Use of smoking cessation strategies			X		
Perceived impact of SiS/QG/TAU on quitting			X		
Appreciation Scale (AS)			X		
(SiS/QG only) Actual app usage - continuously recorded	X	X	X	X	X
(SiS/QG only) Self-reported app usage: weeks -1 to 2		X			
(SiS/QG only) Self-reported app usage: weeks 3 to 6			X		
(SiS/QG only) App likeability & satisfaction			X		
(SiS/QG only) System Usability Scale (SUS)			X		
Other outcomes to be explored in mediational analyses					
Emotional well-being					
PANAS Positive And Negative Affect Schedule (PANAS)	X	X	X	X	X
Happiness single-item measures	X	X	X	X	X
Satisfaction With Life Scale (SWLS)	X	X	X	X	X
Subjective Happiness Scale (SHS)	X	X	X	X	X
Perceived Stress Scale (PSS10)	X	X	X	X	X
Desire to smoke					
Brief Questionnaire of Smoking Urges (QSU)	X	X	X	X	X
Thought action repertoire					
Modified Twenty Statement Test (mTST) - Baseline	X				
Modified Twenty Statement Test (mTST) - Follow-up		X	X	X	X
Processing of self-relevant health information					
Attitudes Towards Smoking (ATS)	X	X	X	X	X

Decisional Balance Inventory For Smoking (DCB-short)	X	X	X	X	X
Single-item pros and cons measures	X	X	X	X	X
Commitment To Quitting Smoking Scale (CQSS)	X	X	X	X	X
Single-item motivation measure	X	X	X	X	X
Descriptors					
Demographics	X				
Mental health diagnoses	X				
Smoking history	X				
Fagerström Test for Nicotine Dependence (FTND)	X				
Previous quit attempts	X				
Recent Quit Methods Used		X	X	X	X
E-cigarette use	X	X	X	X	X
Alcohol use	X	X	X	X	X
Smartphone use	X		X		
Center of Epidemiologic Studies Depression Scale (CES-D-10)	X	X	X	X	X
Generalized Anxiety Disorder Screener (GAD-7)	X	X	X	X	X
Snaith-Hamilton Pleasure Scale (SHAPS)	X	X	X	X	X
Life Orientation Test Revised (LOT-R)	X	X	X	X	X
State Optimism Measure (SOM)	X	X	X	X	X
Brief State Optimism Measure (BSOM)	X	X	X	X	X
Generalized Self-efficacy Scale (GSES)	X				
Personality SIMP	X				
Brief COPE	X	X	X	X	X

As noted in Table 1, in addition to outcome variables, we are also collecting descriptive information to describe the participants in this study on constructs relevant to this study:

- Demographics (at baseline, includes age, gender, ethnicity, race, education level, current student status, current employment status, total family/household income, and rurality of current residence)
- Mental health diagnoses (at baseline, "Has a doctor, nurse, or counselor ever told you that you have a mental or psychological condition?" [yes, no]. If participants select "yes," they asked to select all that apply from a list of Axis I and II psychiatric disorders, or to specify "other mental health diagnosis.")
- Smoking history (at baseline, captures estimated number of cigarettes participant smoked in lifetime, age when participant first tried smoking (even one or two puffs), age when participant first smoked an entire cigarette, and whether participant has ever smoked daily)
- Fagerström Test for Nicotine Dependence (FTND),[68] a 6-item questionnaire characterizing level of physiological nicotine dependence. Answer choices are assigned numerical values which can be sum-scored to obtain level of dependence [i.e., very low dependence, low dependence, medium dependence, high dependence, or very high dependence])
- Previous quit attempts (at baseline, captures whether participant has tried to quit smoking before, number of previous quit attempts, and types of quit methods previously used [e.g., group counseling/class, smoking cessation app])
- Recent quit methods used (at follow-up time points, captures any additional quit methods used since participant's quit day [using the same check-box list as seen in Previous Quit Attempts])
- E-cigarette use (at all time points, captures whether participant has ever used electronic cigarettes, whether participant is currently using electronic cigarettes, number of "bouts" of vaping per vaping day, and number of puffs per "bout" of vaping)

