

FRED HUTCHINSON CANCER RESEARCH CENTER

Current version: 1/22/2022

Version 1	3/20/2020
Version 2	4/15/2020
Version 3	4/30/2020
Version 4	9/21/2021
Version 5	8/22/2022
Version 6	1/22/2023

Title of Protocol:
Randomized Trial of a Smartphone Application to Help Cancer Patients Stop Smoking (Quit2Heal)

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SPONSOR: NCI, NIH

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PROTOCOL SYNOPSIS

Protocol Title	Randomized Trial of a Smartphone Application to Help Cancer Patients Stop Smoking (Quit2Heal)
Protocol Number	10432, RG1007577
Protocol Sponsor	NCI, NIH
Trial Phase	III
Trial Type	Randomized clinical trial
Study Objectives	To conduct a fully powered randomized controlled trial of Quit2Heal (n = 211) versus QuitGuide (n = 211), in order to determine whether: (1) Quit2Heal has significantly higher biochemically verified 30-day point prevalence smoking cessation at 12 months post-randomization relative to QuitGuide, and (2) Quit2Heal's 12-month smoking cessation outcome is significantly mediated by improvements in cancer-related shame, stigma, depression, anxiety, and knowledge about consequences of smoking vs. quitting after cancer diagnosis.
Study Design	2-arm parallel group randomized trial
Population	422 adult cancer patients who smoke and want to quit
Primary Endpoints	30-day biochemically confirmed cigarette smoking cessation at 12 months after randomization
Secondary Endpoints	30-day biochemically confirmed cigarette smoking cessation at 3 and 6 months after randomization
Investigation Device	Quit2Heal smartphone application
Type of control	Active (QuitGuide smartphone application)
Trial Blinding	Participants and outcome assessors will be blinded
Treatment Groups	Intervention, Control
Treatment Schedule	Participants will have access to the Quit2Heal and QuitGuide apps for their 12 month study participation, and encouraged to use the apps as desired
Assessments	Follow-up assessments at 3, 6, and 12 months
Number of trial subjects	N=422
Estimated duration of trial	42 months
Duration of Participation	12 months

ABBREVIATIONS

App	Smartphone-based software application
RCT	Randomized Clinical Trial
NCCN	National Comprehensive Cancer Network

ACS	American Cancer Society
MSK	Memorial Sloan Kettering
TLS	Transport Layer Security

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1.0 GENERAL INFORMATION

This document is a clinical research protocol and the described study will be conducted in compliance with the IRB approved protocol, associated Federal regulations and all applicable IRB requirements.

Rationale: In the US, 15% to 54% of cancer patients are cigarette smokers at the time of their diagnosis. Unfortunately, up to 80% of smokers with cancer continue to smoke after their diagnosis. Persistent smoking after a cancer diagnosis leads to worse clinical outcomes including decreased treatment effectiveness, increased risk of disease recurrence, increased risk of developing second cancers, and higher mortality rates. The National Comprehensive Cancer Network (NCCN) recommends that every cancer patient who smokes be offered an evidence-based cessation intervention. However, limited access to effective tobacco cessation interventions is a key barrier for promoting cessation in the context of cancer care. Needed now is a method for all smokers with cancer to access effective and low-cost interventions designed to help this special population stop smoking. A smartphone application (“app”) could address the access need by providing a widely available tobacco intervention targeted for cancer patients. Apps have potentially high population level reach to cancer patients—especially given that over three quarters (76%) of all smokers own smartphones. Despite their high potential value, there is no evidence about: (1) the effectiveness of smartphone apps targeted to cancer patients who smoke and (2) why these apps would be effective. Also unexplored is who is most likely to benefit from smartphone apps targeted to cancer patients who smoke. We recently developed the first known smartphone app (called “Quit2Heal”) specifically designed to help cancer patients quit smoking.

Objectives: Building on these knowledge gaps and encouraging results, this application proposes to conduct a fully powered randomized controlled trial of Quit2Heal (n = 211) versus QuitGuide (n = 211), in order to determine whether: (1) Quit2Heal has significantly higher biochemically verified 30-day point prevalence smoking cessation at 12 months post-randomization relative to QuitGuide, and (2) Quit2Heal’s (but not QuitGuide’s) 12-month smoking cessation outcome is significantly mediated by improvements in cancer-related shame, stigma, depression, anxiety, and knowledge about consequences of smoking vs. quitting after cancer diagnosis. The project will also explore whether these baseline factors moderate the cessation outcome: (a) cancer type, (b) stage of cancer, (c) time since diagnosis, (d) demographics, (e) having a partner/spouse who smokes, (f) whether participant was advised to quit by oncologist, and (g) recruitment source. If the aims are achieved, this project will advance scientific knowledge about the effectiveness of apps for helping cancer patients quit smoking. Positive results would provide an effective and highly accessible public health intervention for cancer patients.

Phase: Phase III RCT.

Methods: Randomized controlled trial of Quit2Heal (n = 211) versus QuitGuide (n = 211) with 12-month follow-up.

1.1 Protocol Title

Randomized Trial of a Smartphone Application to Help Cancer Patients Stop Smoking (Quit2Heal)

1.2 Sponsor Information

NCI, NIH

1.3 Investigator Information

Jonathan Bricker, PhD, Full Member, Fred Hutchinson Cancer Research Center

1.4 Consultants for the Study

Consultant	Institutional Affiliation	Expertise
Jesse Dallery, Ph.D.	University of Florida	Remote biochemical confirmation of smoking cessation

2.0 INTRODUCTION TO THE PROTOCOL

2.1 Introduction

2.1.1 Cigarette Smoking in Cancer Patients

Cancer patients who smoke are a significant population in need of cessation intervention. In the US, 15% to 54% of cancer patients are cigarette smokers at the time of their diagnosis [1-4]. Compared to patients who quit smoking after their diagnosis, cancer patients who remain smokers have worse treatment outcomes including: 2 to 4 times higher risk of

nonresponse to radiation [7-9], decreased efficacy and tolerance of chemotherapy [10, 11], and 2 to 3.5 times higher risk of postoperative complications such as necrosis, infections, and fistulas [12]. Regardless of the initial cancer type, patients who continue to smoke after diagnosis have 1.5 to 4 times higher risk of second primary cancers (e.g., oral/pharyngeal, esophageal, stomach, lung) [13, 14]. Finally, the mortality rate among cancer patients who continue smoking is 1.3 to 2.4 times higher across all cancer types [7, 15, 16]. By contrast, quitting smoking after a cancer diagnosis dramatically reduces the risk of poor treatment outcomes [7-12, 31] and of a second primary cancer [13, 14], and it lowers rates of cancer-related mortality [7, 15, 16]. Unfortunately, up to 80% of smokers with cancer continue to smoke after their diagnosis [2, 5, 6]. Moreover, 15-25% of those who do quit after a cancer diagnosis will return to smoking within 12 months [4, 33, 34]. In sum, there is enormous need for efficacious smoking cessation interventions tailored to meet the needs of cancer patients.

2.1.2 Barriers to Cessation Treatments

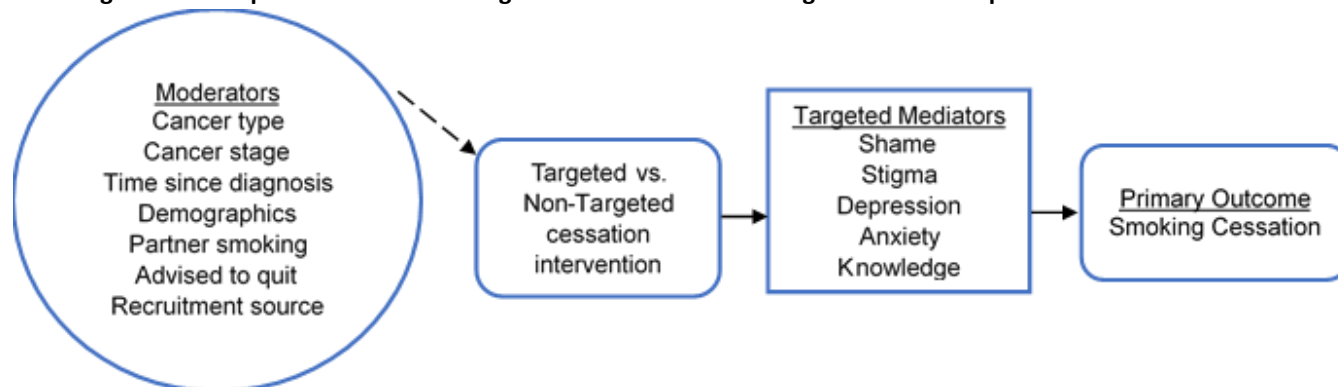
Limited access to effective tobacco cessation interventions is a critical barrier for promoting cessation in the context of cancer care. Only 39% of oncologists routinely provide tobacco cessation treatment to patients or at least refer them to a tobacco treatment program [18]. For example, among 62 National Cancer Institute (NCI)-designated cancer centers surveyed in 2009, only 53% identify patients who use tobacco [19] and only 20% identified have a staff person dedicated to providing tobacco treatment services [19]. Barriers to having access to tobacco treatment include lack of insurance coverage, lack of clinical staff training and time, and lack of systems for universal assessment, referral, and integration of cessation service into routine cancer care [18, 19].

