Study Protocol and Statistical Analysis Plan
ClinicalTrials.gov Cover Page

Title: Pilot Randomized Trial of a Smartphone Smoking Cessation Intervention for Cancer Patients (Quit2Heal Study)

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INVESTIGATORS & KEY STAFF

Jonathan B. Bricker, Ph.D. (PI, Fred Hutch)
Jamie Ostroff, Ph.D. (Co-I, Memorial Sloan Kettering)
Jaimee L. Heffner, Ph.D. (Co-I, Fred Hutch)
Brie Sullivan (Project Manager, Fred Hutch)
Kristin Mull (Statistical Research Associate, Fred Hutch)
Noreen Watson (NIDA Post-Doctoral Fellow, Fred Hutch)

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PROJECT SUMMARY/ABSTRACT (DESCRIPTION)

Cigarette smoking has harmful effects on cancer patients' treatment and prognosis, but there are enormous systemic barriers to delivering smoking cessation interventions to cancer patients, including lack of reimbursement methods, lack of provider training and time, and lack of systems for universal assessment, referral, and integration of cessation service into routine cancer care. One solution for addressing these barriers is to give patients immediate and low-cost access to smoking cessation treatment via a smartphone application.

A smoking cessation smartphone application (app) specifically designed for cancer patients who smoke will address the problems of lack of provider training for smoking cessation, lack of funding and insurance reimbursement to adequately build and sustain an in-person smoking cessation team, and lack of immediate access to treatment. In-person behavioral treatment for cancer patients who smoke is effective, so the Tobacco and Health Behavior Science Research Group has incorporated that treatment in designing a cancer-patient version of the existing iCanQuit smoking cessation app for general population smokers. iCanQuit is the result of four years of clinical and user-centered design research, design, and development work totaling over $700,000. It is the first and only app for smoking cessation to be tested in randomized clinical trial and is supported by more research overall than any of the other 500 English language smoking cessation apps now available. iCanQuit offered the ideal infrastructure for the development of a smoking cessation app designed for cancer patients, named Quit2Heal.

Quit2Heal is engaging and tailored to the specific needs of the cancer patient, which include high prevalence of comorbid mental disorders, distress from cancer diagnosis, and lack of awareness of smoking's effects on treatments and outcomes. The Quit2Heal app can be integrated into routine cancer care, and it offers the potential to reach millions of cancer patients worldwide who smoke, something an in-person treatment is unlikely to be ever be able to offer on the same scale and certainly not at the same cost.

SIGNIFICANCE & SPECIFIC AIMS

Cigarette smoking can impact metabolism of chemotherapy and targeted therapy, increase risk of radiation therapy complications, increase rates of postoperative complication and mortality, increase risk of recurrence, and decrease rates of survival. Despite these effects, 64% of cancer patients who smoke pre-diagnosis will continue to smoke post-diagnosis [1]. Providing smoking cessation programs to help cancer patients quit smoking meets an important healthcare need and fills a necessary gap in oncology treatment. National Comprehensive Cancer Network guidelines for treating smoking cessation provide no guidance for the tailoring of cessation interventions for cancer patients (NCCN.org). A major barrier to provide smoking cessation support to cancer patients are a lack of appropriate resources, lack of provider training and their time to offer cessation treatments [2]. To address these gaps and limitations, we developed the first smartphone app for smoking cessation specifically tailored to cancer patients. The app is called Quit2Heal.

Specific Aim. This pilot project provides a timely opportunity to pursue one key aim: conduct a pilot trial comparing the Quit2Heal application for cancer patient smokers to the NCI Smokefree.gov Quit Guide application for general population smokers.

Our primary aims are to: (1) assess the feasibility of the recruitment methods (e.g., cancer treatment center vs Facebook ads), (2) assess participants' engagement with and receptivity to the Quit2Heal app, (3) assess usability of the Quit2Heal app, and (4) show the Quit2Heal app's cessation progress and outcomes compared to NCI Quit Guide in short-term (2 month) follow-up.