- Alcohol use (at all time points, captures whether participant has drunk alcohol in past 30 days, number of drinks per drinking day, number of days in past 30 days having drunk 5+ drinks per drinking occasion [males], number of days in past 30 days having drunk 4+ drinks per drinking occasion [females], number of weeks in past month having drunk 14+ drinks per week [males], number of weeks in past month having drunk 7+ drinks per week [females], and number of drinks per weekday in past week)
- Smartphone Use (5 item questionnaire captures self-reported frequency of smartphone use over the past 30 days, reason for smartphone use, whether push notifications from study app prompts unrelated smartphone use, whether unrelated smartphone use prompts study app use, and location of study app on smartphone)
- Center of Epidemiologic Studies Depression Scale, 10-item version (CES-D-10),[69] designed to assess degree of depressed mood [e.g., "I was bothered by things that usually don't bother me." 4-point Likert: 0 = Rarely or none of the time (less than 1 day), 1 = Some or a little of the time (1-2 days), 2 = Occasionally or a moderate amount of time (3-4 days), 3 = Most of the time (5-7 days)]
- Generalized Anxiety Disorder Screener (GAD-7),[70] a 7-item scale designed as a screening and severity measure for generalized anxiety disorder, "Over the *last 2 weeks*, how often have you been bothered by the following problems?" [e.g., "Feeling nervous, anxious, or on edge." 4-point Likert: 0 = Not at all, 1 = Several days, 2 = More than half the days, 3 = Nearly every day], includes an additional COVID-19 impact question, "Compared to before COVID-19, how have the frequency and severity of these problems changed during the last 2 weeks?" Sliding scale: 0=Much less, 50 = About the same, 100 = Much more")
- Snaith-Hamilton Pleasure Scale (SHAPS),[71] a 14-item scale designed to measure the ability to experience pleasure [e.g., "I would enjoy my favorite television or radio program." 4-point Likert: 1 = Strongly disagree, 2 = Disagree, 3 = Agree, 4 = Strongly agree])
- Life Orientation Test Revised (LOT-R),[72] a standard psychological tool for measuring optimism consisting of 10 items [e.g., "In uncertain times, I usually expect the best." 5-point Likert: 1 = I disagree a lot, 2 = I disagree a little, 3 = I neither agree nor disagree, 4 = I agree a little, 5 = I agree a lot])
- State Optimism Measure (SOM),[73] a 7-item scale capturing in-the-moment optimism [e.g., "I am feeling optimistic about life's challenges." 5-point Likert: 1 = Strongly disagree, 2 = Disagree, 3 = Neither agree nor disagree, 4 = Agree, 5 = Strongly agree)
- Brief State Optimism Measure (BSOM), a two-item questionnaire capturing in-the-moment optimism in regards to longer-term events [e.g., "In thinking about the challenges in my life, I feel RIGHT NOW that ultimately:" Sliding scale: 0 = Things will get a lot worse, 50 = Things will stay the same, 100 = Things will get a lot better])
- General Self-Efficacy Scale[74], a 10-item scale measuring self-efficacy [e.g., "I can always manage to solve difficult problems if I try hard enough." 4-point Likert: 1 = Not at all true, 2 = Hardly true, 3 = Moderately true, 4 = Exactly true])
- Single-Item Measures of Personality,[75] which consists of five single-item measures with bipolar response scales to measure the Big Five personality traits [e.g., "Generally, I come across as…" with a bipolar response scale between 1 and 9, anchors vary per question])
- Brief COPE,[76] a 28-item scale designed to measure methods of coping with stress [e.g., "I've been getting emotional support from others." 4-point Likert: 1 = I haven't been doing this at all, 2 = I've been doing this a little bit, 3 = I've been doing this a medium amount, 4 = I've been doing this a lot])