2.1.3 Smartphone Apps for Smoking Cessation

One method for all smokers with cancer to access effective and low-cost smoking cessation treatment is via smartphone-based smoking cessation software applications ("apps") [38-40]. Regarding access, apps require no provider training or reimbursement for smoking cessation, they do not require integration into complex hospital systems (e.g., can be freely accessed on an app store), and they are available anytime at arm's reach, at the convenience of the patient [18, 19]. The reach of smoking cessation apps is climbing rapidly, greatly aided by the growing ownership of smartphones: 81% of US adults own smartphones, 72% for those with high school or less education, 71% for \$30,000 or less income, and 66% for those ages 55-75 [51]. The greatest smartphone ownership growth rate has been among US adults age 55 and over [52]. And there are now over 500 smoking cessation apps available in the US [38]. Cessation apps are downloaded to smartphones in the US about 2 million times per year [53], and they are showing solid promise among the general population of smokers [59]. A four-country trial (N = 684) showed that an app combining teaching quitting options with supportive and motivational messages and a quitting benefits tracker was over two times more effective than an informational cessation app without these features (10.2% quit rate vs. 4.8% quit rate; RR= 2.02; 95% CI: 1.08, 3.81) [60]. Building on the rigor of the prior research on apps for the general population of smokers, a targeted intervention can address unique processes that impede cessation among cancer patients.

2.1.4 Conceptual Model for Smoking Cessation for Cancer Patients

Figure 1. Conceptual model of smoking cessation intervention targeted for cancer patients.



Our conceptual model of a smoking cessation intervention for cancer patients (Figure 1) posits that the intervention can impact cessation through five hypothesized processes: (1) shame about being a cancer patient who smokes, (2) cancer stigma (i.e., feeling socially rejected for causing one's cancer [22]), (3) depression [23, 61], (4) anxiety [23, 24], and (5) lack of knowledge about the consequences of continued smoking vs. quitting following a cancer diagnosis [62-64]. These processes have predicted smoking frequency [22, 24, 61], cessation [22-24], and relapse in cancer patients [23]. They serve as strong barriers to seeking help for smoking cessation [26]. Compared to smokers without cancer, smokers with cancer are more likely to be depressed and have generalized anxiety that can interfere with their willingness to seek cessation

treatment, make quit attempts, and persist at trying to quit smoking [27, 28, 65]. A common fatalistic belief of depressed cancer patients who smoke is “the damage is already done,” which may impede cessation attempts [29]. Most unique to cancer patients who smoke, one study demonstrated that those who reported higher levels of shame and stigma were less likely to engage in a smoking cessation intervention or make efforts to quit smoking. By believing thoughts like “I did this to myself,” cancer patients may be less likely to engage and persist in quitting smoking [66, 67]. Cancer patients who feel shame about being smokers and stigmatized about having cancer are also more likely to misreport their smoking status and avoid seeking support from health care providers [65, 67-70]. They may fear that their physicians will not provide them needed cancer treatment if they remain smokers, so they hide their smoking status [26, 65, 71, 72]. Lack of knowledge about consequences of continued smoking vs. quitting following a cancer diagnosis has predicted a lower likelihood of quitting whereas increases in this knowledge is associated with a higher likelihood of quitting [62-64].

2.2 Preclinical Data

Dr. Bricker obtained philanthropic pilot funding from the CVS Health Foundation to modify his smartphone app for smoking cessation in the general population for cancer patients. After developing the tailored content using provider, patient, and caregiver interviews, empirical studies, user-centered research, and prototype testing, we conducted a diary study to obtain ongoing feedback on users’ interactions with Quit2Heal, its design, and content. We conducted a single arm 7-day diary study of the program with 5 adult smokers currently receiving cancer treatment who had varying levels of technical ability and confidence in quitting smoking. All five participants completed: (1) a 30-minute onboarding session, (2) seven nights of a 10-minute survey with closed and open-ended questions about their experience of the app that day, (3) a 10-minute call on day four to discuss their open-ended impressions of the app so far, and (4) a 45-minute exit interview about their overall experience and the usability of the app. All participants rated the app as highly useful overall, were very satisfied overall, and would recommend the app to other cancer patients who smoke. The only major problem area was they were not clear where to start the app’s program. Our remedies included: (1) adding an introduction with screen shots showing how to begin the program and (2) greying out the sections that come later in the program until they become available. After minor usability concerns were remedied, the final version of Quit2Heal was ready for testing in the pilot RCT.

2.3 Clinical Data to Date

The positive results of the beta testing led us to conduct a two-arm pilot RCT comparing Quit2Heal (n = 29) with NCI’s QuitGuide app (n = 30). The pilot RCT design was very feasible with 92% two-month follow-up.

2.3.1 Quit2Heal Pilot RCT Data

Based on our successful methods for national recruitment of general population smokers [83], we developed targeted Facebook ads for nationally recruiting cancer patients currently in treatment, with ongoing monitoring and adjustment of ads based on recruitment yield. We also recruited from two cancer clinic sites (Fred Hutchinson Cancer Research Center and Memorial Sloan Kettering Cancer Center) and their affiliated clinics. (See C.4.2 for more detail our recruitment methods.) These efforts yielded 774 participants screened, 174 eligible (primarily ineligibility reason was cancer diagnosed more than a year ago or not currently receiving cancer treatment), 94 consented, and 59 randomized (36 from Facebook, 3 from other social media (e.g., Craigslist), 1 from a TV news segment, 19 from cancer care clinics). We used randomly permuted block randomization, stratified by heaviness of smoking index (score > 4 [84]), confidence in being smoke-free >70 (on a 0 to 100 scale), and recruitment method (i.e., clinical vs. social media). The two conditions were balanced at baseline on all measured characteristics (all p-values > .05). Participants were mean age 45.2 (12% age 65 and older, consistent with US population of smokers [85, 86]), 25% male, 22% minority, and 29% high school or less education. The most common primary cancer diagnoses were lung (36%) and breast (17%). The most common stages of cancer were stage 1 (36%) and stage 2 (30%). Regarding smoking characteristics, 51% of the sample had high nicotine dependence (i.e., FTND score ≥ 6 [87]) and 56% smoked more than a half pack of cigarettes per day. The characteristics of this sample are very similar to those of other digital health intervention trials [88-90]. To maximize outcome data completion, we followed our team’s successful protocol [83]: four sequential survey modalities (first Web, followed by phone, mail, and postcard). Participants received \$25 for submitting their responses, and received an additional \$10 bonus for completing the Web survey within 24 hours. The achieved outcome survey completion rate of 92% (54/59) provided confidence in the follow-up survey methods. The data retention rate did not differ between study arms (p = .15). Given the pilot budget, cessation data were self-reported. The satisfaction, cessation, and process results were more promising for Quit2Heal than for QuitGuide (Table 1). Compared to QuitGuide participants, Quit2Heal participants: (1) were more satisfied with their assigned app (90% vs. 65%; p = .047), (2) were more likely to report that their assigned app was made for someone like them (86% vs. 62%; p = .04), and (3) opened their app more times during the two-month trial period, although this was not statistically significant [M = 10.0 (SD = 14.40) vs. 6.1 (SD = 5.3); p = .33]. The self-reported 30-day point prevalence quit rate for those who completed the two-month follow-up was 20% for Quit2Heal vs. 7% for QuitGuide (OR = 5.16; 95% CI: 0.71, 37.29; p = .10). Supporting our conceptual model (See Figure 1), from baseline to the two-month follow-up, Quit2Heal participants

showed descriptively greater improvement in internalized shame, cancer stigma, depression, anxiety, and knowledge about consequences of smoking vs. quitting—though none of these changes were significant (all $p > .05$).