RESEARCH STRATEGY

Research Plan and Methods for RCT

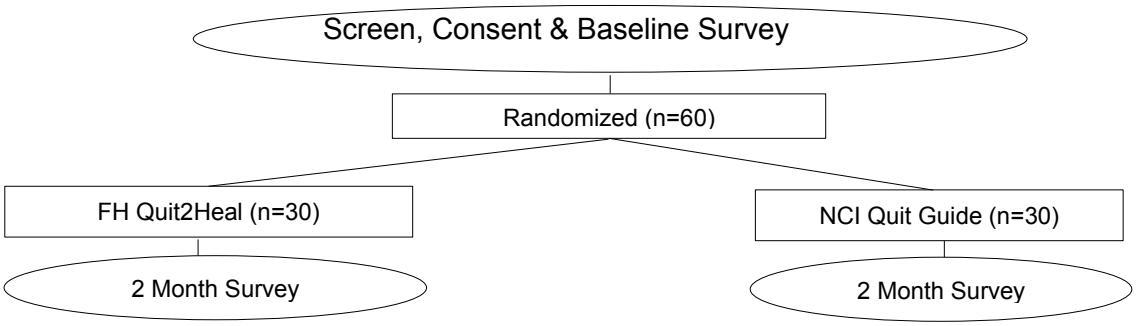
Timeline. Over the course of 18 months, we will recruit, enroll, and randomize participants, conduct a 2-month post-randomization survey data collection, data entry, and quality control, and analysis.

Table 1. Schedule of key activities.

Quarter	**Spring**	**Summer**	**Fall**	**Winter**	**Spring**	**Summer**	**Fall**
1. Recruitment	**X**	**X**	**X**	**X**	**X**		
2. Interventions	**X**	**X**	**X**	**X**	**X**		
3. Outcome Surveys		**X**	**X**	**X**	**X**	**X**	
4. Data Entry & QC			**X**	**X**	**X**	**X**	**X**
5. Analysis						**X**	**X**

Randomized trial experimental design. We will conduct a two-arm randomized controlled trial that compares application-based ACT to an application-based smoking cessation intervention following US Clinical Practice Guidelines (Smokefree.gov). To balance baseline variables between the two conditions, following enrollment we will randomize participants.

Figure 1. Experimental Design



APPROACH

We will conduct a randomized effectiveness trial comparing our ACT smoking cessation application Quit2Heal to the NCI's Quit Guide application. Specifics on our pilot trial, research team, and research strategy are the following:

Eligibility Criteria: (1) age 18 or older, (2) diagnosed with cancer in the past 12 months, or currently receiving or planning in the next 3 months to receive cancer treatment, (3) has smoked a cigarette (even a puff) in the past 30 days, (4) interested in learning skills to quit smoking, (5) willing to be randomly assigned to either smartphone application, (6) resides in US, (7) has at least daily access to their own smartphone, (8) knows how to login and download a smartphone application from the Apple app store or Android Play app store, (9) willing and able to read in English, (10) not currently using cessation medications or enrolled in other smoking cessation programs, and (11) has never used the NCI's Quit Guide smartphone application. To increase follow-up retention, eligiblity criteria also include: (12) willing to complete one follow-up survey, (13) provide email, phone, and mailing address. Participants not eligible for or interested in randomization will be given the given the smokefree.gov website, the 800-QUIT-NOW phone number to reach their state's quitline, and the NCI's Quit Guide smartphone application.

ACT intervention. The overriding goals of the ACT intervention are to (1) develop *acceptance*-related skills for dealing with internal smoking cues while (2) enhancing an enduring commitment to quit smoking [3]. Participants are encouraged to make behavioral choices on the basis of commitment to goals linked to life values, and not on the basis of seeking to modify or alleviate certain sensations, emotions, and thoughts. To achieve these goals, the intervention will focus on ACT's core interdependent processes: *acceptance and commitment.* In ACT for smoking cessation, *acceptance* refers to allowing one's self to have, without defense, the sensations, emotions, and thoughts that cue smoking [3-4, 5-6]. The process of *commitment* in ACT means committing to taking actions to quit smoking even in the presence of sensations, emotions, and thoughts that cue smoking.

Comparison app. To address the question of whether Quit2Heal is more efficacious than an app following USCPG, we chose QuitGuide as the ideal comparison intervention for four key reasons. First, it is one of the few apps (of the 400 available) that follow the USCPG [7]. Second, its content and structure are directly based on Smokefree.gov, the most accessed cessation website in the world. Third, QuitGuide's content is non-proprietary and free to the public, thereby providing maximal transparency, accessibility, and replicability. Finally, because of our pilot RCT and iCanQuit RCT, QuitGuide is now the only app following USCPG with adult quit rate estimates that are based on a clinical trial [8].