Participants will be remunerated according to the following remuneration schedule:

Table 2. Remuneration Schedule

Time Point	Survey*
Baseline & Screening	$25
2-week	$25
6-week	$50
3-month	$25
6-month	$25
$150 per participant * $10 for a survey with missed check items	

Payment will be paid by check, where participants will receive a total of five checks, corresponding to the five study assessments occurring at screening, 2-week, 6-week, 3-month and 6-month follow-up. Participants will receive $25 for each completed online survey, unless they fail to answer 100% of the randomly placed reading alertness check items correctly (e.g.: “Please answer "not at all confident”.”), in which case they receive $10 for a given survey. (Correctly answering all check items is a screening criterion, which is explained to participants during the screening phone call). At the primary endpoint, the 6-week assessment, participants receive an additional $25 for the survey, because this survey is longer than the other surveys.

Risks are expected to be minimal, and include breach of confidentiality, subject discomfort from answering questions about smoking, and discomfort from quitting smoking. We will minimize these risks by safeguarding electronic data capture by using HIPAA-compliant electronic data capture processes, assuring participants that they do not need to answer any questions they do not want to answer, and by providing information on how to manage smoking cessation.

A subject will be removed from the study if he or she no longer wishes to participate for any reason. A subject may also be removed from the study by the PI, if the participant cannot comply with study procedures (e.g., responds incorrectly to survey check items, cannot install the app on his/her smartphone) or causes undue distress to study staff (e.g., becomes belligerent towards study staff).

VI. BIOSTATISTICAL ANALYSIS

Statistical Power. This is a proof-of-concept trial. Therefore, our primary endpoint is a process variable, a shorter-term variable that is linked to subsequent change on the outcome of ultimate interest. In this case, ultimately, the SiS app is hoped to have an effect on smoking cessation 6 months after the chosen quit day. Typically, effect sizes for mHealth interventions for smoking cessation are very small; their public health importance lies in their potential reach, where a small effect in a large population can make a considerable impact on public health. Specifically, for interventions delivered via websites, meta-analyses have reported an overall odds ratio for point prevalence abstinence of 1.14 [1.07-1.22], and Cohen’s d=0.12.[77,78] For text messaging, a Cochrane review estimated a relative risk of 1.54 [1.19-2.00] in favor of automated text messaging interventions compared to minimal smoking cessation support.[79] Such effect sizes require large scale RCTs, which is beyond the scope of this proof-of-concept RCT. Thus, as a process indicator of subsequent smoking cessation, we have selected self-efficacy to abstain from smoking as our primary outcome variable, because self-efficacy has been identified as the primary mediator by which a text-messaging intervention conferred smoking cessation benefit. Similar to our study, this trial used the “Clearing the Air” booklet as the control condition, and

showed that self-efficacy observed one month after the chosen quit day mediated group differences in smoking cessation at the 6-month follow-up.[80]

In selecting the sample size for this proof-of-concept trial, we were guided by the effect observed in that text-messaging trial. Namely, in the text-messaging study,[80] the observed group difference between treatment and control at 1 month post quit day on self-efficacy was d=0.66. Thus, we conservatively powered our proof-of-concept RCT to detect an effect size of d=0.50. Using SAS PROC POWER, we calculated that we would need a sample size of n=64 per group to detect an effect of d≥0.50. Assuming a retention rate of 85%, we would need to enroll n=75 per group in order to retain n=64 by end of treatment. Thus, the total number of participants to be enrolled into this trial is n=225 (3 randomized groups * 75 participants to be enrolled in each group = 225).

Analytic Plan. All successfully enrolled participants (i.e., passed the screening process, was successfully onboarded to the assigned smoking cessation materials) will be included in the outcome analyses. For hypotheses only relevant to the SiS and QG conditions (marked in Specific Aims), only participants successfully onboarded to those conditions will be included in the analyses.

