FRED HUTCHINSON CANCER RESEARCH CENTER

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Title of Protocol:
Full Scale Randomized Trial of an Innovative Conversational Agent for Smoking Cessation (QuitBot)

Investigators List:		
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SPONSOR: NCI, NIH
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PROTOCOL SYNOPSIS

Protocol Title	Full Scale Randomized Trial of an Innovative Conversational Agent for Smoking Cessation (QuitBot)
Protocol Number	10359
Protocol Sponsor	NCI, NIH
Trial Phase	III
Trial Type	Randomized clinical trial
Study Objectives	To determine the effectiveness of a digital conversational agent for smoking cessation; specifically, to conduct a randomized controlled trial of QuitBot (n = 823) versus SmokefreeTXT (SFT) (n = 823), in order to determine whether QuitBot provides higher quit rates than SFT.
Study Design	2-arm parallel group randomized trial
Population	1647 adult male and female daily smokers who currently smoke and want to quit smoking in the next 30 days
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	QuitBot conversational agent (CA)
Type of control	Active (SmokefreeTXT text messages)
Trial Blinding	Participants and outcome assessors will be blinded
Treatment Groups	Intervention, Control
Assessments	Follow-up assessments at 3, 6, and 12 months
Number of trial subjects	1647
Estimated duration of trial	30 months
Duration of Participation	12 months

ABBREVIATIONS

CA	Conversational agent
RCT	Randomized Clinical Trial
SFT	SmokefreeTXT
App	Smartphone application
NLP	Natural language processing
QALY	Quality-adjusted life years

TLS	Transport Layer Security
MS	Microsoft
LUIS	Language Understanding Intelligence Service

Table of Contents

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: Cigarette smoking accounts for 480,000 premature deaths and one third of all cancer deaths annually in the US. There is enormous need for high-impact, cost-effective population-level interventions for smoking cessation. For the past 15 years, mobile phone-delivered text messaging interventions such as the NCI's SmokefreeTXT (SFT) have been a prominent technology addressing this need. However, very much like all widely available technologies for smoking cessation (e.g., websites), text messaging interventions have modest quit rates, driven largely by low engagement. Fortunately, a new technology provides a therapeutic conversation to address the problem of engagement that impacts text messaging and other current digital technologies for smoking cessation. Advances in machine learning, natural language processing, and cloud computing are now making it possible to create and widely disseminate conversational agents (Cas), which are computer-powered digital coaches designed to form long-term social-emotional connections with users through conversations. Cas are supportive, empathic, reflectively listen, provide personalized responses, and offer goal setting and advice appropriately timed to the needs of the user. Regarding Cas for smoking cessation, the major knowledge gaps are: (1) their efficacy, (2) theoretical mechanisms, and (3) the cost-effectiveness. Also unexplored are the potential baseline moderators of Cas for smoking cessation. We recently developed a CA for smoking cessation, called "QuitBot," evaluated it in a diary study, and then tested it in a pilot randomized controlled trial (N = 306), comparing it with the NCI's SFT. The pilot RCT design was very feasible with 93% three-month follow-up. QuitBot had: (a) high participant engagement and (b) high quit rates at the three-month follow-up—very promising in comparison with SFT.
Objectives: Addressing these knowledge gaps and building on the promising results of our QuitBot research, the project will conduct a randomized controlled trial of QuitBot (n = 823) versus SmokefreeTXT (n = 823) with 12-month follow-up in order to determine whether QuitBot: (1) provides higher quit rates than SFT, (2) has smoking cessation outcomes significantly mediated by therapeutic alliance processes and engagement, and (3) is cost-effective vs. SFT. In addition, this study will explore whether these baseline factors moderate the effectiveness of QuitBot: trust, social support, and demographics (e.g., sex). This innovative project will advance the fields of research on Cas both for smoking cessation in particular and for health behavior change in general—regardless of whether the results are positive or null. Positive results could have high population-level impact and stimulate new lines of research into CA dissemination and implementation, and the adaptation of Cas for multiple subpopulations of smokers, languages, and community and medical settings.
Phase: Phase III RCT.
Methods: Randomized controlled trial of QuitBot (n = 823) versus SmokefreeTXT (n = 823) with 12-month follow-up.

1.1 Protocol Title

Full Scale Randomized Trial of an Innovative Conversational Agent for Smoking Cessation (QuitBot)

1.2 Sponsor Information

NCI, NIH

1.3 Investigator Information

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

1.4 Consultants for the Study

Consultant	Institutional Affiliation	Expertise
Lorien Abroms, Ph.D.	George Washington University	SmokefreeTXT interventions
Jesse Dallery, Ph.D.	University of Florida	Remote biochemical confirmation of smoking cessation
Anusua Trivedi	Microsoft	Natural language processing
Adam Rhine	Talosix	Chatbot engineering