Recruitment. Our goal is to have 600 participants screen eligible to randomize 60 study participants. To recruit nationally, we will work with Fred Hutch Communications and Marketing to develop a study media kit that includes a recruitment website, press

releases, and flyers with links to our recruitment website. Depending on the recruitment venue, relevant portions of our media kit will be distributed to Internet media (e.g., online sites and blogs), newspapers, radio stations, television stations, hospitals and community clinics, trade groups, quitlines, cessation websites, and Facebook Ads. We will also recruit through the National Cancer Institute Contact Center (NCICC, also known as NCI's Cancer Information Service), Memorial Sloan Kettering (MSK), and the Seattle Cancer Care Alliance (SCCA) and SCCA affiliate network sites. At NCICC, the trained information specialists will describe the study to potential participants (who call and disclose that they are cancer patients who smoke and would like to quit), using our call script, and will direct them to the recruitment website if they are interested in participating. At MSK and the SCCA clinic and affiliate network sites, fliers, brochures, and TV screen ticker-tape messages can be used to advertise the study, and site research personnel and/or healthcare providers can describe it to eligible participants. Additionally, Donna Manders who runs the cessation program at SCCA SLU will offer the study as an option to eligible patients who have declined participating in her cessation program. Donna and other MSK or SCCA or affiliate network staff will only describe the study and direct patients to the study recruitment website; they will not be involved in the study consent or intervention, which will all take place on the study website and app. We expect to recruit approximately 25% of participants through the NCICC, MSK, SCCA sites and SCCA affiliate network sites.

Enrollment. We will use the identical enrollment method proven successful in our iCanQuit ACT smartphone RCT. Specifically, for participants who screen eligible on the recruitment website and provide their email address, we will instantly send them an email (and two reminders over a 14-day period) inviting them to complete a secured online survey to provide informed consent and complete the baseline assessment. Those not consenting and completing the online enrollment process within 14 days will be sent an email notifying them that they were not enrolled and provide both the smokefree.gov website and the 800-QUIT-NOW phone number to reach their state's quitline. Those randomized will be emailed a secured link to download their app (either Quit2Heal or QuitGuide). All participants will be emailed identical once weekly reminders to use their assigned intervention.

Two-month post randomization follow-up survey. At baseline, we will collect email, phone, and mailing address information as well as optional contact information on at least 2 collateral contacts. At 2 months post randomization, participants will be sent an email with an invitation to complete the 2-month follow-up survey. An additional two reminders will be sent within 9 days. A phone survey will be conducted for those not responding by the 12^{th} day. There will be 12 attempts made over 12 days. Lastly, a reminder letter will be sent that will include a $2 bill pre-incentive to encourage participation. We will send reminder letters at each follow-up for those non-responders using an "Address Service Requested" envelope, for automatic forwarding to new mailing addresses. Each survey and Internet tracking will also collect address information. A final postcard with just two questions will be mailed out if follow-up rates are below 70%. All respondents will be mailed $25 after completing the survey, with a $10 bonus if they complete the survey online within 24 hours.

MEASURES AND STATISTICAL ANALYSIS PLAN

Table 2. Participant surveys and time points when they will be administered. (All participants)

Measure	Screening	Baseline	2-month	Purpose
Eligibility & Enrollment (24 items)	x			Eligibility, Enrollment, & Stratification
Demographics (24 items)		x		Stratification & Exploratory
Nicotine Dependence (6 items)		x	x	Stratification & Aim 1
Smoking/Tobacco History (2 items)		x		Aim 1, Aim 4, and Exploratory
Tobacco Use (9 items)		x	x	Aim 4
Alcohol Use (4 items)		x	x	Aim 4
PTSD Symptoms (6 items)		x	x	Aim 4
Post Traumatic Growth Inventory (21 items)		x	x	Aim 4
Generalized Anxiety Symptoms (7 items)		x	x	Aim 4
Social Anxiety Symptoms (3 items)		x	x	Aim 4
Depression Symptoms (10 items)		x	x	Aim 4
Distress Tolerance (6 items)		x	x	Aim 4
Values (10 items)		x	x	Aim 4
Internalized Shame Symptoms (5 items)		x	x	Aim 4
Self-Compassion (10 items)		x	x	Aim 4
Smoking and Cancer Outcome Expectancies (4 items)		x	x	Aim 4
Quitting Self-Efficacy (1 item)		x		Aim 4 and Exploratory
Internalized and Perceived Stigma Items (9 items)		x	x	Aim 4
Mobile Device Use (6 items)		x		Eligibility and Aim 1
Receptivity/utilization (14 items)			x	Aim 2 and Aim 3
Cessation & Extra Aids (5 items)			x	Aim 1, Aim 3, and Exploratory
Willingness to discuss (1 item)			X	Follow-up
Acceptance of cues (18 items)		x	x	Aim 4 & Exploratory

Analyses. Our aims examining feasibility, engagement, usability, and cessation are all exploratory. Analyses based on follow-up survey items will be limited to participants who complete the 2-month follow-up survey. All other analyses will include all randomized participants.