1. Primary Outcome (Aim 1). In this proof-of-concept RCT, the primary outcome is self-efficacy to abstain from smoking, as measured by the SEQ-12. The primary endpoint is end-of-treatment, which occurs 6 weeks after the originally chosen quit day. To test for differences between randomized groups, we will fit a fixed effects repeated measures model using PROC MIXED, where observations are modeled as nested within persons. Predictors included in the model will be GROUP (i.e., SiS vs. QG vs. TAU), TIME (i.e., BL, Week 2, Week 6, Week 12 and Week 24), and the GROUP*TIME interaction effect. A contrast statement will be used to derive the test statistic for the GROUP comparison at Week 6, our primary endpoint, given the overall longitudinal model. This contrast statement will test the null hypothesis that SiS = QG = TAU. If this null hypothesis is rejected ($p<0.05$), we will conduct pair-wise follow-up tests that compare the three possible pairwise comparisons (i.e., SiS vs. QG, SiS vs. TAU, and QG vs. TAU).

2. Secondary Outcomes (Aim 2). The secondary outcomes in this proof-of-concept RCT are exploratory. Thus, we will not correct for multiple testing. We will fit one model per secondary outcome, using an alpha of 0.05 for all analyses.

    2.1. To test for differences between randomized groups for outcomes that are assessed multiple times (Aims 2a, 2b), our overall modeling approach will be the same as for Aim 1. That is, for each outcome, we will fit a fixed effects repeated measures model, where observations are modeled as nested within persons. Predictors included in the model will be GROUP, TIME, and the GROUP*TIME interaction effect. However, for these secondary outcomes, the definitions of the TIME effect varies across these secondary outcomes, based on their assessment schedule. The distribution of the outcome variables also varies across these variables. Thus, we will implement this overall modeling approach for these variables as follows:

        2.1.1. (Aim 2a) Self-reported 30-day point-prevalence abstinence: the dependent variable will be a binary outcome variable (1=self-reported abstinence for 30 days, 0=not), which will be modeled over three timepoints (i.e., 6, 12 and 24 weeks post quit) using PROC GENMOD, where a binomial distribution with logit link function will be specified. The GROUP effect will include all three groups (SiS vs. QG vs.

TAU), as this outcome will be assessed in all randomized groups. Contrast statements will be used to derive the test statistics for the GROUP comparisons at Weeks 6, 12 and 24, given the overall longitudinal model. These contrast statements will test the null hypothesis that SiS = QG = TAU at the tested timepoints (i.e., Weeks 6, 12 and 24). If this null hypothesis is rejected ($p<0.05$), we will conduct pair-wise follow-up tests that compare the three possible pairwise comparisons (i.e., SiS vs. QG, SiS vs. TAU, and QG vs. TAU).

2.1.2. (Aim 2b) Self-reported past week cigarette reduction: first, we will calculate reductions in cigarette consumption by subtracting the number of cigarettes smoked in the week leading up to the baseline assessment, as measured in the baseline survey, from the number of cigarettes smoked in the week leading up to the 2, 6, 12, and 24 week assessments, as assessed in these respective surveys. The resulting change score will be the dependent variable in the fixed effects repeated measures model, which will be modeled over four timepoints (i.e., 2, 6, 12 and 24 weeks post quit). We anticipate that this dependent variable will be normally distributed, but will also consider other possible distributions (e.g., Poisson). If normally distributed, this model will be fit in SAS using the PROC MIXED procedure. Contrast statements will be used to derive the test statistics for the GROUP comparisons at Weeks 2, 6, 12 and 24, given the overall longitudinal model. These contrast statements will test the null hypothesis that SiS = QG = TAU at the tested timepoints (i.e., Weeks 2, 6, 12 and 24). If this null hypothesis is rejected ($p<0.05$), we will conduct pair-wise follow-up tests that compare the three possible pairwise comparisons (i.e., SiS vs. QG, SiS vs. TAU, and QG vs. TAU).

