'Quit on the Go' Pilot Trial: Innovative Smartphone App for Quitting Smoking for the Seriously Mentally Ill

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Background & Rationale

The smoking rate among adults with serious mental illness (SMI), such as schizophrenia spectrum, bipolar, and recurring depressive disorders is 3 to 4 times the rate of the general population (CDC, 2011). Such high rates of smoking consumption have serious health consequences for people with SMI. As a result of smoking, people with SMI have higher incidence of cancer (McGinty et al., 2012) and live 25 years less than those who don't (Colton & Manderscheid, 2006). This population is also less likely to use preventive medical care (Hackman et al., 2006), receive adequate medical treatments (Wang, Demler, & Kessler, 2002), or possess the financial resources to access medication and treatment (Kessler et al., 2001). Furthermore, even though research shows that people with SMI often want to quit smoking (Irving, Seidner, Burling, Thomas, & Brenner, 1994), these individuals are 2 to 8 times more likely to fail smoking cessation treatments relative to adults without SMI (de Leon, Gurpegui, & Diaz, 2007). In sum, there is a great need for innovative and highly engaging behavioral interventions tailored to this population.

Computer technology offers great promise to develop innovative and highly engaging behavioral treatments for people with SMI. These technologies can deliver behavioral health interventions that are cost-effective, evidence-based, and tailored to each individual's needs. A recent survey among 1592 individuals with a diagnosis of SMI reported that 72% of them had a mobile device (Ben-Zeev, Davis, Kaiser, Krzsos, &

Drake, 2013). As a result, the Center for Medicare and Medicaid is already expanding reimbursement procedures to include technologically-based services. Given that mobile technology is already highly adopted in people with SMI, it holds great promise for smoking cessation treatments in this population.

In 2 previous usability studies funded by the National Institute of Drug Abuse, we examined critical features required by individuals with SMI who use smoking cessation apps. In a first study (Vilardaga et al., 2015), 240 hours of field experience using a standard smoking cessation app, and 10 hours of recorded interviews and task performances revealed that: (a) participants needed guidance to complete critical tasks, and experienced high task completion latencies (M = 4.5 minutes), (b) levels of usability were below industry standards (SUS = 65). Further, qualitative interviews revealed the following themes: (a) the need to simplify data entry and layers' structure, (b) the need of incremental rewards and a focus on the process of cutting down rather than quitting, (c) the importance of coaching and assistance, (d) the need of more interactive and engagement features (e.g., points, gaming), (e) a request for more elaborate psychological skills for quitting and (f) the need for finer-grained cigarette tracking (i.e., half cigarettes).

In a second usability study (Vilardaga et al., 2016) we developed a tailored smoking cessation prototype app for people with SMI and tested it during 10 hours of qualitative interviews. Results indicated that with the tailored app design: (a) users were able to complete tasks with minimal guidance, (b) participants had a positive view of the apps' use of points and rewards, (c) participants enjoyed the use of the psychological skills proposed, (d) levels of usability were above industry standards (SUS = 74). Users comments included: "I wish you guys could send this to me so that I could practice it and learn it... (P1)", "This is very comfortable because the information goes right into your mind (P5)", "Eye catching... this would be kind of fun (P4)", "Awesome, its inviting [...] the cartoons are cute (P3)", "It was simple, informative, easy to use [...] the points... the most exciting (P3)".The results of these 2 studies laid out the foundation of the Pilot Randomized Controlled trial we propose in this application.

Study Purpose

We propose to conduct a Pilot Randomized Controlled trial comparing a novel app tailored to people with SMI, Learn to Quit, to an app based on best-practice smoking cessation standards (QuitGuide). This study will test the feasibility of implementing a novel smoking cessation intervention using a smartphone app in individuals with SMI.

As an adjunct to this feasibility trial we may conduct Single Case Experimental trials in which each individual will serve as their own control. Data from each individual will be used to iterate on critical user centered design features of the Learn to Quit app. Each Single Case Experimental trial will last a maximum of 30 days. We plan to recruit no more than 30 patients for these adjunct single case studies.

Innovation & Significance

The key innovation will be a new model to enhance the effectiveness and reach of smoking cessation interventions in people with SMI. Our intervention will be the first: (1) to use smartphones for smoking cessation in people with SMI; (2) ACT for smoking cessation intervention in people with SMI; (3) smoking cessation intervention to integrate smartphones and pharmacological treatments into ongoing mental health and addiction care.

The proposed study meets NIDA's major programmatic priorities of using innovative technologies (e.g., smartphones) and integrating behavioral and pharmacological interventions to improve substance use treatment and outcomes (NOT-DA-10-019). The proposal addresses a serious problem–high smoking rates in people with SMI—in a high priority, high cost population, by delivering ACT, a promising behavioral intervention for smoking cessation. Finally, it operates in "real-world" settings using a wide reaching technology. If eventually proven effective, the proposed intervention will provide a new model for delivering inexpensive, widely available smoking cessation interventions in adults with SMI.

Study Aims

Primary Outcomes

The primary objective of this pilot trial is to evaluate the usability and user experience (UX) of two smoking cessation smartphone apps – one whose design is tailored to people with serious mental illness; another designed for the general population. We are investigating whether a tailored smoking cessation app for people with serious mental illness results in higher levels of engagement with smoking cessation content as compared to an app designed for the general population.

Engagement with each app
- Frequency of daily app openings in each group throughout the study duration (i.e., 4 months)
- Time of daily app use in each group throughout the study duration (i.e., 4 months)

Usability of app design
- Measured by the System Usability Scale (SUS)

For this pilot trial, we are also looking to test whether smoking cessation mHealth trials can be feasibly conducted with this population. To do this we will be evaluating recruitment, enrollment, and retention rates relative to our established goals.