2.0 INTRODUCTION TO THE PROTOCOL

2.1 Introduction

Text messaging, very much like all widely available technologies for smoking cessation (e.g., websites and smartphone apps), have modest quit rates driven largely by low user engagement [1, 2, 16-21]. Needed now is an intervention model

that can fundamentally shift beyond text messaging and other digital technologies in order to boost user engagement and thereby increase quit success rates.
A new technology provides a therapeutic conversation to address the problem of engagement that impacts text messaging and other current digital technologies for smoking cessation. Advances in machine learning, natural language processing, and cloud computing are now making it possible to create and widely disseminate conversational agents (CAs), which are computer-powered digital coaches designed to form long-term social-emotional connections with users through conversations [22, 23]. Interactions are tailored to the users' unique challenges and barriers to quitting smoking. CAs are supportive, empathic, reflectively listen, provide personalized responses, and offer goal setting and advice appropriately timed to the needs of the user. In addition, CAs have 24/7 availability, absence of judgement, and the ability to quickly calculate and thereby show results and measure progress [24, 25]. CAs are potentially less costly for users than text messaging because they do not require a paid cellular plan. Instead, CAs only need a Wi-Fi or other internet connection. CAs are available anytime and have potentially high population level reach.

Regarding CAs for smoking cessation, the following are unknown: (1) their efficacy, (2) theoretical mechanisms, and (3) the cost-effectiveness. Also unexplored are the potential baseline moderators of CAs for smoking cessation.

2.2 Preclinical Data

Dr. Bricker obtained NCI pilot funding (CCSG Y43 Pilot from NCI P30CA015704) to develop and pilot test a CA for smoking cessation. After developing the QuitBot CA using content analysis, user-centered research, and prototype testing, we conducted a diary study to obtain ongoing feedback on users' interactions with QuitBot, its design, and content. In user-centered design research, a diary study of two weeks with 6 to 12 participants is recommended to obtain this initial feedback [81, 82]. Accordingly, we conducted a single arm 14-day diary study of the program with 9 adults who were smoking at least daily (all smoked 30+ cigarettes/day), interested in quit smoking, and recruited from around the US via Facebook ads. Four were chosen because they were skeptical about CAs being able to help someone quit smoking. All nine participants completed: (1) the 60-minute video-based orientation, (2) 14 evening diary entries (15 minutes each) about their interactions with QuitBot, its design, and content, (3) on day seven, a 15-minute video-based check-in call on their impressions to date, and (4) a 60-minute video-based exit interview. The results showed that, even though the focus was on usability, by day 14, three participants quit smoking and all remaining six reduced to 3-4 cigarettes per day. Ratings for usefulness, satisfaction, and likelihood of recommending to a friend were all very high: 4.33, 4.67, and 4.88 on a 0 (not all) to 5 (extremely) scale. All nine felt highly supported by the QuitBot CA. They liked the skills training for coping with urges and lapses. Their feedback yielded minor content edits and fixes of technical bugs.

2.3 Clinical Data to Date

We recently conducted a multi-step design process that yielded a fully functional CA cessation intervention called QuitBot. Participants were highly receptive to QuitBot in our single-arm diary study. We then tested QuitBot in a pilot randomized controlled trial (N = 306), comparing it with the NCI's SmokefreeTXT. The pilot RCT design was very feasible with 93% three-month follow-up. QuitBot had: (a) high participant engagement and (b) high quit rates at the three-month follow-up. QuitBot participants expressed feeling engaged with and supported by the program.

Based on our successful methods for national recruitment [84], we developed and targeted FB ads with ongoing monitoring and adjustment of recruitment yield. These efforts yielded 1853 participants screened, 974 eligible, 452 consented, and 306 randomized (153 in each arm). Based on evidence from text messaging trials meta-analyses [1], we stratified randomization on biological sex (male vs. female), heaviness of smoking index score (≤ 4 vs >4), and percent confidence in being smoke-free in 12 months (≤ 70% vs. >70%). The two conditions were balanced at baseline on all measured characteristics (all p-values > .05). Participants were mean age 36.3, 67% female, 28% minority, 52% unemployed, 43% high school or less education, 69% smoking at least half pack daily, and 59% high nicotine dependent. The characteristics of this FM sample are very similar to those of m/e-health trials [1, 2, 7]. To maximize outcome data completion, we followed our team's successful protocol [84]: 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 93%, provided confidence in the follow-up survey methods. The data retention did not differ between study arms (p = .374). For example, the point estimate for the number of days from randomization to the last user input showed that QuitBot participants engaged 26.3 (95% CI: 19.7, 33.0; p<.001) days longer than SFT participants. QuitBot's intervention completion results are substantial when considering that each day's content involves a 3 to 5-minute conversation. The 30-day point prevalence (missing=smoking) abstinence rates at three-month follow-up (primary outcome) were 32% for QuitBot vs. 23% for SFT (OR = 2.18; 95% CI: 1.08, 4.39; p =.030). Results for the secondary outcome of cessation from cigarettes and all other nicotine or tobacco products (except FDA-approved nicotine replacement) were promising.

Building on these promising results, a comparative effectiveness randomized trial with a fully-powered sample size (N = 1647) and longer-term follow-up (i.e., 12 months) is now needed to determine whether QuitBot: (1) provides higher quit rates than SmokefreeTXT, (2) operates according to therapeutic mechanisms of change, and (3) is cost-effective vs. SmokefreeTXT.

Study Objectives: Conduct a randomized controlled trial of QuitBot (n = 823) versus SmokefreeTXT (n = 823), in order to determine whether QuitBot:

Objective 1. Has significantly higher 30-day point prevalence abstinence at 12 months post-randomization than SmokefreeTXT. Importance of this objective: will determine both arms' quit rates with precision and whether the QuitBot provides more robust quit rates than SmokefreeTXT.