Table 1. Quit2Heal RCT primary and secondary outcomes

	Quit Guide		Quit2Heal		<i>p</i> value ^a
	<i>n</i>	Summary	<i>n</i>	Summary	
<i>Utilization, mean (SD)</i>					
Number of times app opened ^c	25	6.1 (5.3)	27	10.0 (14.4)	.33
<i>Participant acceptability, % (n)</i>					
Satisfied overall	26	65% (17)	21	90% (19)	.047
Recommend to friend	28	57% (16)	23	74% (17)	.21
App was made for someone like me	26	62% (16)	21	86% (18)	.04
<i>Smoking outcomes at 2 months, % (n)</i>					
30-day quit rate, complete case	29	7% (2)	25	20% (5)	.10
30-day quit rate, missing=smoking	30	7% (2)	29	17% (5)	.17
<i>Process indicators, mean (SD)</i>					
Change in cancer-related shame	29	0.2 (3.5)	25	-0.5 (4.7)	.27
Change in cancer-related stigma	29	-1.3 (8.8)	24	-3.0 (9.9)	.48
Change in depression score	27	-0.9 (6.5)	24	-3.5 (5.0)	.38
Change in anxiety score	28	0.0 (5.6)	25	-2.8 (6.8)	.56

Building on these promising results, we will conduct a fully-powered two-arm randomized controlled trial comparing Quit2Heal ($n = 211$) to QuitGuide ($n = 211$) with a 12-month follow-up, biochemically-validated main outcome of smoking cessation. We will use randomly permuted block randomization, stratified by heaviness of smoking index (score > 4 [84]), confidence in being smoke-free > 70 (on a 0 to 100 scale), and recruitment method (i.e., clinical vs. social media). Moderators will be measured at baseline, mediators at 3 and 6 months post randomization, and cessation outcomes at 3, 6, and 12 months post randomization.

2.3.2 Study Objectives

Study Objectives: Conduct a randomized controlled trial of Quit2Heal ($n = 211$) versus QuitGuide ($n = 211$), in order to determine whether:

Objective 1. Quit2Heal has significantly higher biochemically verified 30-day point prevalence smoking cessation at 12 months post-randomization relative to QuitGuide.

Objective 2. Quit2Heal's (but not QuitGuide's) 12-month smoking cessation outcome is significantly mediated by improvements in cancer-related shame, stigma, depression, anxiety, and knowledge about consequences of smoking vs. quitting after cancer diagnosis.

Exploratory Objective: Explore whether these baseline factors moderate the cessation outcome: (a) cancer type, (b) stage of cancer, (c) time since diagnosis, (d) demographics, (e) having a partner/spouse who smokes, (f) whether participant was advised to quit by oncologist, and (g) recruitment source.

Impact: If the aims are achieved, this project will advance scientific knowledge about the effectiveness of apps for helping cancer patients quit smoking. Positive results would provide an effective and highly accessible public health intervention for cancer patients.

Sections on Study Agent, Dose Rationale, and Other Agents have been removed as not relevant since this is not a drug trial.

2.4 Risks/Benefits

2.4.1 Potential Risks.

The main risk to participation in this study is breach of confidentiality.

A breach of confidentiality could possibly occur if, for example, an unauthorized person accesses the study's database records, app analytics database, and/or study hard copy records, or if 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, and will have the option to opt out of the trial at any time.

2.4.2 Protection Against Risk

Protection against breach of confidentiality. Our research group uses the following confidentiality procedures: All data records are stored in secured 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.

Once randomized, participants in each treatment group will have access to their assigned intervention application downloaded to their smartphone. Both interventions will be accessed via password-protected login any time after randomization. The analytics databases for both apps (which automatically record their utilization of the app) will be located on a Microsoft Azure server that is integrated into the Center network and is protected by a firewall. The analytics database firewall permits no access to the server at all from outside the Fred Hutch, except through the database server port using a secure, encrypted channel. Each app will inform participants: (1) we are recording their utilization of their assigned app only for research purposes, (2) where their utilization data is stored and how it is transmitted, and (3) the nature of the data encryption.

The study management database will be located on a server integrated into the Center network and protected by a firewall. The study management database firewall similarly permits no access to the server at all from outside the Center, 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 database administrators maintain a rigorous system of backups of the database and web servers.

Study participants will be recruited using a publicly accessible web site running on the Apache web server on a Linux operating system. Internal servers are made available outside the Fred Hutch firewall directly via specific firewall allowances to connect to specific resources. After indicating interest in the study, participants will complete online surveys via HTTPS using Transport Layer Security (TLS). Employment of the TLS protocol will prevent anyone from intercepting data passed between the end user's web browser and the web server. All connections to the enrollment website will be via HTTPS using Transport Layer Security (TLS).

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 ten years for other research studies in which participants enter information about themselves. Surveys are hosted on a Web site running on the Apacheweb server on a Linux operating system. 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 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 via HTTPS using Transport Layer Security (TLS). Employment of the TLS 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. These will include referral to local mental health resources listed on the websites of the American Psychology Association (www.apa.org), Anxiety and Depression Association of America (www.adaa.org), and the Association for

Behavioral and Cognitive Therapies (www.abct.org). Listings of these resources will also be provided on the study recruitment website.

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 both treatment groups provide strategies designed to cope more effectively with symptoms of nicotine withdrawal. Finally, each app in the study provides participants 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. The breach/complaint will be reported to the IRB office, and the participant will be referred to the Fred Hutch IRO Director.

2.4.3 Potential Benefits of the Proposed Research to Research Participants and Others

Successfully assisting cancer patients who smoke to quit would have significant positive benefits to their health. Overall, participants assigned to either of the two interventions have the potential to benefit by quitting smoking and the potential short- and long-term health benefits of quitting during and after cancer treatment. We believe the low risks and non-invasive nature of the proposed research are greatly outweighed by the potential benefits to participants and others.

2.4.4 Knowledge to be Gained

Our Quit2Heal project has potential to develop an effective, resource-sensitive intervention for smoking cessation in cancer patients that overcomes access barriers and can be integrated into routine care. This innovative project will advance scientific knowledge about the effectiveness of apps for helping cancer patients quit smoking, and positive results would provide a highly accessible public health intervention for cancer patients. Given the low and reasonable risks to participants, we believe the potential benefits and knowledge to be gained outweigh the risks.

3.0 OVERVIEW OF CLINICAL TRIAL

3.1 Study Objectives

3.1.1 Primary Objective

- The primary objective is to conduct a randomized controlled trial of Quit2Heal (n = 211) versus QuitGuide (n = 211), in order to determine whether Quit2Heal provides higher quit rates than QuitGuide.

3.1.2 Primary Endpoint

- The primary endpoint is 30-day biochemically confirmed cigarette smoking cessation at 12 months after randomization.

3.1.3 Secondary Endpoints

- The first secondary endpoint is 30-day biochemically confirmed cigarette smoking cessation at 3 months after randomization.
- The second secondary endpoint is 30-day biochemically confirmed cigarette smoking cessation at 6 months after randomization.

3.1.4 Secondary Objectives

- One secondary objective is to determine whether Quit2Heal's (but not QuitGuide's) 12-month smoking cessation outcome is significantly mediated by improvements in cancer-related shame, stigma, depression, anxiety, and knowledge about consequences of smoking vs. quitting after cancer diagnosis.
- An additional objective is to explore whether these baseline factors moderate the cessation outcome: (a) cancer type, (b) stage of cancer, (c) time since diagnosis, (d) demographics, (e) having a partner/spouse who smokes, (f) whether participant was advised to quit by oncologist, and (g) recruitment source. Mediators will be assessed by responses to the surveys listed in Appendix B.

3.2 Study Population

We aim to recruit 422 adult male and female cancer patients who smoke and want to quit. Participants will be recruited nationally through social media from Fred Hutch and ACS, and from clinic fliers posted in SCCA and mailed to eligible MSK patients by study staff at MSK.

Inclusion of Women & Minorities. Women and minorities will be recruited. Recruitment and eligibility screening methods are designed to achieve a broad representation of adult smokers that is 70% female and 30% minority race/ethnicity. If there is not adequate recruitment of minorities or women into the study, targeted recruitment strategies will be taken to improve recruitment (e.g., specifying on advertisements).

3.3 Study Design

We will conduct a fully-powered two-arm parallel randomized controlled trial comparing Quit2Heal to QuitGuide. We will use randomly permuted block randomization, stratified by heaviness of smoking index (score > 4 [84]), confidence in being smoke-free >70 (on a 0 to 100 scale), and recruitment method (i.e., clinical vs. social media). Moderators will be measured at baseline, mediators at 3 and 6 months post randomization, and cessation outcomes at 3, 6, and 12 months post randomization.

3.3.1 Primary Endpoint

The primary endpoint is 30-day biochemically confirmed cigarette smoking cessation at 12 months after randomization.

3.3.2 Secondary Endpoint

Secondary endpoints are 30-day biochemically confirmed cigarette smoking cessation at 3 and 6 months after randomization.