Recruitment rates
- Percentage of subjects enrolled relative to recruitment goal

Participant retention
- Percent of subjects who complete 4-month follow-up assessments

Feasibility of measurement strategy
- Percentage completion of assessment measures

Secondary Outcomes

Number of cigarettes smoked per day

Biochemically verified abstinence
- Percentage of subjects in each group reporting abstinence (determined by self-report)
- <= 6 ppm in carbon monoxide testing

Point-Prevalence abstinence rates
- 30-day, 7-day, & 24-hr self-report smoking tobacco usage

Quit attempts

Nicotine dependence
- Scores on the Fagerstrom Test for Nicotine Dependence

Cravings and negative affect

Nicotine Replacement Therapy usage

Psychiatric symptoms
- Scores on the PANSS and BSI

Design & Methodology:

In a two-arm pilot randomized controlled trial, this study will compare Learn to Quit (n = 60) to an app based on best-practice smoking cessation standards, QuitGuide (n = 60; see Figure below). Both arms will receive Combined Nicotine Replacement Therapy and a proof-of-concept smartphone coaching procedure delivered by research staff.

Participants will be given a smartphone with the corresponding app downloaded, and will use it over the next 16 weeks, coming in for four follow-up appointments at 1-month, 2-month, 3-month, and 4-month time points.

During the baseline and follow-up appointments, we will conduct assessments for mental status, substance abuse, health status, smoking status, and usability ratings of participants. We will be interviewing participants about their experience when using the app, and audio recording these sessions to be transcribed. We will also be tracking participants' app usage over the course of the study as they use it in their everyday lives using Google Analytics and downloading this onto the Duke Medicine server.

To balance baseline variables between the two arms, treatment assignment will use an automated algorithm stratifying factors known to predict dropout from smoking cessation treatments: female (yes/no), ≥20 cigarettes per day (yes/no), a current mood disorder (yes/no). Participants will be given a smartphone with the corresponding app downloaded, and will use it over the next 16 weeks, coming in for four follow-up appointments at 1-month, 2-month, 3-month, and 4-month time points.
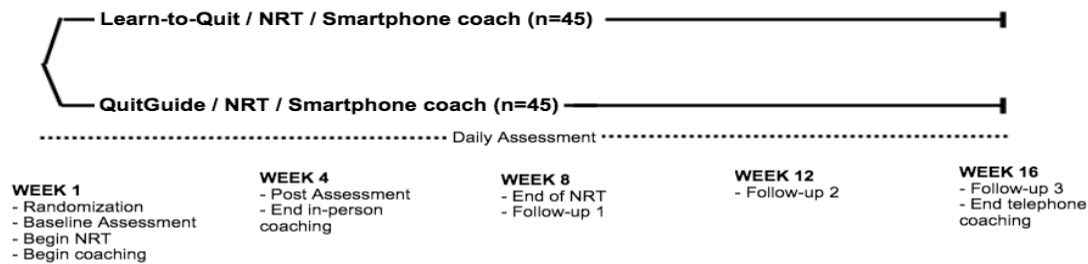
Subjects

Selection of Subjects

The population will be up to 120 participants for the randomized controlled trial (30 for the single-case trials). Inclusion/exclusion criteria are:

(1) Currently receiving mental health treatment

(2) Current ICD-10 diagnosis of schizophrenia, schizoaffective, bipolar or recurring depressive disorder;

(3) The patient smoking ≥ 5 cigarettes per day over the past 30 days (as indicated by self-reported daily smoking), and biochemical verification by a carbon monoxide breath test at baseline (cutoff: CM > 6 ppm);

(4) Desire to quit smoking in the next 30 days;

(5) Age 18 and older;

(6) Willing and medically eligible to use Nicotine Replacement Therapy;

(7) Fluent in spoken and written English;

(8) Have a working email, mailing address, or alternative contact person;

(9) Adherence to psychiatric treatment as prescribed by their provider;

(10) Have stable housing

Exclusion Criteria

(1) Problematic alcohol or illicit drug use in the last 30 days triangulated from substance use disorder diagnosis, self-report, and provider feedback;

(2) Acute psychotic episode, unsafe to participate in the study, or psychiatrically unstable determined by self and provider report as well as research staff observation;

(3) Being pregnant, breastfeeding, or the intention to become pregnant in the next 4 months;

(4) Hearing, comprehension, or visual limitations that preclude study participation;

(5) Currently receiving any pharmacological and/or behavioral intervention or counseling for smoking cessation;

(6) Using non-cigarette forms of tobacco as the primary source of nicotine (e.g. e-cigarettes, chew)

Participants for the single case experimental trials will meet the same eligibility criteria as those for recruited for the Randomized Controlled Feasibility trial.

When contacting treatment providers, research team members will ask them to verify if they seem to be a good fit for the study per inclusion/exclusion criteria.

The Principal Investigator will ultimately make the determination of whether a participant is eligible to participate and document this.

Subject Recruitment

Our research team will recruit subjects using a variety of methods.

For two methods, we will utilize medical records querying systems to identify and pre-screen possibly eligible subjects. These include the use of medical record query tools to identify patients we want to reach and pre-screening them before having their healthcare provider send an invitation to participate in the study. Additionally, after a report is generated from the medical records of patients meeting our defined criteria, our research team will use patient portals to directly invite selected patients to participate in the study.

In order to access these records, we will obtain a Waiver or Alteration of Consent and HIPAA Authorization from our IRB. When using the medical records query tools, someone from the research team will notify and ask potential subject's treatment provider about the eligibility of the potential participant. If the provider indicates the patient may meet the study's eligibility, a member of the research team will send a recruitment letter to the patient on behalf of the treatment provider, with an option to "opt out" of further contact by researchers. For those providers who would prefer to opt out of the letter, they may approach their patient about the study during an appointment with them. Some clinics may utilize other clinic staff (e.g. nurses, medical assistants) to approach patients about the study. We may also utilize alerts and other tools within the medical records system to facilitate communication between research staff and providers, and providers with their patients.

Unless a patient opts out of further contact, research staff will follow-up with a phone call after 10 business days of sending the letter to invite the patient to participate, answer study questions, and confirm eligibility criteria. If the patient indicates interest in participating, research staff will tentatively schedule a baseline assessment at the research lab.

For the use of patient portals, patients will be sent the invitation to participate in the study. They can indicate on the portal whether or not to seek more information about the study which will send a communication to the research team. Those who indicate interest in participating will be contacted by the research team to proceed to the initial screening phase.