2.2. To test for differences between randomized groups for outcomes that are only assessed at end of treatment (Aims 2c – 2l), for each outcome, we will use a fixed effects model, where GROUP is the only predictor, and score at end of treatment is the dependent variable. Histograms will be used to guide selection of the most appropriate distribution. We anticipate that we will use the normal distribution for the CSQ-8 (Aim 2c), use of strategies (Aim 2e), perceived impact (Aim 2f), the AS (Aim 2g), actual app usage (Aim 2h), self-reported app usage (Aim 2i), likeability of the app (Aim 2j), satisfaction with the app (Aim 2k), and the SUS (Aim 2l), as implemented via the PROC MIXED procedure in SAS. We anticipate that we will use the Poisson distribution for time spent applying content (Aim 2d), as implemented via the PROC GENMOD procedure in SAS. If the GROUP effect is statistically significant ($p<0.05$), we will conduct pair-wise follow-up tests that compare the three possible pairwise comparisons (i.e., SiS vs. QG, SiS vs. TAU, and QG vs. TAU). These follow-up analyses will not be necessary for secondary outcomes that are only assessed for the SiS and QG conditions (i.e., Aims 2j-2l).

3. Exploratory mediational models (Aim 3): We will use mediational modeling, using the product-of-coefficients approach[81,82] and a fully lagged model[83] to test if hypothesized within-person changes (see Figure 1) occur, and if they are linked to subsequent abstinence. The independent variable will be randomized group assignment (i.e., SiS vs. TAU), and the outcome variable will be self-reported 30-day point prevalence abstinence as measured at 6-month follow-up). The mediators will be our theorized mechanisms of change, as listed in the Aim 3 (i.e., self-efficacy, emotional well-being, desire to smoke, breadth of thought-action-repertoire, processing of processing of self-relevant health information,). Baseline values on these constructs will be included in the model to control for individual differences

on these measures. The mediator will be scale scores observed at mid-treatment, at the 2-week assessment, which marks the end of the cessation phase.[84] We will use multiple mediation to determine the relative importance of each mechanism, and moderated multiple mediation to identify differences in mechanisms across subgroups (e.g., males vs. females, young adult vs. older adults), similarly to our approach in delineating mechanisms of behavior change in Alcoholics Anonymous.[85-87]

VII. RISKS AND DISCOMFORTS

Potential Risks: Participation will last 6 months, where surveys will be administered at enrollment, 2-week, 6-week, 3-month, and 6-month follow-up. Participants will use the provided smoking cessation support materials for a strongly encouraged period of 7 weeks (1 week before, 6 weeks following the quit attempt), and optional continued use thereafter. As such, the potential risks in the study are considered minimal and include (1) potential discomfort related to completing questionnaires about potentially sensitive information such as smoking, (2) potential breach of confidentiality and/or privacy, and (3) potential discomfort in quitting smoking (i.e., withdrawal symptoms, craving, etc.).

Protection Against Risks: For the possibility of subjective discomfort from answering questions, any distress will be minimized by assuring participants that they can refuse to answer any question that they do not feel comfortable addressing and that they may withdraw from the study at any time without penalty. To protect against breach of confidentiality, we will assign a numeric study ID to each participant, which will be the primary identifier by which this person's progress through the trial will be reviewed. The database linking names and study identification numbers will be kept in REDCap, where staff access to this information can be monitored and is password protected. Only study staff will have access to this database. All staff are or will be fully trained in relevant ethical principles and procedures, including confidentiality. All assessment and treatment procedures will be closely supervised by the PI. All data will be captured electronically. For surveys and data entry by study staff, we will be using Partners implementation of REDCap (Research Electronic Data Capture) https://redcap.partners.org, which is a secure, web-based application designed to support data capture for research studies, and which is fully compliant with HIPAA-Security guidelines. The data generated by using our SiS app (i.e., app usage data) will be kept on secure servers behind a firewall within the MGB network. The app will be hosted by secure ERIS/Partners servers. All data collected through the app will be transmitted using Transport Layer Security (TLS) encryption to prevent eavesdropping and tampering information while it is in the transmission pipeline. All data for all participants will be kept strictly confidential, except as mandated by law. Regarding the potential discomfort in quitting smoking, participants will receive information about how to alleviate cravings as part of their study participation. Given that study participants are nondaily smokers, who regularly abstain from smoking for several days, these discomforts are expected to be minimal.