3.4 Estimated Accrual: 422 participants

3.5 Name of Sponsor/Funding Source: NCI, NIH R01CA253975

4.0 SAFETY CONSIDERATIONS

4.1 Stopping Rules

4.1.1 Stopping Rules for the Individual Participant

We have an established protocol in place with a referral policy for the clinical management of these participants with active suicidal/homicidal ideation. If patients contact the study email or use the 'Ask Nancy' Quit2Heal intervention app feature and report suicidal/homicidal ideation, study staff will immediately notify Dr. Bricker, who will contact the patients within 24 hours. He is acquainted with appropriate referral facilities and processes of identifying treatment available throughout the United States. These will include referral to local mental health resources listed on the websites of the American Psychology Association (www.apa.org), Anxiety and Depression Association of America (www.adaa.org), and the Association for Behavioral and Cognitive Therapies (www.abct.org).

4.1.2 Stopping Rules for the Specific Study

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

Outside of the IRB or CTO's suspension decisions, there are no formal stopping rules including statistical and administrative procedures for early termination, because this is a remote, digital intervention for behavior change. Including such rules in this type of trial would yield a study that was inconclusive about the risks versus benefits of the treatments.

5.0 SUBJECT ELIGIBILITY

5.1 Inclusion Criteria

5.1.1 Demographic Criteria

- (1) age 18 or older;

5.1.2 Cancer-Related Criteria

- (2) diagnosed with cancer within the past 24 months or currently receiving or planning to receive cancer treatment in the next 3 months;

5.1.3 Smoking Criteria

- (3) smoked a cigarette (even a puff) in the past 30 days;
- (4) interested in learning skills to quit smoking;

5.1.4 Treatment Accessibility Criteria

- (5) willing to be randomly assigned to either smartphone application;
- (6) live in the United States and will remain in the US for the next 12 months;
- (7) have at least daily access to their own smartphone;
- (8) know how to download a smartphone application;
- (9) be willing and able to read English;

5.1.5 Other Criteria

- (10) not currently (i.e., within past 30 days) using other smoking cessation interventions;
- (11) have never participated in our prior research trials;
- (12) have never used the NCI's QuitGuide app;
- (13) being willing to complete a follow-up survey at 3, 6, and 12 months post-randomization;
- (14) providing email, phone number(s), and mailing address.

5.2 Exclusion Criteria

- (1) currently (i.e., within past 30 days) using other smoking cessation interventions;
- (2) has participated in our prior research trials;
- (3) has used the NCI's QuitGuide app;
- (4) not willing to complete a follow-up survey at 3, 6, and 12 months post-randomization;
- (5) not providing email, phone number(s), and mailing address.

Participants not eligible for the study will be given the smokefree.gov website and 800-QUIT-NOW to reach their state's quitline.

6.0 SUBJECT REGISTRATION

For this trial, we will follow the Quit2Heal pilot RCT registration process, which was based on our successful WebQuit R01 protocol [83]. We will use our recruitment website to provide information about the study, FAQs, a brief video describing the study, information about the study team and Fred Hutchinson Cancer Research Center (Fred Hutch), and a secured portal to the informed consent form, screening survey, baseline survey, and to enroll into the trial. Participants will be referred to the recruitment website through nationwide social media (primarily Facebook Ads) and two US cancer centers (Memorial Sloan Kettering, Seattle Cancer Care Alliance/Fred Hutch, and their affiliated clinics). In smoking cessation RCTs we have conducted since 2010, and in the Quit2Heal pilot RCT of cancer patients, we have successfully recruited study participants via Facebook Ads and other social media ads. Collaborating with the Fred Hutch Communications Department, we will design social media ads (e.g., Facebook Ads) for referring potential participants to the recruitment website. Recruitment from the two cancer centers will be via their clinic fliers, brochures, waiting room television screen ticker-tape messages, and emailing the study flyer to their current cancer patients who smoke (identified through the Electronic Medical Record). In 2018, there were 5,569 patients identified as current smokers receiving cancer treatment at Memorial Sloan Kettering, and 2,145 patients at Seattle Cancer Care Alliance/Fred Hutch. To help meet our recruitment target (N = 422; 211 per arm), the American Cancer Society (ACS) will assist with national recruitment by: (1) posting on the ACS's cancer.org website's smoking cessation page, which had 1,911,000 page views in 2018, a notice about the study along with a link to the recruitment website, (2) posting on the ACS's Facebook page (1,176,000 followers) a

weekly notice about the study along with a link to the recruitment website, (3) an ACS press release about the study (including a link to recruitment website).

We will use our successful multi-pronged strategy to recruit at least 30% minorities (the Quit2Heal pilot RCT had 22% minority): (1) Targeted ads and website content: we will use culturally-relevant online ads and enrollment website content targeted to minority smokers; (2) Minority-specific news media: we will reach out to minority-specific newswire and media services to publicize the study; and (3) Limit non-minority recruitment: we will program the recruitment website to limit non-minority recruitment to 70%. We will use a very similar multi-pronged strategy to recruit at least 30% men (the Quit2Heal pilot RCT had 25% men) and 12% age 65 and over (as consistent with 12% of all US adult smokers being age 65 years and older; the Quit2Heal pilot RCT had 12% age 65 and over).

We will use the registration protocol from the Quit2Heal pilot RCT, which was based on our prior eHealth intervention protocols. Specifically, those who screen eligible in the recruitment website and provide their email address will be instantly sent 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. To deter fraud, we will use (1) CAPTCHA authentication, (2) IP addresses that were previously used or suspicious will cause ineligibility, and (3) research staff will call participants if survey response times, email, or preferred communication method appear suspicious. Those not completing the online enrollment process within 14 days will be sent a follow-up email notifying them that they were not enrolled and provide both the Smokefree.gov website and the 800-QUIT-NOW phone number. Those completing the enrollment process and randomized will be emailed a secured link with instructions to download their randomly assigned app (either Quit2Heal or QuitGuide).

Feasibility of data collection: all of these methods have proven feasible in our published trials [83] and in our pilot trials, including the Quit2Heal pilot trial described in section 2.3 Clinical Data to date.

7.0 TREATMENT PLAN

The treatments in this study are remote digital interventions, delivered on smartphones (i.e., the terms “inpatient” and “outpatient” do not apply here.) Additionally, descriptions will not include in-patient administrations drug-specific specifications (e.g., toxicities, prophylaxis, interactions, etc.) Specifically, participants will be randomized to either the Quit2Heal app intervention or the QuitGuide app intervention.

7.1 Intervention Overview

Quit2Heal smartphone app intervention: Quit2Heal is a behavioral intervention specifically designed to help cancer patients stop smoking by providing skills to cope with cancer-related shame, stigma, depression, anxiety, and cancer-specific health consequences of continued smoking vs. quitting. Users first set up a personalized quit plan that includes NCCN recommendations for FDA-approved cessation medications, their proper use, side effects, and safety [17], and how to obtain them on their own. Users can then go to the home screen where they can progress through all levels of the behavioral intervention content, receive on-demand help in coping with smoking urges, and track their daily smoking behaviors. The program is self-paced, and content is unlocked in a sequential manner. For the first five levels, the content and exercises are designed to prepare the users for their chosen quit day and exercises are unlocked immediately after the prior exercise is completed. A tobacco treatment guide navigates the user through the app and teaches skills for coping with cancer-related depression, anxiety, shame, stigma, and common triggers to smoke (e.g., being around other smokers). The last four levels contain content and exercises designed to help the user stay smoke-free after their quit date, and each level corresponds to seven days of being smoke-free. Therefore, within each level, exercises are unlocked immediately after the prior exercise is viewed; however, the next level will not unlock until users record seven consecutive smoke-free days. These levels contain 25 exercises that focus on coping with cancer-related depression and anxiety, withdrawal symptoms, slips, and potential weight gain, and building a smoke-free life with activities in line with the user’s values. If a participant lapses (e.g., records having smoked a cigarette), the program encourages (but does not require) the participant to set a new quit date and return to first five levels for preparation.