Objective 2. Has smoking cessation outcomes significantly mediated by therapeutic alliance processes and engagement indicators in a serial multiple mediator model. Importance of this objective: will show how CAs work and identify communication processes needing further targeting. This knowledge is valuable both for CA smoking cessation interventions in particular and CA behavior change interventions in general.

Objective 3. Will be cost-effective vs. SmokefreeTXT (SFT), as measured by cost per quitter, cost per life year gained, and cost per quality-adjusted life year (QALY) gained. Importance of this objective: will provide payors and policymakers an assessment of value to inform decisions about whether to adopt QuitBot.

Exploratory Objective: Explore whether these baseline factors moderate the cessation outcomes of QuitBot, as compared to SmokefreeTXT: (a) trust, (b) social support, (c) demographics (e.g., sex). Importance of this objective is to identify: (1) who benefits most so that they can be provided the intervention; (2) who benefits least so that future research can explore why and determine how best to improve the intervention for them.

Impact: This study will advance the fields of research on CAs both for smoking cessation in particular and for health behavior change in general—regardless of whether the results are positive or null. Positive results could have high population-level impact and stimulate new lines of research into CA dissemination and implementation, and the adaptation of CAs for multiple subpopulations of smokers, languages, and community and medical settings.

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

2.3.1 Intervention Development

For the pilot, a version 1.0 of the QuitBot CA program was developed by the study staff in collaboration with Data Scientists in the Hutch Data Commonwealth (HDC) department. To create the greater technological complexity of incorporating more NLP for more sophisticated human-like conversational engagement, partnership with Data Scientist experts in Microsoft AI for Good, led by Anusua Trivedi, joined study staff. Also, after further review of privacy and security considerations associated with Facebook Messenger, we opted to create our own smartphone app to host version 2.0 of the QuitBot CA program. This will allow for greater privacy protections for participant information and greater capacity for secure data collection.

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, QuitBot app records, text message log, 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. The electronic database resides on a server that is in a locked cabinet in a locked server room, with strictly limited, key-card access. The server also lies behind the Center's firewall, which 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 Project web server also resides in the same secure room as the database server, and is similarly protected by firewalls, with no user access except through the web server software. The database administrators maintain a rigorous system of daily full tape backups of the database and web servers. The backups include sets of tapes stored at a secure distant site.

Study participants will be recruited using a publicly accessible web site running on the Apache web server on a Linux operating system. Internal servers are made available outside the 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 made using 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 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. 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 using the TLS protocol. Employment of the TLS protocol will prevent anyone from intercepting data passed between the end user's web browser and the web server.

The QuitBot CA is implemented within the Microsoft Bot Framework. The core bot logic is developed in Node.js using the Microsoft Bot Builder Software Development Kit (SDK). The code is compiled, hosted, and run as an App Service on a private Fred Hutch account on the Microsoft Azure cloud, which uses a Linux operating system. In the same cloud environment, relevant user data (e.g. users' current positions within the cessation dialogues, their predicted quit dates, etc.) is stored using Azure Table Storage. The CA utilizes the Microsoft Bot Connector to interact with the table storage, and to route messages (securely over Transport Layer Security [TLS]) to and from the frontend of the QuitBot CA, a custom smartphone application. The Bot Connector is tied directly to the Fred Hutch owned QuitBot application. After being randomized to the QuitBot arm, study participants will be sent a link enabling them to download and login to the QuitBot app and then interact with the QuitBot CA, as using the login verifies them as a valid, active participant. Once confirmation is received, QuitBot will begin serving cessation dialogue content to the participant, first by initiating contact (twice daily, at user-specified times) via proactive messaging, then by reactive responses to the participant's chat input. At multiple points throughout the cessation dialogues, the bot will utilize Microsoft's Language Understanding Intelligent Services (LUIS) to perform more detailed analysis on participants' messages, including categorical classification, identification of specific types of user responses, routing of conversations into specific topics, etc. This LUIS service will also be hosted within Fred Hutch's Azure cloud environment, and integrated with the Bot Framework via Azure Bot Services. The QuitBot CA intervention app will be accessed via password-protected login any time after randomization. The analytics database for the CA (which automatically records participants' utilization of the CA) 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. We will inform participants: (1) we are recording their utilization of their assigned intervention 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 SmokefreeTXT text messaging program is hosted by ICF, a consulting services company contracted with the Federal government to manage the program. ICF provided Dr. Bricker with a copy of the SmokefreeTXT message library for the QuitBot pilot trial, and study programmers host it on a secure server behind the Fred Hutch's firewall, which has the same

access restrictions and backup system as the database server described above. Text message delivery will occur through Nexmo SMS API, which is also used to send study survey reminders.

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. Furthermore, the QuitBot is programmed to respond to any mention of "suicide" and self-harm keywords by referring the participant to the National Suicide Prevention Lifeline number and by confidentially alerting the study staff and Dr. Bricker.

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, participants in both treatment groups will be given information on pharmacotherapy for smoking cessation (e.g., nicotine patch) and how to obtain these medications.