VIII. POTENTIAL BENEFITS

Potential Benefits: All participants will receive smoking cessation support as part of their study participation. Consequently, participants in this study may quit smoking as a result of their participation, which would have a positive impact on their health. Furthermore, study

participation will provide generalizable knowledge about the process of smoking cessation in nondaily smokers, which can be used to guide the development of further treatments to support smoking cessation in this growing population of smokers.

IX. MONITORING AND QUALITY ASSURANCE

Oversight of internal monitoring of the participants' safety will be conducted by the PI, Dr. B. Hoeppner. Dr. S. Hoeppner will also participate in the development and administration of the plan. The PI will meet weekly with study staff on the project, at which time she will evaluate the progress of the trial, review data quality, recruitment, and study retention, and examine other factors that may affect outcome. She will review the rates of adverse events to determine any changes in participant risk and will consult with Co-I Dr. S. Hoeppner and named consultants on the grant (Drs. Christopher Kahler (Brown University), Dr. Elyse Park (MGH), as necessary. (Consultants will not have access to identifiable information, nor data other than in summary form, as prepared by study staff.) A brief report will be generated annually for the study record and forwarded to Massachusetts General Hospital's Institutional Review Board. The Investigators will be available to meet outside of the weekly meetings, if necessary, due to concerns regarding a particular participant or any problems that may arise for participants. If necessary, they will make appropriate recommendations for changes in protocol. Dr. B. Hoeppner will conduct daily oversight of participant safety.

Any adverse events that are observed and/or reported will be immediately reported to Dr. B. Hoeppner. Adverse event reporting will follow the MGB IRB's guidelines for reporting unanticipated problems, including adverse events. Reports of unanticipated problems and adverse events outlined in this policy that occur during the conduct of the study, after study completion, or after subject withdrawal or completion will be reported by the principal investigator, Dr. B. Hoeppner within 5 working days/7 calendar days of the date she first becomes aware of the problem through Insight/eIRB. SAEs will also be reported in writing to the American Cancer Society. Adverse events will be reported to the Massachusetts General Hospital IRB and the American Cancer Society annually.

The PI will oversee the collection, maintenance, and analysis of all data. During weekly meetings with study staff and co-investigator, the PI will review the accuracy and completeness of the study questionnaires, consent forms, and app data. The study procedures and plans will also be reviewed during these meetings to ensure that they remain in line with the approved protocol.

To protect the privacy of each participant, we will assign a numeric study ID to each participant, which will be the primary identifier by which this person's progress through the trial will be reviewed. The database linking names and study identification numbers will be maintained in REDCap, which is password protected, and where access is limited to study staff, and access to study information is traceable. Only study staff will have access to this database. All staff are or will be fully trained in relevant ethical principles and procedures, including confidentiality. All assessment and treatment procedures will be closely supervised by the PI. All of the data will be captured electronically. For surveys and data entry by study staff, REDCap (Research Electronic Data Capture) will be used, which is a secure, web-based application designed to support data capture for research studies, and which is fully compliant with HIPAA-Security guidelines. The data generated by using our SiS app (i.e., app usage data)

will be kept on secure servers behind a firewall within the Partners network. The app will be hosted by secure ERIS/Partners servers. All data collected through the app will be transmitted using Transport Layer Security (TLS) encryption to prevent eavesdropping and tampering information while it is in the transmission pipeline.

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