7.2 Control Overview

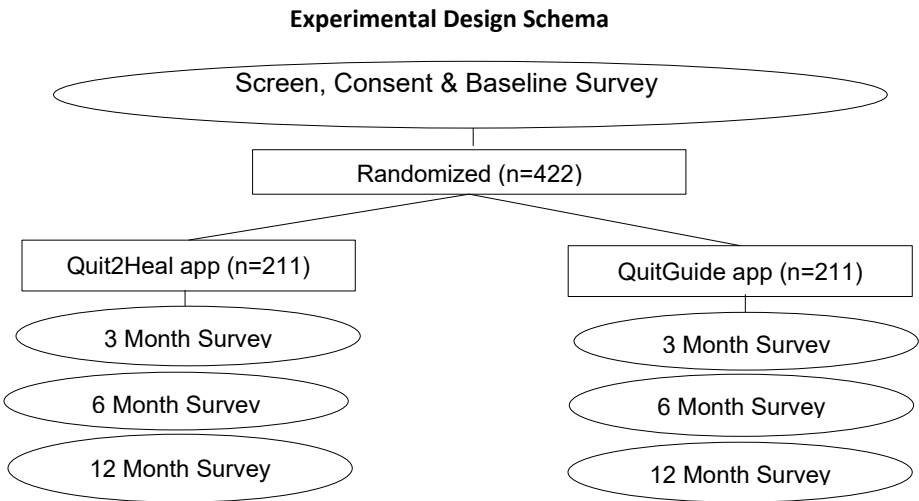
NCI QuitGuide comparison intervention: NCI’s QuitGuide app will be posted on the Google Play and Apple Store in a password-protected private format branded “Quit2Heal” (for blinding). We selected QuitGuide as the comparison because: (1) QuitGuide is a widely available smartphone app—the treatment delivery modality identical to our experimental Quit2Heal arm, and thus avoids confounding treatment content with treatment delivery modality; (2) QuitGuide’s content is based directly on the NCI’s smokefree.gov website, a well-established e-health intervention resource recommended by

NCCN Clinical Practice Guidelines for cancer patient smoking cessation; (3) it is one of the few apps (of over 500 available) that follow the US Clinical Practice Guidelines; and (4) QuitGuide is non-proprietary and free to the public, providing maximal transparency, accessibility, and replicability. Overall, comparison of Quit2Heal with QuitGuide will determine whether Quit2Heal is a scientific and clinical advance over a recommended practice e-health resource for helping cancer patients quit smoking. QuitGuide has four sections of content: (1) “Thinking about quitting”, which focuses on motivations to quit by encouraging users to list reasons for quitting and providing information on the general health consequences of smoking and quitting; (2) “Preparing to Quit”, which helps users develop a customized quit plan, identify smoking behavior, triggers, and reasons for being smoke-free, identify social support for quitting, and education on FDA-approved cessation medications, their proper use, side effects, safety, and how to obtain them on their own; (3) “Quitting”, which teaches skills for coping with cravings to smoke, such as finding replacement behaviors (e.g., chewing on carrot sticks) and staying busy; and (4) “Staying Quit”, which presents tips, motivations, and actions for remaining smoke-free and skills for coping with slips, cravings, and staying positive.

A table comparing the two treatments is included, and screenshots of both treatment apps are in Appendix A.

Table 2. Comparisons between Quit2Heal and QuitGuide.

Content covered in <i>both</i> Quit2Heal & QuitGuide. (All content follows USCPG Guidelines [82])	Content covered <i>only</i> in Quit2Heal: <i>Targeted</i> to Cancer Patients who Smoke
1. Identifying personal motivations to quit smoking. 2. General education on continued smoking vs. quitting. 3. Quit planning, including setting quit date. 4. Seeking general social support for quitting. 5. Education on FDA-approved cessation medications. 6. Identifying triggers for smoking. 7. Teaching skills to cope with cravings and other common triggers. 8. Relapse prevention, including skills to cope with withdrawal and slips.	1. Education on continued smoking vs. quitting for cancer patients. 2. Skills to cope with cancer-related <i>shame</i> . 3. Skills to cope with cancer-related <i>stigma</i> . 4. Skills to cope with cancer-related <i>depression</i> . 5. Skills to cope with cancer-related <i>anxiety</i> .



7.3 Duration of Therapy

During the entire 12-month follow-up period, both smartphone app digital interventions will remain fully available anytime their randomly assigned study participants wish to use them.

7.4 Duration of Follow-Up

We will follow the 3, 6, and 12-month outcome survey data collection protocol we have used in four NIH trials (R01CA166646; R01CA192849; R01DA038411; R21DA030646) and in the Quit2Heal pilot RCT. 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. The online-telephone-mailed sequence protocol is as follows: Day 0: First email invitation with link to secured online version of survey; Days 5 and 9: Second and third email invitation with link to online survey; Days 14 to 21: Eight attempts to complete telephone version of survey (one call per day from a trained surveyor); Day 22: Send a paper version of the survey via US mail. Participants receive \$25 for survey completion. As proven successful in our prior

trials, we will: (1) mail a \$2 pre-incentive letter (noncontingent incentives increase retention) 7 days before the first online survey invitation (i.e., Day -7); (2) provide a \$10 bonus incentive (\$10 + \$25 = \$35) for completing the online survey within 24 hours of the initial email invitation; and (3) send a second copy of the mailed survey 10 days after the first mailing (i.e., Day 29). Based on our recent large RCT comparing two digital interventions, we estimate an 85% overall survey response rate. In that RCT, 92% of those who completed the 12-month outcome survey responded online. We thus expect about 92% of survey completers will do so online and thus minimize survey mode bias.

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.

Feasibility of data collection: all of these methods have proven feasible in our published trials [83] and in our pilot trials, including the Quit2Heal pilot trial described in section 2.3 (Clinical Data to date.) For example, the outcome data collection protocol has obtained 85-90% follow up in our previous studies [83].

Participation is considered ended after completion of the final survey.

8.0 SUBJECT EVALUATION

8.1 On-Study Clinical Evaluations

To assess cancer-related shame, we will use the Cancer-Related Internalized Shame Scale [102]; to assess stigma, the Internalized Stigma subscale of the Lung Cancer Stigma Inventory [22]; to assess depression, the Center for Epidemiological Studies-Depression scale (CES-D) [103]; to assess anxiety, the Generalized Anxiety Disorder 7-item (GAD-7) [104]; and to assess knowledge about consequences of smoking vs. quitting after cancer diagnosis, the Knowledge subscale of the Smoking Knowledge, Attitudes, and Services scale (K-SAS) [136]. These surveys were used in the population of smokers with a cancer for an intervention of smoking cessation [137]. All are psychometrically valid, standardized questionnaires which will be included in the baseline survey, and can be found in Appendix B.

9.0 SUBJECT DISCONTINUATION OF ACTIVE TREATMENT

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

10.0 CONCOMITANT MEDICATIONS

In the three follow-up assessments, participants will be asked about their use of FDA-approved quit-smoking medications [nicotine patch, nicotine gum, nicotine lozenge, nicotine nasal spray, nicotine inhaler, Chantix (varenicline), or Wellbutrin (Zyban/bupropion)]. Information about these medications is provided in both the Quit2Heal and QuitGuide app interventions, and use of these medications during the screening phase and during the study is permitted. Use of SSRIs during the screening phase and during the study is permitted.

11.0 ADVERSE EVENTS

11.1 Adverse Event

According to ICH guidelines (Federal Register. 1997; 62(90):25691-25709) and 21 CFR 312.32, IND Safety Reports, and ICH E2A, Definitions and Standards for Expedited Reporting, an adverse event is defined as follows:

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Abnormal laboratory values for laboratory parameters specified in the study should not be recorded as an adverse event unless an intervention is required (repeat testing to confirm the abnormality is not considered intervention), the laboratory

abnormality results in a serious adverse event or the adverse event results in study termination or interruption/discontinuation of study treatment.

Medical conditions present at screening (i.e., before the study treatment is administered) are not adverse events and should not be recorded on adverse event pages of the CRFs. These medical conditions should be adequately documented on the subject chart. However, medical conditions present at baseline that worsen in intensity or frequency during the treatment or post-treatment periods should be reported and recorded as adverse events.

For this trial, an example of an unexpected event that is not adverse is a participant who has become very unhappy with trial procedures. Adverse events (AEs) are any untoward occurrence with a trial participant whether or not it can be considered to be related to their smoking cessation intervention (the Quit2Heal or QuitGuide app programs). 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.

11.2 Serious Adverse Event

An adverse event should be classified as an SAE if it meets one of the following criteria:

Fatal	Adverse event results in death.
Life threatening:	The adverse events placed the subject at immediate risk of death. This classification did not apply to an adverse event that hypothetically might cause death if it were more severe.
Hospitalization:	It required or prolonged inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before enrollment in the treatment plan or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization.
Disabling/incapacitating	Resulted in a substantial and permanent disruption of the subject's ability to carry out normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject exposed to the molecule or treatment plan regimen before conception or during pregnancy.
Medically significant:	The adverse event did not meet any of the above criteria, but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above.