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

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

Successfully assisting people 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. 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 QuitBot project has potential to develop an effective, resource-sensitive public health intervention for smoking cessation while advancing research on CAs and the science of communication in technology. This innovative project shows exciting promise for cost-effectively improving the success rates of cessation, and thereby lowering healthcare costs and reducing premature tobacco-related deaths on a population level. 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 QuitBot (n = 823) versus SmokefreeTXT (SFT) (n = 823), in order to determine whether QuitBot provides higher quit rates than SFT. The primary endpoint is 30-day biochemically confirmed cigarette smoking cessation at 12 months after randomization. Secondary endpoints are 30-day biochemically confirmed cigarette smoking cessation at 3 and 6 months after randomization.

3.1.2 Secondary Objectives

One secondary objectives is to determine whether QuitBot versus SFT operates according to therapeutic mechanisms of change, where cessation outcomes are significantly mediated by therapeutic alliance processes and engagement indicators in a serial multiple mediator model, which will show how CAs work and identify communication processes needing further targeting. Another secondary objective is to determine whether QuitBot is cost-effective vs. SFT), as measured by cost per quitter, cost per life year gained, and cost per quality-adjusted life year (QALY) gained. Additional objectives are to explore whether these baseline factors moderate the cessation outcomes of QuitBot, as compared to SFT: (a) trust, (b) social support, (c) demographics (e.g., sex).

3.2 Study Population
Adult male and female daily smokers (healthy volunteers) who currently smoke and want to quit in the next 30 days.

3.3 Study Design
We will conduct a fully-powered two-arm parallel randomized controlled trial comparing QuitBot to SmokefreeTXT (SFT). Based on evidence from text messaging trials meta-analyses [1], we will stratify randomization on biological sex (male vs. female), heaviness of smoking index score (≤ 4 vs >4), and percent confidence in being smoke-free in 12 months (≤70% vs. >70%). Moderators will be measured at baseline, mediators at 3 and 6 months post randomization, and cessation and cost-effectiveness 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: 1520 participants. **Actual Accrual:** 1647 participants.

3.5 Name of Sponsor/Funding Source: NCI, NIH R01CA247156

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.

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 [127].

5.0 SUBJECT ELIGIBLITY

5.1 Inclusion Criteria
Inclusion criteria: (1) age 18 or older, (2) smokes at least one cigarette a day for the past 12 months, (3) wants to quit cigarette smoking within the next 30 days (consistent with text messaging intervention trials [1, 2]) (4) if concurrently using any other nicotine or tobacco products, wants to quit using them within the next 30 days, (5) interested in learning skills to quit smoking, (6) willing to be randomly assigned to either intervention, (7) resides in US, (8) has at least daily access to their own smartphone, (9) has text messaging on their smartphone and knows how to download a smartphone application (criterion 8 and 9 are needed minimum requirements to receive each interventions' content), (10) willing and able to read in English, and (11) not using other smoking cessation interventions. (This eligibility requirement helps ensure results are due to the treatments we recommend rather than those that participants are doing on their own.) Participants not eligible for were given the smokefree.gov website and 800-QUIT-NOW to reach their state's quitline.

5.2 Exclusion Criteria
Exclusion criteria: the reverse of the inclusion criteria.

6.0 SUBJECT REGISTRATION

For this trial, we will the follow the QuitBot pilot RCT registration process, which was based on our successful WebQuit R01 protocol [84]. First, we will use our registration website to provide information about the study, FAQs, a brief video describing the study, information about the study team and Fred Hutch, and a portal to the informed consent form, screening, and baseline surveys. Second, collaborating with the Fred Hutch Communications Department, we will design Facebook and Google online ads for referring potential participants to the registration website. We will use our successful three-part strategy to register at least 30% minorities (the QuitBot pilot RCT had 28% minority): (1) use culturally-relevant online ads and enrollment website content targeted to minority smokers; (2) reaching out to minority-specific media newswire services to publicize the study; (3) program the registration website to limit non-minority registration to 70% and continue registration until the minority registration goal of at least 30% is reached. We will use a very similar 3-part strategy to register at least 40% men (the QuitBot pilot RCT had 33% men) and 12% age 65 and over.

We will use the registration protocol from the QuitBot pilot RCT, which was based on our WebQuit R01 protocol [85]. Specifically, those who screen eligible in the registration 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 registration process within 14 days will be sent an email notifying them that they were not registered and provide both the smokefree.gov website and the 800-QUIT-NOW phone number. Those completing the registration process and randomized will be emailed a secured link connecting them to QuitBot or to SFT.

Feasibility of data collection: all of these methods have proven feasible in our published trials [84] and in our pilot trials, including the QuitBot 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 and personal computers (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 QuitBot CA intervention or the SmokefreeTXT intervention.

QuitBot CA intervention: following randomization, participants in the CA arm will be sent a secured link to connect them to QuitBot by downloading and logging into the app hosting the CA. The QuitBot program consists of 42 days of 3 to 5-minute focused conversations (one conversation per day) over two phases: 14 days pre-quit and 28 days post quit. The content matches that of SFT, and follows US Clinical Practice Guidelines for cessation intervention [79]. The program content is presented as a continuous conversation, built on user input (e.g., stated motivations to quit, triggers to smoke, number of cigarettes smoked) from prior conversations. The program is proactive: at the user’s preferred time, QuitBot provides daily prompts to start a 3-5 minute structured text conversation—e.g., “Hi Alex, are you free to chat?” And on-demand/anytime, the user can get help with an urge, mood, and slips.