The research team will approach other clinics in the community that serve our population, presenting the study to those clinic providers. Treatment providers then may refer their patient to the study if they believe they are possibly eligible. We may also have people who call other research labs interested in participating in a study. If the candidate seems to qualify for our study, they may be referred to our research team by the research team of the other lab.

Research staff will post flyers with the study contact information at various locations in the community (e.g. clinic, library). We may advertise in local newspapers, newsletters, internet postings (e.g. craigslist.com, researchmatch.org, dukelist.edu). Candidates may find our study through an advertisement, or web posting. They can call in to the lab, or take the web screening survey. The research team may also do public outreach at relevant events, handing out study flyers and leaflets, answering questions about the study from the public, and providing the chance for people to take the web screening survey on a lab-managed electronic tablet or laptop.

Those interested in learning more about the study will call in, and if they are willing, a research staff member will go through the screening questions with the candidate. If the candidate seems eligible after the phone screen, and they decide they would be

interested in enrolling, a research staff member will schedule a time to conduct a consent session.

We will also implement a peer referral system which encourages already randomized, current research subjects to refer people they think might qualify for the study to us. When new subjects are enrolled into the study, research staff will ask if someone already in the study had referred them to us. We will then compensate those subjects $10 for every enrolled subject they referred.

Approaching Subjects to Participate:

Research staff will approach potential participants by telephone calls in private offices so patient information cannot be overheard. However, for those patients pre-screened and recruited through the medical records, their' treatment providers will be the first contact (i.e. letter, in-person approach) they have about the study.

During public outreach, research staff will use a "pull strategy" allowing people to come up to staff to learn more about the study.

In order to approach candidates for participation, the research team will need to collect certain personal information (e.g. names, contact information, psychiatric treatment details). Only the research team will have access to this information, which is stored in a database hosted on a secured server.

Once described, and if still interested, research staff will ask screening questions to the interested patient. Those that decline to participate at any point will have their right to refuse participation acknowledged, and be thanked for their time. In order to avoid approaching people multiple times, we will track those we approach noting whether they refused, screened out, or interested in participating at a later time.

Minimizing Coercion

The research team will stress to candidates that participation is voluntary and that they can change their minds or withdraw from the study at any point without penalty.

Research staff will emphasize that the patient's decision to participate (or not) in the study should not affect the services they receive, and that study data will not be shared with anyone outside the research team, or those contracted by the team without their written permission.

Requirements to Participate

All subjects require their treatment provider's approval to receive the study interventions. In order for the research team to obtain this, we ask all subjects to complete a Release of Information (ROI) to talk with primary treatment providers.

Subjects are required to complete study visits and use the study app assigned to them. We offer both in-person and remote methods for completing these visits. There may be some circumstances where a study visit will need to occur in-person. In that case, we expect subjects to have transportation to the location of where the study visit is to be completed.

Subjects must be the primary possessor of the study phone while actively enrolled in the study. They are advised to keep the security settings and to retain the study phone passcode programmed for the device set for them at the beginning of the study by research staff for the duration of their enrollment.

Subjects need not incur any costs to participate in these studies.

Target Population Distributions

Inclusion of Women: In a previous clinical trial by members of the mentoring team in a similar setting, women made up 34% of our sample. We expect a similar distribution.

Inclusion of Minorities: We expect the demographics of participants who participate in this project will reflect the overall racial and ethnic characteristics of the Greater Durham area. Based on information from the United States Census Bureau, Durham demographics are 48.3% Caucasian, 40% African American, 4.7% Asian American, 0.2% Native American, 2.8% Some other race, 3.9% Multi-racial. Fifteen percent are Hispanic.

Steps for Withdrawing

When a subject withdraws from the study, we will be consider them "inactive" in the study from their participation "stop date". After this "stop date", we will not collect any further study data from them. Unless a subject asks us to remove their data, we will retain any data the subject has already provided during their participation in the study.

If a subject decides to withdraw from the study, they will need to communicate this to the research team. We will count the date of this communication as the subject's "stop date". As an alternative to full withdrawal, we may ask subjects to continue scheduled evaluations without the study intervention(s). In these cases, their "stop date" will be the date of their last study session.

Subjects who initially enroll in the study during the consent session but before randomization the research team deems ineligible, we will consider them a "Screen Fail". Once we have determined this for a subject, we will notify them that they are not eligible to continue participating in the study. We will consider them inactive in our study and we will not initiate any further study procedures. The date of the previous consent session will count as the subject's "stop date".

The PI may decide to withdraw a subject if they determine that the study is harmful to the subject, that participating is no longer feasible for the subject, or that they are inappropriate to continue participating in the study. This "Withdrawal by PI" will be applicable after we have randomized the subject to the treatment condition. In this case, the subject's "stop date" will be the day the PI makes this withdrawal determination.

Subjects may be passively withdrawn by becoming "Lost to Follow-Up". This is when we consider the subject inactive in the study if they do not complete certain study sessions within a given timeframe. This can happen under two conditions: If they either don't complete their baseline visit 30 days after their initial consent visit (or schedule within this timeframe); or if they don't complete their last follow-up session within 90 days after its due date. When a subject becomes "Lost to Follow-Up", we will no longer initial communication with them about completing the study. However, if these subjects initiate contact with us and/or provide further study data, we may continue communicating with them. The "stop date" for these subjects will be the day of their last completed study visit.

Regardless of method, withdrawn subjects will need to return the study phone given to them for use while participating in the study. Even if we consider a subject inactive, we will continue to contact that subject until the study phone is recovered. In addition, we would request that we conduct a final follow-up interview to get any last words on their experience with the study app and the trial more generally.

If subjects lose more than one study phone during the course of their participation, we may not give out a replacement. However, these subjects may still continue to participate in the study without the app intervention by completing non app-related outcome measures during study follow-up sessions.

Sampling Frame

Since this will be a feasibility trial we expect the intervention effect sizes to have notable variance (i.e., wide confidence intervals), thus the relevance of the current study is linked to its significance and potential impact to the field, and not on its ability to estimate parameter estimates in the population. In this scenario, a precision (rather than power) approach is especially suited, since calculating confidence intervals is ideal for preliminary or pilot investigations, and facilitates that sample size is determined by practical rather than formal considerations.