11.3 Unexpected Adverse Event

An unexpected adverse event is defined as an event that has a nature or severity, or frequency that is not consistent with the applicable investigator brochure, or the prior medical condition of the subject or other treatment given to the subject. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed and reported in preclinical or clinical studies rather than an experience that has not been anticipated based on the pharmacological properties of the study drug.

11.4 Monitoring and Recording Adverse Events

All AEs will be assessed by the investigator or qualified designee and recorded in the CRFs. The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the adverse event and/or serious adverse event and not described as the individual signs or symptoms. The following information should be recorded:

- Description of the adverse event using concise medical terminology
- Description as to whether or not the adverse event is serious, noting all criteria that apply

- The start date (date of adverse event onset)
- The stop date (date of adverse event resolution)
- The severity (grade) of the adverse event
- A description of the potential relatedness of the adverse event to study drug, a study procedure, or other causality
- The action taken due to the adverse event
- The outcome of the adverse event

11.5 Attribution of an Adverse Event

The Principal Investigator, in consultation with the Co-Investigators and Project Manager, 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 interventions (the Quit2Heal or QuitGuide app programs).
- Not Related – Aes that are doubtfully related or clearly not related to the smoking cessation intervention (the Quit2Heal or QuitGuide app programs).

11.6 Adverse Event Recording Period

Throughout the study, the Principal Investigator, Co-Investigators, 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 PI.

Study staff will be trained, and required, to report all unexpected and adverse events to the PI during the study recruitment, intervention, and follow up periods. 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.

11.7 Adverse Event Reporting Requirements

1. SAEs: For Aes 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 sent by the Principal Investigator to the IRO office 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. Aes 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. Ues that do not meet the criteria for Aes: 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.

Classification		Reporting Time	Reporting Action	Contact Information
SAE	Fatal or life-threatening	Within 24 hours of research team* awareness	Email notification to Sponsor's Medical Monitor	<u>Medical Monitor email:</u> tillb@fredhutch.org <u>ISIOC email:</u> ISIOC@fredhutch.org
	All SAEs	Within 2 business days of research team* awareness	Submit completed Institution-Sponsored IND SAE Reporting Form signed by PI or designated sub-Investigator	ISIOC Fax: 206-667-6068 ISIOC email: ISIOC@fredhutch.org
Non-serious AE		Per CRF completion guidelines	Record information on appropriate CRFs	N/A

*Research team is defined as the individuals listed on the delegation of authority log. Physicians listed on the study's delegation of authority log as attending physicians delegated authority to administer informed consent will not be considered part of the research team unless additional responsibilities related to the conduct of the study have been delegated to them by the Principal Investigator.

12.0 DATA AND SAFETY MONITORING PLAN

Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, FHCRC Clinical Research Support (CRS) coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating subjects. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

Data and safety monitoring reports will be reviewed in the course of the trial on a monthly basis by Dr. Bricker. A Data and Safety Monitoring Board will not be required since this is a minimal risk behavioral intervention, but twice a year Dr. Bricker and the Co-Investigators will review the study protocol and study data concerning registration, randomization, retention, compliance, form completion, gender and minority inclusion, intervention effects, safety, protocol violations, adverse events, and any other relevant topics in order to assure participant safety and study integrity. They will also review interim analyses of outcome data to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data. If in-person meetings are not possible, meetings will be held by conference call. More frequent meetings will be convened as necessary.

13.0 DATA MANAGEMENT/CONFIDENTIALITY

The investigator will ensure that data collected conform to all established guidelines. Each subject is assigned a unique subject number to protect subject confidentiality. Subjects will not be referred to by this number, by name, or by any other individual identifier in any publication or external presentation. Subject research files are stored in a secure place (or database). Access is restricted to authorized personnel.

13.1 Source Data

There are 6 sources of survey data for the study: (1) screening survey (2) baseline survey, (3) contact form, (4) 3-month follow-up survey, (5) 6-month follow-up survey, and (6) 12-month follow-up survey. We will also collect automated utilization data from the Quit2Heal app program and NCI QuitGuide program. There are two project databases where this information is stored: 1) the study management database, which includes the recruitment website secure portal, all online surveys, and participant contact and survey data collection from the six sources listed above, and 2) the app analytics database, which includes the automated utilization data collection from the app programs. All data will be collected directly from consenting adult participants. A description of these sources of data follows. The Baseline Survey, hosted on our secured recruitment website, will collect data on (1) cancer information (type of cancer, stage of cancer, time since diagnosis) (2) demographics (age, sex), (3) partner who smokes, (4) advised to quit by oncologist, (5) nicotine and tobacco use, (6) nicotine dependence, (7) cessation pharmacotherapy, (8) readiness to quit, (9) quit attempts, (10) cancer-related shame, (11) cancer stigma, (12) depression, (13) anxiety, (14) knowledge of smoking/quitting consequences, and (15) 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 3-month survey will primarily collect data on mediators (e.g., internalized shame and stigma), cessation progress and outcomes (e.g., 30-day abstinence), and the participant's experiences with their assigned smoking cessation intervention, which will also be collected at 6-months to assess whether the mediator changes were enduring and predictive of the 12-month main outcome. The 12-month survey will primarily collect data on cessation progress and outcomes.

13.1.1 Quit2Heal and QuitGuide apps utilization data and security.

The Quit2Heal and QuitGuide app programs will be accessible to participants when they access the login links sent to them in their secure trial enrollment email. Our secure analytics database on a will collect objective data on engagement with each intervention over the 12-month trial period. As the standard digital intervention engagement metric, the primary engagement measure will be the number of times users interacted with assigned intervention. Secondary measures of engagement will be: (1) number of days from first to last use and (2) unique number of days of user engagement. This information will be extracted over a secure connection and stored on a secure internal Fred Hutch server, 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. The programmers will prepare de-identified utilization data for analysis.

13.1.2 Biochemical verification data and security.

10% of all participants will be selected to complete biochemical verification of smoking cessation at the 3, 6, and 12-month surveys. Study staff will mail each participant an Alere saliva-based smoking cessation verification test in the mail. Participants will take the test and upload photos of themselves taking it and their test results in a secure online survey. Anyone having difficulty with the online version of the test can contact study staff, who will help participants conduct the test and display their results using Doxy.me live video-conferencing website accessible via smartphone, tablet, or desktop computer by clicking on a link emailed to the user or entered directly into a browser. Following training from consultant Dr. Dallery, our staff will: (1) confirm identity by asking to see photo identification, (2) guide participants through each step of the test, (3) observe the participant conduct the test, (4) and observe and record the result. The Doxy.me software is accessible via smartphone, tablet, or desktop computer, does not require participants to set up accounts or download software, enable plugins, or other installations because it works in all popular web browsers. It uses 128-bit encryption, does not record PHI or store data, and is compliant with HIPAA and HITECH requirements. The online version of the biochemical verification has the same security features as our other online surveys: information will be extracted over a secure connection and stored on a secure internal Fred Hutch server, 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. The programmers will prepare de-identified utilization data for analysis.

13.1.3 Participant Compensation

Participants will receive \$25 for completing each of the 3, 6, and 12-month surveys, and offered an additional \$10 for responding to the initial web-based survey within 24 hours. Additionally, we will provide those who self-report 30 days of abstinence at each follow up assessment an additional \$35 for completing the remote biochemical verification. Thus, participants will receive up to \$70 for completing each assessment.

13.2 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.

13.3 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.

13.4 Monitoring Data Quality and Integrity

Several procedures will be used to maintain data integrity. Participants and data collectors will complete all study assessments 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 Apacheweb server on a Linux operating system behind the Fred Hutch firewall. 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 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 via HTTPS using Transport Layer Security (TLS). Employment of the TLS protocol will prevent anyone from intercepting data passed between the end user's web browser and the web server. The data generated by the app programs will be extracted over a secure connection on a weekly basis, and stored on a secure internal Fred Hutch server. A raw copy of the data serves as an additional backup beyond the ongoing built-in Azure storage backup processes. Paper data will be kept in a locked cabinet. 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. All data entry and hand computations will be double-checked. Queries and data reports will be generated on a routine basis to monitor data quality.

14.0 STATISTICAL CONSIDERATIONS

14.1 Study Design

We will enroll 422 adult cancer patients who smoke and want to quit. Participants will be randomly assigned (with 0.5 probability) to (1) the Quit2Heal smartphone app or (2) the QuitGuide smartphone app. We will use randomly permuted block randomization, stratified by heaviness of smoking index (score > 4 [84]), confidence in being smoke-free >70 (on a 0 to 100 scale), and recruitment method (i.e., clinical vs. social media). Moderators will be measured at baseline, mediators at 3 and 6 months post randomization, and cessation outcomes at 3, 6, and 12 months post randomization. Random assignments will be computer-generated after consent.