Smokefree comparison intervention: for initial evidence of whether CA is a fundamental shift beyond text messaging, SmokefreeTXT (SFT) is the ideal comparison. A 42-day program, SFT is the most widely accessible text messaging program in the US. It is non-proprietary and free to the public, thereby providing maximal accessibility and replicability. Daily messages are sent about the importance of quitting smoking, setting a quit date, preparing to quit, quitting, and maintaining abstinence. Daily messages check in about quit status. Three keywords can be sent by users to receive anytime help: “CRAVE” (on how to cope with urges), “MOOD” (on how to cope with moods triggering smoking), and “SLIP” (on how to cope with lapses). See Figure 3 for sample message. NCI’s SFT contractor (ICF International) provided us the full content of SFT so that we could internally host a secured private version for research. For blinding, the intervention was called “QuitBot.” Comparisons between QuitBot and SFT are shown in Table 2. In both SFT & QuitBot, participants receive two prompts per day (three on the quit day), with those not responding to prompts continuing where they left off.

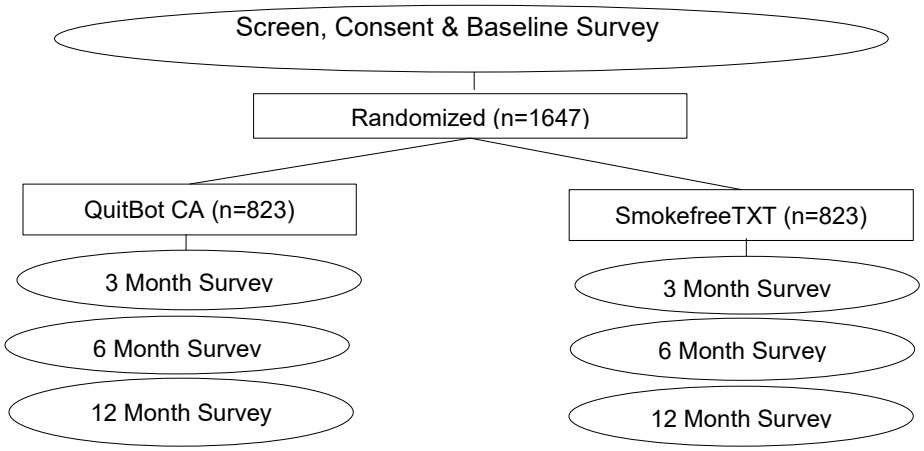
Table 2. Comparison of Conversational Agents (CAs) with Text Messaging Interventions.

Engagement Feature	CA	Text
Personified digital coach (e.g., has name, background, and story)	Yes	No
Coach responds to user’s natural language (e.g., word choice, semantics)	Yes	No
Tailors responses to user’s unique motivations, triggers, and barriers to behavior change	Yes	No

Expresses empathy to user	Yes	No
Reflectively listens	Yes	No
Provides self-disclosures tailored to user's disclosures	Yes	No
Engages in social dialogue (e.g., "How are you?")	Yes	No
Provides meta-relational communication (i.e., talk about relationship)	Yes	No
Provides empirically supported behavior change content	Yes	Yes
Provides multiple short messages throughout the day or week	Yes	Yes
To operate, requires text messaging pricing plan (e.g., unlimited, limited, per-message)	No	Yes[1]

[1] *In the US, text messaging cessation interventions require a cellular texting plan [3]*

Experimental Design Schema



7.1 Duration of Therapy

Both therapies (the digital intervention programs) consist of 42 days of smoking cessation content.

7.2 Duration of Follow-Up

The follow-up period lasts for 12 months and consists of three surveys. 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). 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; Day 7: Second email invitation with link to online survey; Days 10 to 18: Eight attempts to complete telephone version of survey (one call per day from a trained surveyor); Day 19: 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 [106]) 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; 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 [85], we estimate an 85% overall survey response rate [84]. In that RCT, 92% of those who completed the 12-month outcome survey responded online [84]. We thus expect about 92% of survey completers will do so online and thus minimize survey mode bias. Nonetheless, we will examine if mode of survey completion is associated with the cessation outcome.

Each assessment timepoint (at 3, 6, and 12 months) has a 90-day time window from when the follow up sequence begins: from Day 0, with the first email invitation, and then for 61 days after the second copy of the mailed survey is sent on Day 29, to allow for delayed responses. On Day 90, the collection window is closed. Any assessments returned after the window is closed are not included in the assessment data set for analysis.

Feasibility of data collection: all of these methods have proven feasible in our published trials [84] and in our pilot trials, including the QuitBot 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 [84].

Participation is considered ended after completion of the final survey.

8.0 ADVERSE EVENTS

8.1 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 QuitBot CA or SmokefreeTXT 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.

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.

8.2 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.

8.3 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

8.4 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 QuitBot CA or SmokefreeTXT programs).
- Not Related – AEs that are doubtfully related or clearly not related to the smoking cessation intervention (the QuitBot CA or SmokefreeTXT programs).

8.5 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.