Given that retention is a key issue in smoking cessation studies, we will focus on this primary outcome. Prior studies in the general population show 93% 6-month data retention for ACT, and 70% for standard of care. Achieving a minimum retention rate of 75% in each condition with a two-tailed precision of +/-5% will require 76 subjects. Ninety participants (45 per arm) will thus provide even higher precision of the retention rate estimate.

Risks & Benefits

Nature and Degree of Risk

The anticipated physical, psychological, social, or legal risks are all minimal. The possible side effects of using Nicotine Replacement Therapy in this study include skin irritation at site of patch placement, insomnia, rapid heart rate, dizziness, nausea, and diarrhea. As in all studies (including qualitative interviews), there is the possibility of unauthorized disclosure of confidential information; discomfort or embarrassment related to their ability to use a mobile device. Both the PI and the Research Study Coordinator are mental health professionals, and can use their clinical judgment to assess how much risk a participant may be put in by doing this interview.

Minimizing risk of harm and protecting subjects' rights and welfare

To address the possible side effects from Nicotine Replacement Therapy (NRT) patches, we will have our study doctor, Dr. Paolo Mannelli to be available to monitor and evaluate participants' use in addition to consulting with the research team. We will also emphasize placing the NRT patch in varying locations and replacing the patch every morning, to reduce possible skin irritation. The research team will monitor use of the NRT as well as reviewing any reported changes in medications by the subject.

Applicants will be screened to eliminate candidates with disorders or conditions that are contraindicated (see inclusion/exclusion criteria) or those who are not able to provide informed consent. We work to coordinate the subject's participation in the study with the medical/mental health care they are already receiving.

The research team will be sensitive to issues surrounding confidentiality and other forms of participant risk, taking steps to maintain confidentiality and reduce the risk of unauthorized disclosure of subject data. For instance, we will use a research subject identification number (subject ID) as the identifier for research data rather than using personally identifiable information (PII).

We will emphasize the confidential nature of the data collected in this, explaining our safeguarding procedures study to potential and enrolled research subjects. We will note which de-identified data will be shared, and how we work to ensure its security.

If at any time a participant expresses discomfort over any aspect of the study procedures, the research team member may discontinue the distressing activity.

Possibility of discovering a subject's previously unknown condition

We will use a set of safety procedures to ensure safe participation during the research trial. The research team has medical personnel on staff nearby (i.e. Duke University

Medical Center) that are available to deal with any unforeseen medical complications that may arise.

The research team will assess medical and psychiatric safety, treatment compliance, and data completion for each subject. We will deal with psychological problems or distress should it arise. If needed, research staff can assist participants over to the Emergency Department.

Consistent monitoring of participant progress provides one level of safety procedures. Another level of safety procedures involves evaluation of data collected (especially items related to aggression/suicidality in the BSI) and of verbal reports of suicidal and/or homicidal intent to staff members. All reports of suicidal or homicidal ideation will be immediately reported to the PI as well as to the patient's treating clinician. All research staff will receive training in identifying suicide/homicide risks and/or signs of dangerous intoxication and in following the steps needed to appropriately respond to these signs.

Participants judged by study investigators at any point to be a danger to self or others or who are judged to be in grave danger due to continued drug use and/or to medical/psychiatric problems will be discontinued from the study but actively connected with their treating clinician.

Anticipated benefits of research on individual subjects

Participants might benefit from the study in quitting smoking. We will be providing free nicotine patches to participants, and the monitored use of the smoking cessation apps may contribute to quitting smoking.

Anticipated benefits of research on society, benefits outweighing risks

Smoking directly causes 480,000 deaths a year in the United States. Sixty to 88% of individuals with serious mental illness smoke. Furthermore, half of the cigarettes sold in the US are bought by individuals with serious mental illness.

Information derived from the study could help improve the effectiveness and reach of smoking cessation treatments for adults with serious mental illness. This may benefit society and other clients of treatment programs. Participants in the study may see improvement in the physical, psychological, occupational, familial, and economic problems associated with their tobacco cessation.

The interviews proposed in this research may guide the development of tools to treat tobacco addiction in this population. Given that levels of access to mental health providers depends on geographical location, this study may help develop low-cost and high-reach smoking cessation tools for individuals with serious mental illness in areas where there are few smoking cessation services or are lacking (e.g., rural areas).

Therefore, the minimal risks to participants are reasonable in relation to the anticipated benefits.