14.2 Primary/Secondary Endpoints/Hypotheses and Analytical Methods

The primary endpoint will be saliva-based verification of 30-day point prevalence at 12 months post randomization. Secondary endpoints will be 30-day biochemically confirmed point-prevalence at 3 and 6 months post randomization. Consistent with remote digital cessation study methods, biochemical confirmation will be conducted at 3, 6, and 12 months on 10% of participants randomly selected at randomization.

Our primary outcome hypothesis is that Quit2Heal will have significantly higher 30-day point prevalence abstinence at 12 months post-randomization than QuitGuide. For each comparison of treatment arms on the primary and all secondary outcomes, we will use a logistic regression model. Using standard smoking cessation trial intent-to-treat analysis, all missing outcomes will be coded as smokers [42-47]. The model will adjust for all stratification factors as well as baseline factors that are both imbalanced after randomization and significantly related to the outcome. We will conduct these sensitivity analyses: (1) multiple imputation of missing outcomes [121-123], (2) complete case analysis of those providing follow-up data, and (3) adjustment for baseline use of other tobacco and nicotine products. We will also conduct a subgroup analysis of those who used other interventions or cessation medications after study enrollment.

14.3 Additional Efficacy Hypotheses, Outcome Measures, and Statistical Methods

Based on the Conceptual Model in Figure 1 above, we hypothesize that Quit2Heal's (but not QuitGuide's) 12-month smoking cessation outcome will be significantly mediated by improvements in cancer-related shame, cancer stigma, depression, anxiety, and knowledge about consequences of smoking vs. quitting after cancer diagnosis. For each mediator, the model is expressed as three regression equations that relate the main independent variable X (intervention arm), the mediator M (change from baseline to 3-months post randomization in the mediator variable), 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): $\text{logit}(Y) = \gamma_1 + \tau X$, 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): $\text{logit}(Y) = \gamma_3 + \tau' X + \beta M$. 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 [124-126]. For significant mediation effects, we will calculate the proportion of the treatment effect explained by each mediator. Analyses will be repeated wherein the mediator is measured as the change from baseline to 6-months post randomization. Randomization should remove potential confounding effects [125, 127], and if needed, we will adjust each model by covariates that differ at baseline and predict outcome. Following VanderWeele and Preacher methods [128, 129], we will also explore any interactions between mediators and treatment arm. Based on the conceptual model described in Section 2.1.4., the mediators will be assessed using psychometrically valid, published

standardized questionnaires, which are provided in Appendix B and described in section 8.1. These surveys were used in the population of smokers with a cancer for an intervention of smoking cessation [137]. And we will explore whether utilization of assigned app and usage of outside cessation pharmacotherapy mediates cessation outcomes.

Analysis of Sex as a Biological Variable: Consistent with NIH guidelines [130], we will report data by sex, to the consider the potential influence of sex in interpretation of study results. For all analyses described above, we will examine the difference in effect sizes between men and women by incorporating interactions between treatment and sex in a regression model, or by separately analyzing results by sex.

14.4 Exploratory Analysis

Exploratory Objective: We will explore whether these baseline factors moderate the Aim 1 cessation outcome: (a) cancer type (lung/head and neck vs. others), (b) stage of cancer (0-2 vs. 3-4), (c) time since diagnosis (<6 months vs. ≥ 6 months), (d) demographics (e.g., age, sex), (e) having a partner/spouse who smokes, (f) whether participant was advised to quit by oncologist, and (g) recruitment source (clinic vs. social media). For each moderator variable, we will calculate separate logistic regressions that include: the moderator (Z), group assignment (X), an interaction between moderator and group assignment (X*Z), and 30-day abstinence at 12-months post randomization as the outcome (Y). Statistically significant interactions will be assessed with subgroup analyses corresponding to the prediction of Y from X at each value of moderator Z.

14.5 Sample Size and Power

We determined sample size for binomial proportions aimed at 80% power for Primary Aim 1 using the following parameters: (1) randomized to one of the two interventions; (2) conservative 12-month outcome survey response rate of 85%, based on our most recently published large RCT comparing two digital interventions [83]; (3) 80% return rate of CO samples [109, 115]; and (4) two-sided test with $\alpha = .05$. We adjusted all power analyses for expected non-response rates and biochemically-confirmed cessation rates so that outcomes would not be inflated.

Power for Objective 1: Objective 1 will compare 12-month quit rates between Quit2Heal vs. QuitGuide. Projected quit rates at 12-month follow-up were conservatively calculated using (1) quit rates at 2-month follow-up in our pilot RCT, along with (2) well-established relapse curves, which provide a data-derived estimate (i.e., 15-25%) of the rate of decay of intervention effects by 12-month follow-up [4, 33, 34, 91-93]. We estimated a relapse of 20% (between 2 and 12 month-follow-up) and survey response and CO sample return rates of 85% and 80%, respectively. Thus, we expect a 10.9% biochemically confirmed cessation rate at 12 months for Quit2Heal, which corresponds to a 2-month pilot quit rate of 16% (i.e., $16\% * 0.85 \text{ data retention} * 0.80 \text{ CO sample retention} = 10.9\%$). The 12-month quit rate for QuitGuide is conservatively estimated as 3.8%, as consistent with the projected 12-month relapse rates from our pilot RCT and the 4.8% 6-month quit rate from the most rigorous RCT of an app to date [48, 60, 88, 89]. As shown in Table 3, obtaining 80% power to significantly detect a quit rate as low as 10.9% for Quit2Heal (vs. 3.8% for QuitGuide) requires 422 randomized participants, with 211 in each study arm.

Table 3. Objective 1 Sample Size Estimates.

	Projected relapse rate				
	15%	17%	20%	23%	25%
	12-month follow-up 30-day point prevalence quit rate				
Quit2Heal	11.6%	11.3%	10.9%	10.5%	10.2%
QuitGuide	4.0%	3.9%	3.8%	3.6%	3.5%
Total in each arm	195	201	211	215	222
Total randomized	390	402	422	430	444

This very conservatively estimated 10.9% quit rate would have high public health impact—187% higher impact than the projected 3.8% quit rate for QuitGuide. If the quit rates were 10.9% vs. 3.8%, then for every 14 smokers, Quit2Heal would yield one more person who quits as compared to using QuitGuide (number needed to treat [NNT] = 14.1; [132]). When scaled to a population level, the impact is high. For example, for every 100,000 cancer patients who smoke, an additional 7,100 patients would quit smoking by using Quit2Heal vs. QuitGuide.

Power for Objective 2: Statistical power for testing the mediation effect of changes in internalized shame, cancer stigma, depression, and anxiety was estimated based on the following: (1) conservative estimates of the post-treatment standardized effect size for each hypothesized mediator (i.e., a small-medium effect size of $\alpha\beta = 0.07$ [133]); (2) two-sided test with $\alpha = .05$; and (3) 85% follow-up rate for mediator data collection. Conservatively, power calculations do not account for any increased power from covariate adjustment (e.g., stratified randomization factors). The PROCESS analysis method implemented in SAS [121] uses the bootstrap method to estimate the indirect effect, which provides high power

while still maintaining an accurate type-I error rate [134]. Fritz and MacKinnon [135] showed that a sample size of 148 provides 80% power to detect small-medium mediation effects (e.g., $\alpha\beta = 0.07$) when using the bias-corrected bootstrap method. A sample size of 422, with at least 359 expected to report mediation measures at follow-up, will provide high power to detect small-medium mediation effects for each of the four hypothesized mediators.

The last objective is exploratory so no power analysis was conducted.

Power for Sex as a Biological Variable: We will compare quit rates between Quit2Heal and QuitGuide in the male and female subgroups. With 422 participants, and an expected ratio of 70% female:30% male, we expect to randomize 295 females and 127 males. Given these sample sizes, and assuming a 3.8% 12-month quit rate for QuitGuide, the minimum detectable odds ratios with 80% power are 3.71 for females and 6.22 for males. Our reporting of data by sex will provide the research community results for calculating sex differences in the effect sizes of apps for cancer patient smoking cessation in pooled meta-analyses.

14.6 Stopping Rules

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

Outside of the IRB or CTO's suspension decisions, there are no formal stopping rules including statistical and administrative procedures for early termination, because this is a remote, digital intervention for behavior change. Including such rules in this type of trial would yield a study that was inconclusive about the risks versus benefits of the treatments.

14.7 Randomization

We will use computer generated randomly permuted block randomization. Participants and outcome assessors will be blind to random assignment throughout the entire duration of the trial. Randomization will be stratified on heaviness of smoking index (score > 4 [84]), confidence in being smoke-free >70 (on a 0 to 100 scale), and recruitment method (i.e., clinical vs. social media).