8.6 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	Medical Monitor email: tillb@fredhutch.org ISIOC email: ISIOC@fredhutch.org
	All SAEs	Within 2 business days of research team* awareness	Submit completed Institution-Sponsored IND SAE Reporting	ISIOC Fax: 206-667-6068

			Form signed by PI or designated sub-Investigator	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.

9.0 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 Consortium Data and Safety Monitoring Committee (DSMC), 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.

10.0 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.

10.1 Source Data to be Recorded Directly

There are 6 sources of 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 QuitBot CA program, Google Analytics, and SmokefreeTXT program. All data will be collected directly from consenting adult participants. A description of these sources of data follows.

Survey Data. The Baseline Survey, hosted on our secured recruitment website, will collect data on (1) demographics, (2) nicotine and tobacco use, (3) nicotine dependence, (4) readiness to quit, (5) quit attempts, (6) smoking costs, (7) quality of life, (8) interpersonal trust, (9) social support, and (10) 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 intervention processes (e.g., therapeutic alliance), cessation progress (e.g., quit attempts) and outcomes (e.g., 30-day abstinence), and the participant's experiences with their assigned smoking cessation intervention. The 6- and 12-month surveys will primarily collect data on cessation progress/outcomes.

QuitBot CA utilization data and security. The QuitBot CA program will be accessible to participants when they access the download and login link sent to them in their secure trial enrollment email. During the enrollment process, participants check their smartphone storage requirements and opt-in to download the app. If the participant is then randomized to the QuitBot arm, a randomly-generated opt-in ID is sent to the QuitBot backend, where it is whitelisted and connected to their user data, which allows them to fully interact with the bot content. Non-whitelisted users who attempt to download the app will not be able to login and will receive a single generic response, redirecting them to the study website page for more information. The CA will collect information on participants' responses to the program, including triggers to smoke (physical, emotional, and situational triggers), motivations to quit, barriers to quitting, and number of cigarettes smoked in end-to-end encrypted "private conversations", and it will not collect PHI. Data will also be collected on usage information: the number of days user interacted with assigned intervention and whether users completed assigned intervention. This information 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. An automated script creates a fully de-identified and cleaned copy of the data, to send to the study team analysts. This usage data can be tied to the survey data using the aforementioned randomly generated opt-in IDs.

SmokefreeTXT utilization data and security*.* Participants randomized to the SmokefreeTXT arm will be asked to provide a quit date on a website with data transmission via Transport Layer Security (TLS.) A schedule of text messages is set up based on the quit date. Participants can request that messages be stopped at any time. Date stamps and content of the outgoing messages and incoming messages with participant responses to queries about mood, cravings, relapse, and smoking status will be stored on secured Fred Hutch servers. These data will only be accessible to Fred Hutch Shared Resource programmers and not accessible via websites. The programmers will prepare de-identified utilization data for analysis.

Remote biochemical verification data and security. After completing each survey, 10% of all participants randomly selected at randomization to complete the biochemical verification procedure will be mailed a Alere saliva-based smoking cessation verification test and instructions. 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, an encrypted live video-conferencing software available at Fred Hutch. The Doxy.me software is accessible via smartphone, tablet, or desktop computer, does not require participants to set up accounts or do downloads, plugins, or 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 survey 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.

10.2 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.

10.3 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.

10.4 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 QuitBot CA program will be extracted over a secure connection on a weekly basis, and stored on a secure internal FH 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.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design

We planned to enroll 1520—and actually enrolled 1647—adult daily smokers who want to quit smoking. Participants will be randomly assigned (with 0.5 probability) to (1) the QuitBot conversational agent (CA) or (2) SmokefreeTXT text messaging. Based on evidence from text messaging trials meta-analyses [1], we will stratify randomization on biological sex (male vs. female), heaviness of smoking index score (≤ 4 vs >4), and percent confidence in being smoke-free in 12 months (≤ 70% vs. >70%). Moderators will be measured at baseline, mediators at 3 and 6 months post randomization, and cessation and cost-effectiveness outcomes at 3, 6, and 12 months post randomization. Random assignments will be computer-generated after consent.

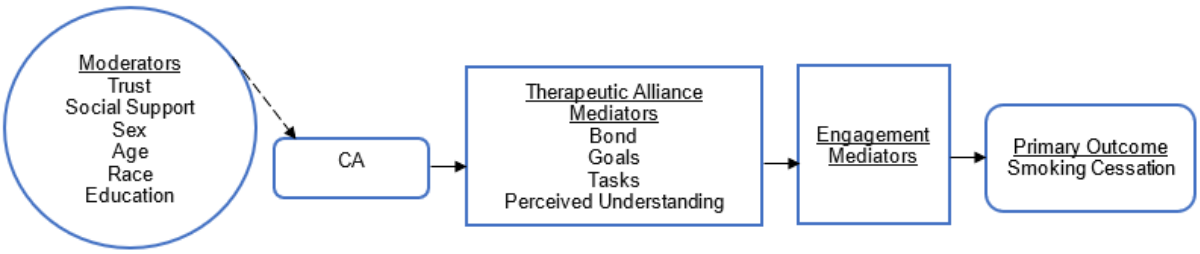
11.2 Primary/Secondary Endpoints/Hypotheses and Analytical Methods

The primary endpoint will be biochemically-verified 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 [1, 18], biochemical confirmation will be conducted on participants self-reporting no smoking at all in the last 30 days.