Duration of the Study

The randomized controlled trial will last for 4 months (or 16 weeks). We plan to run this study for 18 months from enrolling our first research subject. Once all subjects complete their participation in the study, we expect to take another 18 months to complete data analysis, publish results of the trial, complete all reporting requirements, and close out the study.
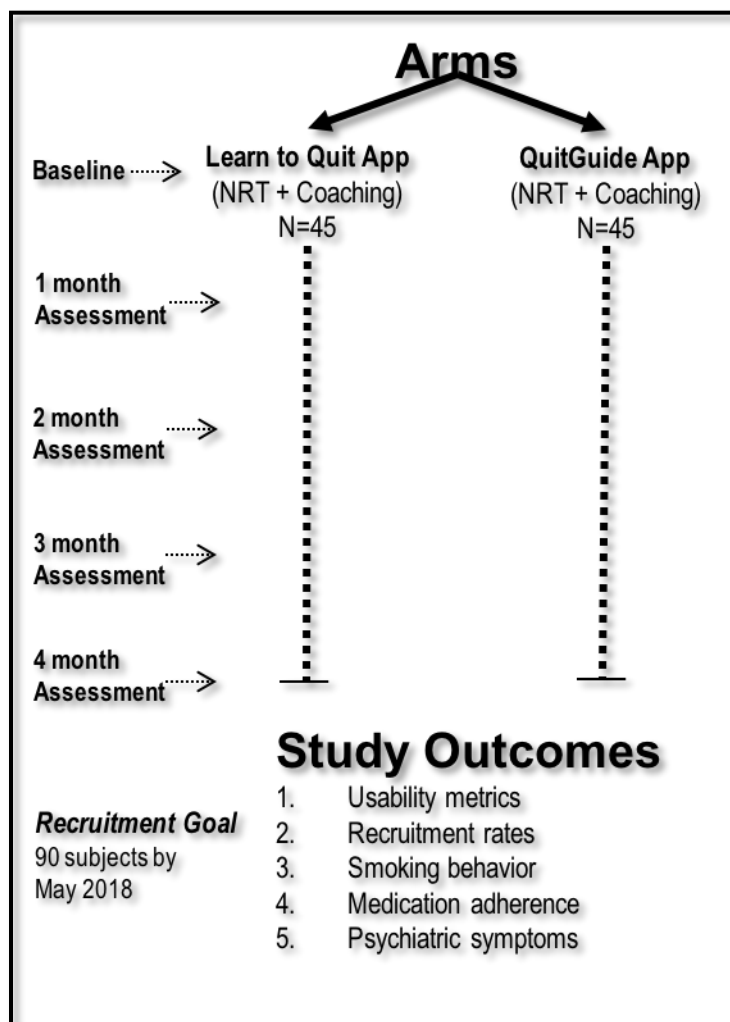
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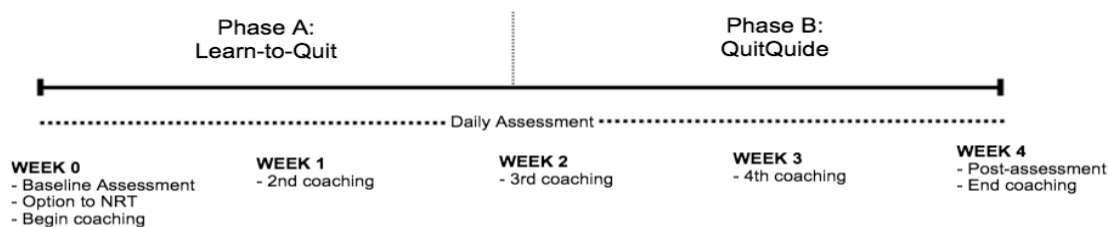
Study Interventions

***Experimental manipulation*:**

a. *Learn to Quit* – a smartphone app developed in collaboration between the research team and Smashing Ideas designed for helping those with SMI quit smoking using Acceptance and Commitment Therapy (ACT). It incorporates a learning component of skills acquisition, gaming feature to keep users engaged, and a tracking component to record smoking habits and moods (see Appendix A for screenshots).

b. *NCI QuitGuide* – a smartphone app developed by the National Cancer Institute which uses the similar principles to smokefree.gov. NCI QuitGuide has the following intervention components: (a) psycho-education about the impact of smoking in health, (b) tracking of smoking habits, and (c) Tips for quitting (e.g., distraction strategies). (see Appendix B for screenshots)

***All participants will receive*:**

c. *Nicotine Replacement Therapy* - Standard 8-week course of nicotine replacement therapy (see NRT section for more details) All participants will be given nicotine replacement therapy lozenges in conjunction with the nicotine patches following recommendations contained in the US DHHS Clinical Practice Guideline. They will receive about a week's supply of lozenges for when they come up with a quit date, and instructed to use them for the week or so following the quit date. NRT used in this study is available as over-the-counter medication. We do not plan to study the NRT itself, nor do we plan to submit any data about it to the FDA. The study physician will provide oversight of nicotine replacement therapy dispensing and monitoring, and consultation as needed with the research team.

d. *Smartphone coaching* – 4-weeks of coaching on how to use the smartphone apps. Research staff will provide the coaching as proof-of-concept of the coaching procedure to be ultimately delivered by care providers. The first coaching session will be completed by a research staff member trained on the study apps. This session will cover orientation to the smartphone and assigned app. Research team members will complete later

coaching sessions either over the phone or in-person. These coaching meetings will be brief (~15 minutes), done on a weekly basis, and will have a focus on providing technical assistance. These sessions will be audio recorded and sent to a Duke-approved contracted agency for transcription.

Nicotine Replacement Therapy (NRT)

The study interventions have been described above. However, we'll explain the dosage and administration of the nicotine replacement therapy (NRT) more in-depth.

According to the FDA, the use of these drugs does not constitute "Human Subject Research". Although our study involves "human subjects", as our participants will be a recipient of the NRT patches, we are not developing information about the NRT patches or lozenges for submission to, or inspection by, the FDA. The research team will direct subjects to use the study drug (i.e. NRT) according to labelled instructions. We will not be using an Investigational Drug Service (IDS), and will conduct all of these activities stated below ourselves. We will be asking subjects at follow-up sessions about their use of the study NRT or any other NRT they have been using during their participation in the study.

If after randomization, a subject's use of NRT is found by a healthcare professional to be detrimental enough to their health we will discontinue use of the NRT for the duration of the study. These subjects may continue to be enrolled in study using the smartphone smoking cessation app intervention until completing participation.

Nicotine Patch (21mg, 14mg, 7mg)

Subjects enrolled in either study will be given an 8-week course of Nicotine Replacement Therapy (NRT) patches. The "standard" 8-week course of NRT (for those who smoke over 10 cigarettes a day) includes trans-dermal nicotine patches starting at 21mg/24h for 4 weeks, and then transitioning to 14mg/24h for 2 weeks, and finally to 7mg/24h for the last 2 weeks, following recommendations contained in the US DHHS Clinical Practice Guidelines. For those who smoke 10 cigarettes or less a day, an "adjusted" 8-week course of nicotine patches will be given instead of the "standard" course. This "adjusted" course starts at 14mg/24h patches for 6 weeks, and then transitions to the 7mg/24h patches for the final 2 weeks.

Participants will be instructed to place the patch on clean, dry, and relatively hairless part of the skin between the neck and waist. They will also be taught to replace their patch every morning. Overall this would mean per participant: (standard) 28 doses on 21mg, 14 doses on 14mg, and another 14 doses on 7mg; (adjusted) 42 doses on 14mg, 14 doses on 7mg

We will be initially giving participants the first 4-weeks of NRT patches during the baseline session. During their first follow-up appointment, participants will be given the next 4-week installment of NRT patches. For participants who we anticipate not being able to make their first follow-up session in-person, we will give them the full NRT course at the baseline session.