14.8 Ethnic and Gender Distribution Chart

Projected Target Accrual
ETHNIC AND GENDER DISTRIBUTION CHART

TARGETED / PLANNED ENROLLMENT: 1520			
Ethnic Category	Sex / Gender		
	Females	Males	Total
Hispanic or Latino	20	9	29
Not Hispanic or Latino	275	118	393
Ethnic Category Total of All Subjects*	295	127	422
Racial Categories			
American Indian / Alaska Native	6	2	8
Asian	6	2	8
Native Hawaiian or Other Pacific Islander	3	2	5
Black or African American	39	16	55
White	220	96	316
More Than One Race	21	9	30
Racial Categories: Total of All Subjects*	295	127	422

15.0 INVESTIGATOR OBLIGATIONS

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

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

16.0 STOPPING THE STUDY

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

Outside of the IRB or CTO's suspension decisions, there are no formal stopping rules including statistical and administrative procedures for early termination, because this is a remote, digital intervention for behavior change. Including such rules in this type of trial would yield a study that was inconclusive about the risks versus benefits of the treatments.

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18.0 APPENDICES

- Appendix A: App screenshots
- Appendix B: Participant measures and timepoints they will be administered
 - B.1: Cancer-Related Internalized Shame Scale
 - B.2: Internalized Stigma subscale, Lung Cancer Stigma Inventory
 - B.3: Center for Epidemiological Studies-Depression (CES-D)
 - B.4: Generalized Anxiety Disorder 7-item (GAD-7)
 - B.5: Knowledge subscale, Smoking Knowledge, Attitudes, and Services scale (K-SAS)

18.1 APPENDIX A: App screenshots

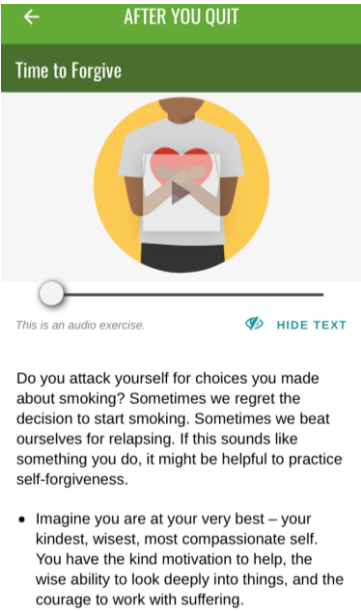
Quit2Heal screenshots



Home page



Smoking after Cancer

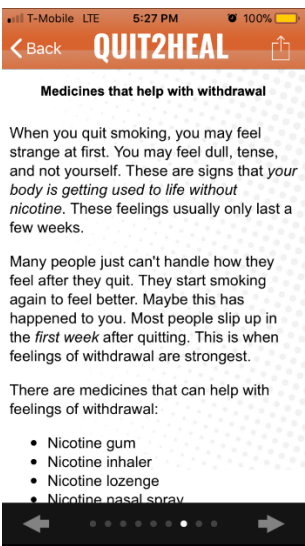


Self-Compassion

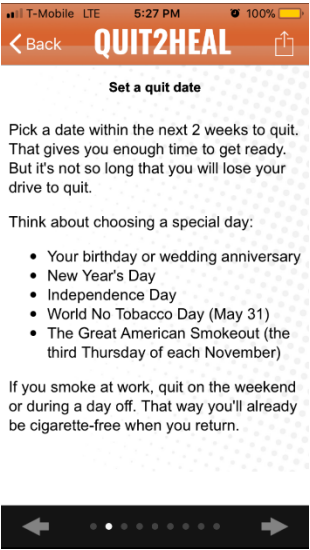
QuitGuide screenshots



Home page



Cessation Medications



Quit Date Plan

18.2 APPENDIX B: Participant measures and time points they will be administered.

Measure (# items)	Screen	Baseline	3 month	6 month	12 month	Purpose
Eligibility Criteria (14)	X					Eligibility
Demographics (7)		X				All Aims
Nicotine & Tobacco Use (12)		X	X	X	X	All Aims
Nicotine Dependence (6) [87]		X	X	X	X	All Aims
Cessation Pharmacotherapy (8)		X	X	X	X	All Aims
Readiness to Quit (1) [101]		X	X	X	X	Aim 1
Quit Attempts (2)		X	X	X	X	Aim 1
Cancer-Related Shame (5) [102]		X	X	X		Aim 2
Cancer Stigma (9) [22]		X	X	X		Aim 2
Depression (10) [103]		X	X	X		Aim 2
Anxiety (7) [104]		X	X	X		Aim 2
Knowledge of Smoking/Quitting Consequences (4) [136].		X	X	X		Aim 2
Cancer Type, Stage, & Time Since Diagnosis (3)		X				Exploratory Aim
Partner who smokes (1)		X				Exploratory Aim
Advised to quit by oncologist (1)		X				Exploratory Aim
Total number of items	14	82	70	70	29	
Mean duration, in minutes	6	31	26	26	14	

B.1 Cancer-Related Internalized Shame Scale [102]

Below is a list of statements. Please circle or mark one number per question to indicate how much you agree with each statement.

	Strongly disagree	Disagree	Agree	Strongly agree
1. I feel others think I am to blame for my illness.	1	2	3	4
2. I do not feel I can be open with others about my illness.	1	2	3	4
3. I fear someone telling others about my illness without my permission.	1	2	3	4
4. I feel I need to keep my illness a secret.	1	2	3	4
5. I feel I am at least partially to blame for my illness.	1	2	3	4

B.2 Internalized Stigma Scale, Lung Cancer Stigma Inventory [22]

To what degree has each of the following happened to you since your lung cancer diagnosis?

	Not at all	Slightly	Somewhat	Moderately	Extremely
1. I have felt regret about my cancer.	1	2	3	4	5
2. I have felt I did something to cause my cancer.	1	2	3	4	5
3. Thinking about cancer has made me wish I had lived my life differently.	1	2	3	4	5
4. Having cancer has made me feel like I've made mistakes.	1	2	3	4	5
5. I have wondered if I could have prevented cancer by changing certain behaviors.	1	2	3	4	5
6. I have felt bad about the burden that cancer puts on my family.	1	2	3	4	5
7. I have thought that past behavior contributed to my cancer.	1	2	3	4	5
8. I have felt guilty about my cancer.	1	2	3	4	5

9. I have blamed myself for having cancer.	1	2	3	4	5
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B.3 Center for Epidemiological Studies-Depression (CES-D) [103]

Check the box next to the statement which best describes how often you felt or behaved this way DURING THE PAST WEEK.

	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of the time (3-4 days)	Most or all of the time (5-7 days)	Prefer not to answer
DURING THE PAST WEEK:					
1. I was bothered by things that don't usually bother me.	☐	☐	☐	☐	☐
2. I had trouble keeping my mind on what I was doing.	☐	☐	☐	☐	☐
3. I felt depressed.	☐	☐	☐	☐	☐
4. I felt everything I did was an effort.	☐	☐	☐	☐	☐
5. I felt hopeful about the future.	☐	☐	☐	☐	☐
6. I felt fearful.	☐	☐	☐	☐	☐
7. My sleep was restless.	☐	☐	☐	☐	☐
8. I was happy.	☐	☐	☐	☐	☐
9. I felt lonely.	☐	☐	☐	☐	☐
10. I could not get "going".	☐	☐	☐	☐	☐

B.4 Generalized Anxiety Disorder 7-item (GAD-7) [104]

Over the last 2 weeks, how often have you been bothered by the following problems?

	Not at all	Several days	More than half the days	Nearly Every Day	Prefer not to answer
1. Feeling nervous, anxious or on edge.	☐	☐	☐	☐	☐
2. Not being able to stop or control worrying.	☐	☐	☐	☐	☐
3. Worrying too much about different things.	☐	☐	☐	☐	☐
4. Trouble relaxing.	☐	☐	☐	☐	☐
5. Being so restless that it is hard to sit still.	☐	☐	☐	☐	☐
6. Becoming easily annoyed or irritable	☐	☐	☐	☐	☐
7. Feeling afraid as if something awful might happen.	☐	☐	☐	☐	☐

B.5 Knowledge subscale, Smoking Knowledge, Attitudes, and Services scale (K-SAS) [136]

What is your level of agreement or disagreement with the following statements?

	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly agree
1. The hazards of smoking have been clearly demonstrated.	1	2	3	4	5
2. The hazards of second-hand smoke have been clearly demonstrated.	1	2	3	4	5
3. I am aware of community resources to help people quit smoking.	1	2	3	4	5
4. I have the required skills to quit smoking.	1	2	3	4	5