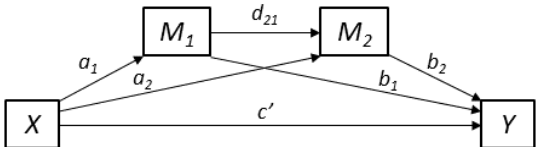
Our primary outcome hypothesis is that QuitBot will have significantly higher 30-day point prevalence abstinence at 12 months post-randomization than SmokefreeTXT. For each comparison of the treatment arms on the primary and all secondary endpoints, we will use a logistic regression model. Using standard smoking cessation trial intent-to-treat analysis, all missing outcomes will be coded as smokers [31, 35-39]. The model will adjust for all stratification factors as well as baseline factors that are imbalanced after randomization and significantly related to the outcome. In addition, we will conduct these sensitivity analyses: (1) multiple imputation of missing outcomes [107-109], (2) complete case analysis of those providing follow-up data, (3) using a secondary cessation outcome of no use of cigarettes and other nicotine or tobacco products except FDA-approved nicotine replacement therapies, (4) adjusting for baseline usage of other tobacco and nicotine products, and (5) adjust for usage of other interventions and cessation medications after study enrollment.

11.3 Additional Efficacy Hypotheses, Outcome Measures, and Statistical Methods

Conceptual model of conversational agents for smoking cessation



Based on the Conceptual Model above, we hypothesize a serial multiple mediator model with two sets of mediators: the four therapeutic alliance processes (M_1) and the three engagement indicators (M_2). As shown in the figure below, we hypothesize that these mediators operate in a serial sequence: QuitBot's treatment assignment (but not SFT's) will impact therapeutic alliance processes (path a_1), the therapeutic alliance processes will in turn impact treatment engagement variables (path d_{21}), and the engagement variables will in turn impact the 12-month primary cessation outcome (path b_2). The serial mediation model is summarized by three equations, which we will analyze using the bootstrap confidence interval method of the PROCESS analysis macro developed for SAS [110]: (1) $M_1 = i_{M_1} + a_1X + e_{M_1}$; (2) $M_2 = i_{M_2} + a_2X + d_{21}M_1 + e_{M_2}$; (3) $Y = i_{M_2} + c'X + b_1M_1 + b_2M_2 + e_Y$. Treatment assignment (X) affects cessation outcome (Y) through four pathways. There are three indirect pathways: (1) from X to Y through M_1, estimated by a_1b_1, (2) from X to Y through M_2, estimated by a_2b_2, and (3) from X to Y through both M_1 and M_2, in sequence, with M_1 affecting M_2 [110], estimated by $a_1d_{21}b_2$. Finally, the fourth pathway is direct from X to Y, without passing through either mediator, estimated by c'. Finally, we will calculate the proportion of treatment effect explained by each of these mediators [111-113]. Number of participant engagements will be adjusted with poisson regressions that account for the number of prompts a participant received. A secondary model will examine whether therapeutic alliance processes impact cessation knowledge gained (path d21), and knowledge gained in turn impacts the primary cessation outcome (path b2).



We hypothesize that QuitBot will be cost-effective vs. SmokefreeTXT (SFT), as measured by cost per quitter, cost per life year gained, and cost per quality-adjusted life year (QALY) gained. Analyses: We will use current good practices of estimating cost-effectiveness [114], as applied to smoking cessation interventions [115]. To examine whether QuitBot costs less than SFT to help a person quit, we will estimate the incremental cost-per-quitter: difference in total cost of delivering the two interventions [116] divided by the difference in the number of 30-day abstinent participants at 12-months (Total CostQuitBot – Total CostSFT/# AbstinentQuitBot – # AbstinentSFT). Total cost assessments are described in Section C.5.5. Second, to estimate whether QuitBot represents good value vs. SFT per life year gained [115], we will calculate the standard metric of cost per life year gained as: Total CostQuitBot – Total CostSFT/# Life Years AddedQuitBot – # Life Years AddedSFT). Life years added attributable to each intervention's 12-month primary endpoint effect size will be derived from the life years estimates, reported in Stapleton & West [115], that conservatively account for gender, age, discounting, relapse, and unaided cessation. Lastly, to examine whether QuitBot represents good value vs. SFT per QALY [116], an additional analysis of the cost-per-QALY gained will be conducted as: (Total CostQuitBot – Total CostSFT)/(QALYQuitBot – QALYSFT). This analysis will be calculated by adding a Generalized Linear Model-based weighted quality of life parameter derived from the standard EQ-5D quality of life measure [96] taken at the 12-month endpoint. For the cost per life year and cost per QALY analyses, we will assess cost-effectiveness relative to implied willingness to pay in the U.S. of $100,000 [117]. In each of the three analyses, we will conduct probabilistic sensitivity analyses with 5,000 Monte Carlo simulations that will derive a cost-effectiveness plane (and 95% CI ellipse) across a range of total costs and effect sizes [118]. Similar cost-effectiveness analyses will be conducted for these subgroups: biological sex (male vs. female), age (50 or older vs. 49 or younger), race/ethnicity (non-Hispanic white vs. all other races), and education (high school or less vs more than high school). All will adjust costs to 2019 U.S. dollars and discount future costs and benefits incurred after one year at 3% per annum as is recommended by the panel on cost-effectiveness [105, 119].