Feasibility of recruitment methods. We will assess the number and proportion of study participants recruited directly by the cancer treatment center and through Facebook ads. A table with N (%) by treatment arm will be provided.

Engagement and receptivity to the Quit2Heal app. We will assess the number of times participants log into their assigned apps and total time spent on the apps based on data automatically logged on the secure server. Receptivity to the apps will be assessed by two items on the 2-month follow-up survey. One asks participants to rate the overall usefulness of their assigned Quit2Heal app for quitting smoking. Ratings will be dichotomized as "somewhat", "mostly", or "very" useful vs. lower ratings. The second item allows participants to provide comments or suggestions that will allow us to qualitatively assess receptivity to the app and aid in future development of the app. Tables with N (%) or Mean (SD) by treatment arm will be provided.

Usability of the Quit2Heal app. We will compare the two arms on items measuring the usability of the assigned program using descriptives. If participants indicate that they are willing to discuss their experience in the study, we will contact them to inquire about their user experience with the app. Responses will be used to qualitatively assess ease of use, appeal of the app design, and suggestions users may have for improvements.

Cessation outcomes and cessation progress at 2-month follow-up. We will report the 30-day point prevalence quit rate at 2-months post randomization, as well as secondary cessation outcomes 7-day and 24-hour point prevalence abstinence. We will provide both complete case and missing=smoking results for each study arm. Quit2Heal vs. NCI Quit Guide cessation rates will be compared using logistic regression, adjusting for the three factors used in stratified randomization: Heaviness of Smoking Index, Commitment to Quitting Smoking Score, and recruitment method.

Cessation progress outcomes will include number of 24-hour quit attempts, change in number of cigarettes smoked per day since randomization, nicotine dependence level, acceptance of cravings to smoke, commitment to quitting, and use of nicotine replacement therapy or medications to aid quitting. Tables with N (%) or mean (SD) by treatment arm and p-values obtained from logistic regression, linear regression, or negative binomial regression models adjusted for randomization factors will be provided.

PROTECTION OF HUMAN SUBJECTS

Risks to the Subjects

Human subjects' involvement and characteristics. We will conduct a two-arm randomized controlled trial that compares the Quit2Heal cancer-patient specialized application-based ACT to an application-based smoking cessation intervention following US Clinical Practice Guidelines (Smokefree.gov). To balance baseline variables

between the two conditions, following enrollment we will randomize with stratification according to these known predictors of smoking cessation: nicotine dependence (Heaviness Smoking Index cut off score of 4 [9]), motivation to quit (Commitment to Quitting Scale cutoff score of 4 [10], and recruitment method (clinic vs. social media). The hypothesized moderators will be measured at baseline. The hypothesized mediators will be assessed at both baseline and two months post randomization, while cessation and progress outcomes will be measured at 2 months post randomization.

Potential Risks

Main risks. The main risk to participation in this study is a *small risk of breach of confidentiality*. A breach could possibly occur if, for example, an unauthorized person accesses the study's database records and/or hard copy records, telephone enrollment or 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 survey. Finally, some smokers making quit attempts may experience some short-term discomfort associated with nicotine withdrawal.

PROTECTION AGAINST RISK

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

Protection against breach of confidentiality. 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. 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. The public web server is segregated from the rest of the Fred Hutch network within a DMZ (demilitarized zone). After indicating interest in the study, participants will complete online surveys via the secure sockets layer protocol (SSL). Employment of the SSL protocol will prevent anyone from intercepting data passed between the end user's web browser and the web server. Once randomized, each treatment group will have access to their assigned smartphone application protected upon successful download. All connections to the enrollment website will be made using the secure sockets layer (SSL).

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. The public web server is segregated from the rest of the Fred Hutch network within a DMZ (demilitarized zone). Study participants who complete these online surveys will only have access to data that they have entered on in-process surveys. Participants may access partially completed surveys via a participant-specific link provided by email and entry of the participant's birthdate. Once surveys are complete, the data are inaccessible from the web site. Participants and others will be prevented from accessing any other data on the Web server by a number of operating system, web server, and application controls. Users will connect to the web site to complete the surveys using the secure sockets layer protocol (SSL). Employment of the SSL protocol will prevent anyone from intercepting data passed between the end user's web browser and the web server.