Research staff will instruct them on proper sequence of the patches as stated above. We will continue to provide oversight during the duration of their participation in the study.

For the Single Case Experimental trials, we will distribute the rest of the NRT patches for the 8-week course in the same manner as for the primary study. However, as the study is only 4-weeks long, we will not have oversight for the last half of the 8-week course with these participants.

Research staff will be dispensing the NRT patches to participants, coaching them on how to use it properly. We will be storing the patches in a locked storage space in the lab - keys only accessible to research staff. To manage our NRT supplies, we will be documenting and tracking how much is given to a participant and have the participant report how much they used them. Research staff will document which doses of NRT were dispensed and how much of it is given to a subject.

Nicotine Lozenge (4mg)

Each participant enrolled in either study will be given 81, 4mg NRT lozenges to be taken orally as nicotine cravings arise (average 10 lozenges per day). We will direct subjects to use them for the week or so following their quit date, using no more than once every 1-2 hours.

Research staff will give participants the full course of NRT lozenges during the baseline session. We will be dispensing the NRT lozenges to participants, coaching them on how to use it properly. We will be storing the lozenges in a locked storage space in the lab.

We will manage and document our NRT lozenge supplies in the same way as the patches.

Study Procedures

All study sessions are completed either via private phone call, private interview room, or through a confidential online survey. Most of the study sessions will take place at the offices of the research team. However, in some circumstances we may complete study sessions with subjects at outpatient clinic locations and in community settings where there is a reasonable expectation of privacy.

Measures & Assessments

All measures listed below are entered through REDCap unless noted otherwise. Some measures may be completed on their paper versions.

• *Tobacco Usage* – a short questionnaire assessing current and lifelong smoking habits. We will complete these with subjects at the consent session; takes approximately 2 minutes to complete.

• *Breath-Tests* –Smokerlyzer®, piCO+™ CO Monitor a breath carbon monoxide monitor, will be used to obtain biochemical verification of smoking during baseline and follow-ups (cutoff: CM > 6 ppm). The user blows into the handheld monitor, which provides feedback about the user's smoking status and nicotine dependence by displaying carbon monoxide (CO) levels in the body. This device is available for the public to purchase, though clinicians often use it for their clients to monitor their CO levels over time. We have no plans to study the item itself, or submit data about this to the FDA. This measure takes approximately 1 minute to complete.

• *Drug Abuse Screening Test (DAST-10)* – a 10-item screening tool for assessing drug use (excluding alcohol and tobacco use) in the past month. It will be used to inform whether someone meetings eligibility criteria, and given at the consent session. This measure takes approximately 2 minutes to complete.

• *Alcohol Use Disorders Identification Test (AUDIT)* – a brief assessment of drinking behavior and detecting possible alcohol dependence. This measurement will be used to inform whether someone meetings eligibility criteria, and given at the consent session. This measure takes approximately 2 minutes to complete.

• *Demographics* – A series of questions assessing common demographic information such as sex, race/ethnicity, income, etc. We administer this measure to subjects at the consent session only. This measure takes approximately 5 minutes to complete.

• *Mini International Neuropsychiatric Interview (MINI)* - a brief standardized structured interview for the major Axis I psychiatric disorders in the ICD-10 with good reliability and validity. We use this measure to assess both substance use and other psychiatric diagnoses. Scores on the MINI assist the research team in informing our clinical judgment on the subject's appropriateness to continue participation. This measure takes approximately 20 minutes to complete.

• *Theory of Mind Picture-Sequencing* – This theory of mind task comprises four sets of 4-card picture stories. Subjects rearrange picture cards to show a logical sequence of events, which we then score for accuracy. We administer this measure to subjects at the consent session only. This measure takes approximately 20 minutes to complete.

• *Urine Pregnancy Test* – To verify that female subjects of child-bearing potential are not pregnant, research staff will ask subjects to complete a urine pregnancy test. Unless indicated otherwise, this we only request this test from aforementioned subjects at the consent session. This test takes approximately 4 minutes to complete.

• *Barriers to Study Participation Survey* – a brief 16-item survey to assess potential barriers that participants may face when participating in research studies. This measure will be completed at the end of the consent session on Qualtrics. This measure takes approximately 3 minutes to complete.

• *Brief Assessment of Cognition (BAC)* - Assesses cognitive impairments in a wide variety of subject populations.. The measure is created and maintained by NeuroCog Trials (NCT). The research team administers it through an iPad app at baseline to get a sense of the sample's range of cognitive functioning. Data will be available to research staff and NeuroCog Trials, and saved onto Duke Medicine servers. This measure takes approximately 20 minutes to complete.

• *Psychiatric Treatment Tracking* – a brief survey to assess current psychiatric treatment including medications taken and other types of therapies utilized to treat mental health. We give this measure at baseline and follow-up sessions. We also use this measure to monitor changes in treatment that may require medical and/or psychiatric consultation. This measure takes approximately 2 minutes to complete.

• *Avoidance and Inflexibility Scale* – a scaled 9-item measure of willingness to experience and not act on physical urges to smoke (i.e., acceptance). This measure assesses theory-based processes of change at baseline and follow-ups. This measure takes approximately 4 minutes to complete.

• *Fagerström Test for Nicotine Dependence* – a scaled 6-item measure for assessing the severity of nicotine dependence. We will complete these with subjects at baseline and monthly follow-ups. This measure takes approximately 2 minutes to complete.

• *Smoking Abstinence* – a series of questions to assess smoking status including point-prevalence and prolonged abstinence from smoking cigarettes. We will also ask about any other nicotine consumption and treatment used. We will give this measure at baseline and all follow-ups. This measure takes approximately 3 minutes to complete.

• *Alcohol/Drug Use Follow-up* – a brief measure of substance use adapted from the Addiction Severity Index (ASI). We will use this measure during baseline and follow-up sessions to track relevant drug and alcohol use during the course of participation. This measure takes approximately 2 minutes to complete.

• *12-item Short Form Health Survey (SF-12)* – A brief health survey providing indications into mental and physical functioning and overall health-related-quality of life. We use this

measure to describe the level of medical severity of the sample at baseline. This measure takes approximately 3 minutes to complete.