Analysis of Sex as a Biological Variable: Consistent with NIH guidelines [120], we will report data by sex, in order to the consider the potential influence of sex in the interpretation of study results. Specifically, for all the analyses described above, we will examine the estimated 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. We will also stratify random assignment by sex.

11.4 Exploratory Analysis

Exploratory Objective: Explore whether these baseline factors moderate the cessation outcomes of QuitBot, as compared

to SmokefreeTXT: (a) trust, (b) social support, (c) demographics (e.g., sex). For each moderator variable, we will calculate separate logistic regression models that will 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 plots showing how the slope of Y on X is dependent on the value of Z. The slopes will be derived from logistic regressions that correspond to the prediction of Y from X at a single value of moderator Z.

11.5 Sample Size and Power

We determined sample size for binomial proportions aimed at 80% power for Primary Objective 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 [84]; (3) 80% completion rate of biochemical verification [103, 104]; (4) intent-to-treat analysis where, as standard in digital intervention smoking cessation trials, all those with missing data (including missing biochemical data) are coded as smokers [1, 121]; and (5) two-sided test with α = .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 QuitBot vs. SFT. Projected quit rates at 12-month follow-up were conservatively calculated using (1) quit rates at 3-month follow-up in our pilot RCT, along with (2) well-established relapse curves, which provide a data-derived estimate (i.e., 20-35%) of the rate of decay of intervention effects by 12-month follow-up [90, 91, 122]. We estimated a relapse of 27% (between 3 and 12 month-follow-up) and survey response and biochemical verification completion rates of 85% and 80%, respectively. The 12-month quit rate for SFT is conservatively estimated as 9.3%, as consistent with the projected SFT 12-month relapse rates from the pilot RCT and the 8.4% average quit rate from the most recent meta-analyses [1, 2, 18-21]. As shown in Table 5, obtaining 80% power to significantly detect a quit rate as low as 13.9% for QuitBot (vs. 9.3% for SFT) requires 1,520 randomized participants, with 760 in each study arm.

Table 3. Objective 1 Sample Size Estimates.

	Projected relapse rate				
	20%	25%	**27%**	30%	35%
	QuitBot 12-month follow-up 30-day point prevalence quit rate				
	15.2%	14.3%	**13.9%**	13.3%	12.4%
Total in each arm	484	653	**760**	983	1,579
Total randomized	968	1,306	**1,520**	1,966	3,158

This very conservatively estimated 13.9% quit rate would have high public health impact—49% higher impact than the projected 9.3% quit rate for SFT and 65% higher than the average 8.4% quit rate observed in text messaging interventions [1, 2, 18-21].

Power for Objective 2: Statistical power for testing the serial mediation of therapeutic alliance and engagement measures for smoking cessation was estimated based on the following: (1) conservative estimates of the post treatment standardized effect size for each hypothesized mediator (i.e., a small effect size of .14 [123]; (2) two-sided test with α=.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 (described in Section C.7.2) uses the percentile bootstrap method to estimate the indirect effect, which provides high power while still maintaining an accurate type-I error rate [124]. For even a small three-path mediation effect (e.g.,$0.01 \leq a_1 d_{21} b_2 < 0.05$), according to Taylor et al. [124], a total sample size of 1,000 will attain statistical power of 99%, while power to detect larger mediation effect approaches 1. In addition, Fritz [113] showed that a sample size of 558 provides 80% power to detect small indirect effects passing through one mediator (e.g., $a_1 b_1 = 0.02$). Thus, a sample size of 1,520 in this trial, with 85% follow-up, will provide high power (>99%) to detect at least small three-path and two-path mediation effects of therapeutic alliance and engagement measures.

Power for Objective 3: Statistical power is not an explicit consideration in cost-effectiveness analysis, but probabilistic sensitivity analyses will draw from model input distributions based on 95% CIs in Objective 1. Given the power in Objective 1 outcomes, we expect to obtain precise estimates of in-trial cost-effectiveness in Objective 3.

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

Power for Sex as a Biological Variable: We will compare quit rates between QuitBot and SmokefreeTXT in the male and female subgroups. With 1,520 participants, and an expected ratio of 60% female:40% male, we expect to randomize 912

females and 608 males to the study. Given these sample sizes, and assuming a 9.3% 12-month quit rate for SmokefreeTXT, the minimum detectable odds ratios with 80% power are 1.78 for females and 2.00 for males.

11.6 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 [127].

11.7 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 biological sex (male vs. female), heaviness of smoking index score (≤ 4 vs >4), and percent confidence in being smoke-free in 12 months (≤70% vs. >70%).

11.8 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	40	65	105
Not Hispanic or Latino	872	543	1415
Ethnic Category Total of All Subjects*	912	608	1520
Racial Categories			
American Indian / Alaska Native	27	17	44
Asian	4	2	6
Native Hawaiian or Other Pacific Islander	4	2	6
Black or African American	121	78	200
White	675	445	1120
More Than One Race	80	64	144
Racial Categories: Total of All Subjects*	912	608	1520

12.0 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 studycompletion.

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.

13.0 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 [127].

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