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

Protection against discomfort of nicotine withdrawal. Participants who quit smoking may experience some discomfort associated nicotine withdrawal. Participants will also be fully informed of the symptoms of nicotine withdrawal during the informed consent process. Interventions in 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; if unsuccessful, the breach/complaint will be reported to the IRB office, and the participant will be referred to Karen Hansen, Fred Hutch IRO Director.

Potential Benefits of the Proposed Research to the Subjects 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 on their cancer treatment and prognosis, and overall lifetime health.

Importance of Knowledge to Be Gained. The proposed intervention shows exciting promise for improving cessation rates among cancer patients, who currently do not have standard cessation interventions as part of their treatment. If effective, the public health impact of this low-cost intervention is significant. Even if the intervention is not better than our standard care control, it suggests the new intervention should be disseminated as a reasonable alternative to other publicly available application-based interventions.

INCLUSION OF WOMEN AND MINORITIES

The population for this study will be 60 adult male and female cancer patients who currently smoke and want to quit, or have quit smoking within in the past 30 days. Recruitment and eligibility screening methods are designed to achieve a broad representation of adult smokers that is 50% female and 25% minority race/ethnicity. The expected gender and race/ethnic distribution of the trial participants is reported in the Targeted/Planned Enrollment Table.

TARGETED/PLANNED ENROLLMENT TABLE

Total Planned Enrollment: 60

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender[1]**		
	Females	**Males**	**Total**
Hispanic or Latino	2	2	4
Not Hispanic or Latino	43	13	56
Ethnic Category: Total of All Subjects *	45	15	60

Racial Categories			
American Indian/Alaska Native	1	0	1
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	7	4	12
White	36	9	44
More Than One Race	1	1	2
Racial Categories: Total of All Subjects *	45	15	60

* The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: Total of All Subjects.”

INCLUSION OF CHILDREN

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

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

DATA SAFETY AND MONITORING PLAN

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

Data Management. In addition to and in combination with meeting HIPAA regulations, data collected and managed will be securely handled to prevent unauthorized access or modification. All those in the study staff who have access to data on those screened and/or participating in the study will follow these procedures when handling the data: (1) education about the need for security and confidentiality, (2) signing a confidentiality agreement, (3) using passwords to control access to the electronic databases and

regular changing of passwords, (4) keeping paper versions of surveys and any other paper versions of screened/participating individuals' data in a locked room, & (5) servers will be protected by firewalls, McAfee Virus Scan Enterprise anti-virus software, daily full tape backups stored in a locked room, and encryption via the https protocol.

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

Monitoring Data Quality and Integrity. Several procedures will be used to maintain data integrity. All databases will be stored in a centralized location at FHCRC on a secure server. Data will be backed up daily and access will be password protected and limited to persons working on the project. Persons will only have access to specific data required for their project tasks. Identifying information will be stored separately from the assessment data. Data will be audited on an ongoing basis to ensure confidentiality safeguards are being maintained and data integrity is being maintained. Data entry systems will be set-up to allow field checks, range checks for continuous variables, valid value checks for categorical variables, and checks for logical consistency of responses. Queries and data reports will be generated on a routine basis to monitor data quality.

GUIDELINES FOR MONITORING AND REPORTING UNEXPECTED AND ADVERSE EVENTS

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

Reporting. Study staff will be trained, and required, to report all unexpected and adverse events to the Principal Investigator. An on-line form will be available for this purpose. Adverse events beyond what would be expected in the course of smoking cessation will be reported to the FHCRC's IRB in accordance with FHCRC policy.

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

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

Attribution*.* The Principal Investigator, in consultation with the Co-Investigator, will decide if a UE should be classified as an AE. If an event is classified as an AE, further attribution will be determined, as follows:

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

Reporting.

1. **SAE's:** For AE's meeting the criteria for an SAE, regardless of its attribution, a FHCRC SAE Report form will be completed. The SAE Report form will be faxed by the Principal Investigator to the IRO office at 206-667-6831 within 24 hours of the internal report. All available information will be submitted. Should additional information become available after the initial report, a revised report will be submitted within 15 days.
2. **AE's that do not meet the criteria for SAE:** For these events, the Principal investigator or the Study Coordinator will complete and submit an FHCRC Adverse Event Reporting form within seven (7) calendar days of learning of the events.
3. **UE's that do not meet the criteria for AE's**: For these events, the Study Coordinator will complete and submit an FHCRC UE Reporting Form within seven (7) calendar days of learning of the events.

A Data Safety Monitoring Board will not be required since this is a minimal risk application-based behavioral intervention.

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