• *Brief Symptom Inventory (BSI)* - a brief 53 item self-report symptom scale. Assesses psychiatric symptoms within the last 7 days, and will be used to track symptoms at baseline and follow-ups. This measure takes approximately 5 minutes to complete.

• *Internet Access and Use Survey* – an 11-item questionnaire assessing technology access and use. We will ask about previous experience with smartphones, as well as information on smartphone ownership. We will only ask this during the baseline session. This measure takes approximately 3 minutes to complete.

• *System Usability Scale (SUS)* – a 10-item questionnaire, measuring various metrics of usability of a design using a 5-point Likert Scale. We complete these with subjects at each follow-up. This measure takes approximately 2 minutes to complete.

• *User Experience (UX) Interviews* – a qualitative interview completed to assess the experience of the subject as an app user. Research staff trained on UX interview techniques will ask subjects to provide their perspective on the app assigned to them. We complete these with subjects at each follow-up. This measure takes approximately 10 minutes to complete.

• *Positive and Negative Syndrome Scale for Schizophrenia (PANSS)* – a 30-item clinician-rated assessment, measuring positive and negative psychotic symptoms on four different scales. Research team members complete the full measurement at baseline and follow-ups. This measure takes approximately 15 minutes to complete.

• *Research Participant Perception Survey (RPPS)* – Questionnaire used to assess the research participation experiences of participants to help the research team potentially improve the experience of clinical trial research participants. We are using a shortened 13-item version of the original 77-item measure. Research staff will provide the survey to the participant at the end of their study participation. Participants will enter this information in directly in order to avoid social desirability effects. This measure takes approximately 2 minutes to complete.

• Automated app usage – Access and engagement with the app will be measured with data such as number of app openings, duration of app use and app features that were used the most. Google Analytics for Mobile Apps will be used to track app usage. The developers of both apps (Learn to Quit – Smashing Ideas, QuitGuide – NCI) will have access to this data as well as research staff.

Sequence of Study Activities

Recruitment

We will utilize various recruitment methods in order to meet our recruitment targets. We will query medical records to identify a subset of patients who meet specific eligibility criteria for the sole purpose of study recruitment. We will approach the primary treatment providers for those who meet eligibility criteria on initial screening through the medical records. We will ask the providers if they feel the candidates meet eligibility requirements, and request they invite their patient to participate in the study. A letter briefly explaining the study will be sent to eligible patients from their provider, including an option to opt out of further contact by researchers. A research team member will follow-up with a phone call to invite participation, explain the study, answer any questions, and request permission to move to screening questions. Then, research staff will ask eligibility questions and determine the individuals' eligibility to participate in the study. If individuals meet eligibility criteria and are still interested in participating, research staff will set up a time to meet individually for a consent session appointment.

The research team will also be reaching out to mental health clinics in the community. Treatment providers who are knowledgeable about the study and eligibility criteria may provide their patients with study information. Interested patients can contact the research team, who will explain the study, answer any questions, and request permission to move to screening questions. For those patients who seem to qualify based on the screening call, research staff will set up a consent session appointment.

For people who contact the research team, we will briefly explain the study, and give room for answering any questions potential participants may have. We will ask permission to proceed to the screening questions if they indicate interest in participating.

Once the screening call is completed, and the person seems to be eligible for the study, research staff will set up a consent session appointment

Consent Session

Those who indicated interest in participating in the study will be required to complete a consent session. Research staff will give potential subjects a presentation on the study purpose, procedures, and what will be expected of them as participants. While going through the consent process, the research staff member will be looking to make sure the participant understands what is being asked of them if they were to enroll in the study, and their rights as participants. The research staff will be evaluating whether the potential participant is tracking the conversation, and eliciting understanding of the study from the potential participant. If the potential participant is unable to comprehend the consent process, the research staff will screen them out of the study.

For those who would like to enroll, we will invite them to sign the consent form and a Release of Information (ROI). Research staff will obtain contact information from the participant in order to follow-up with them including alternative contacts such as case managers, friends, and family. For those who enroll, research staff will complete

additional screening measures (e.g., DAST, AUDIT, demographics, MINI, ToM picture-sequencing task, urine pregnancy test).

Once the consent session is completed, the research team will contact health providers listed on the ROI to ask them if they believe their patient would meet study eligibility criteria. Once this information is collected, the PI will review the subject's information to confirm whether or not the subject meets study eligibility criteria. If the PI determines a subject to be eligible, research staff will schedule a baseline session with the participant.

Baseline Session

The next study session to be completed is the baseline session. This is the session where subjects are randomized to treatment conditions (i.e. Learn to Quit or QuitGuide), given NRT in preparation for their quit date, and provided an orientation to the study smartphone and assigned app. We expect subjects to complete this session on the same day. If they are not able to complete the session in one day, we will ask them to return as soon as possible to finish it.

The baseline session will need to take place within 30 days after completing the initial consent session, unless an appointment is made within the next week following the 30-day window. Otherwise, the subject will be considered "Lost to Follow-Up" and be considered inactive in the study. However, those yet to be randomized and considered "Lost to Follow-Up" may become active in the study again. Before we can randomize someone who had been "Lost to Follow-Up" between consent and baseline sessions, the research team will need to re-verify the subject meets screening criteria and contact their treatment providers again to make sure they're still fine with their patient participating in the study. If we have not completed a baseline session with the subject two weeks after getting initial approval from their treatment provider, we will need to also contact their provider again to ensure the provider approves of their patient participating in the study. During the baseline session, we will review consent assessment questions with a 30-day timeframe or less to ensure these measures are up-to-date for anyone who has had their consent session completed over 30 days.

Before starting the baseline measures, each subject will be verified again by research staff (i.e. reviewing screening questions, CO breath test). If the subject does not seem to meet eligibility criteria at this time, the staff member will stop the session. Under certain circumstances subjects may be able to complete the baseline session at a later point, if all the above criteria for starting the study interventions are met.

Research staff will complete baseline measures with the subject. Once these are completed, research staff will randomize the subject to either NCI QuitGuide or Learn to Quit (50/50 chance of either). We stratify randomization is based on whether the subject is diagnosed with a primary mood or psychotic disorder.

Once the app is assigned, research staff will then conduct the first coaching session where they provide the subject with a study smartphone and demonstrate both the app assigned to them and the study smartphone functionality. To identify the subject in the apps' user analytics reports, research staff will add a unique tracking ID (similar to the subject ID) to the study app. They will be oriented to the coaching available to them, provided by research staff over the course of their participation in the study.

We will give subjects Nicotine Replacement Therapy (i.e. patches and lozenges), the dosages of which are determined by how much the subject has been smoking during the last week. While dispensing the NRT to subjects, research staff will provide instructions for their use to them. Research staff will ask subjects to demonstrate understanding of proper NRT usage before dispensing them to subjects.

Research staff will set up an appointment for the participant's in-person follow-up interview and for a coaching session the next week.

Coaching Sessions

Participants will communicate with research staff to continue coaching on a weekly basis for the first 4-weeks. Coaching sessions will be done over the phone, or in-person at the research lab if necessary. These coaching sessions are mainly for working through any technical issues with the study smartphone and/or the assigned study app. We also assess for any AEs during these sessions. These sessions are audio recorded to help improve our coaching procedures with users.

There is a 4-day window to complete coaching visits (2 days before the due date, 2 days after the due date). The second coaching session will be due 7 days after the completion of the baseline/1st coaching session. Each subsequent coaching session's due date will be an additional 7 days from the previous one.

Once the current coaching session has ended, research staff will schedule their next coaching session for the following week.

For subjects enrolled in the single-case trials, during the course of the 4-week period, some will shift to a different app intervention. This phase change will be determined prior to the beginning of the study and will require participants to meet with research staff to conduct a qualitative interview and additional coaching

After the first 4 weeks, participants will no longer have in-person coaching sessions. However, they will be able call research staff for more brief consultations over the phone until their participation with the study is finished.

Follow-up Sessions

These sessions are monthly visits completed either in-person, over the phone, or completed as an online survey. During the follow-up sessions, research staff will conduct further assessments, assess for any AEs, and complete a user experience (UX) interview with the subject.

Subjects enrolled in the randomized controlled trial will have four follow-up sessions to complete. For subjects in the single-case trials, there will be only one follow-up session.

The first follow-up session is due 30 days after completion of the baseline. Each subsequent follow-up session's due date will be an additional 30 days from the previous follow-ups due date (i.e. 60 days after baseline for 2nd follow-up, 90 days for the 3rd follow-up, 120 days for the 4th follow-up). There is a 14-day window for completing these follow-up sessions (7 days before the due date, 7 days after the due date).

During the first follow-up session, research staff will give participants the second half of the 8-week NRT patches (unless we dispensed the entire course to the subject during the baseline session). We will ask the subject about what psychiatric treatment they have been receiving recently. We will note changes in medications and the PI will determine (possibly in consultation with the study physician) whether to contact subject's treatment provider to avoid any contraindications between study interventions and current medical care.

The research team will spend the last part of the follow-up session conducting an audio-recorded UX interview with the subject.

Subject Compensation

Participants can receive a total of $110 for completing all study sessions. We will use incremental payments to compensate for those participants who engage in continuous engagement through follow-up (See Table below). Those who come in for an in-person consent session will be compensated $10 for their time. For those who complete follow-up study visits over the phone, we will take $5 off of the standard compensation to reflect the missing biometric data when these visits are conducted in-person – as well as the fact that more effort is required to come in-person for an appointment. All withdrawn subjects will be given compensation according to what study sessions they have completed.

In addition to monetary compensation, participants will: 1) have access to smartphone data and cell phone for a period of 4 months (within the limits of the pre-paid plan used for the study, valued ~ $180), and 2) be able retain the study smartphone for personal use after study completion (valued ~ $200).

Assessment Time Point	Sessions Completed In-Person	Sessions Completed Remotely

Consent	$10	$5
Baseline	$10	$10 (in-person required)
Follow-up #1	$15	$10
Follow-up #2	$20	$15
Follow-up #3	$25	$20
Follow-up # 4 (final)	$30	$25
Total	$105	$85
Throughout Study	Compensation	
Smartphone Use	4-months of data, telephone and text messaging (value ~ $180)	
Smartphone Ownership	Ownership of smartphone at study completion (value ~ $200)	
Peer Referral	$10 for each referral of a successfully enrolled research subject	

Single Case Experimental Trials

Participants will receive a total of $50 (See Table below). Compensation with will follow a similar pattern to the randomized controlled trial described above. Although participants in this sub-study will have access to Internet, phone, and text messaging on the provided smartphone during their time with the study (value ~ $45), participants will need to return it once they complete the study.

Assessment Time Point	Amount in Gift Cards
Baseline	$10
App Switch	$15
4-weeks Follow-up	$25
Total	$50
Throughout Study	Compensation
Smartphone Use	4-weeks of data, telephone and text messaging (value ~ $45)
Peer Referral	$10 for each referral of a successfully enrolled research subject

In accordance with guidance for the Duke Primary Care Consortium, we are offering compensation to providers and clinic staff for their time and service. The research team will compensate clinics and providers based on how much time a provider has spent interacting with their patients and the study team (e.g., in-person approaches to patients about the study, putting up flyers in clinic space), and not based on referrals to the research team. This provider compensation is optional and we only offer it to clinics that are capable of or willing to accept it. We will determine the appropriate compensation levels on an individual clinic/health system basis, after consulting with them about it.

We will make immediate necessary medical care available to subjects in the event they are injured as a result of their participation in this research study. However, there is no commitment by the research team and institution to provide monetary compensation or free medical care to subjects in the event of a study-related injury.

Adverse Events & Reporting

Our research team defines an adverse event (AE) as any harmful event that occurs to a research subject while participating in a clinical trial. Any new illness, symptom, sign or worsening of a pre-existing condition is considered an AE.

We define serious adverse events (SAEs) as adverse events that:

- End in death
- Are life-threatening
- Require inpatient hospitalization or prolong an existing hospitalization
- Result in persistent or significant disability/incapacity
- Are a congenital anomaly/birth defect
- An event that required intervention in order to prevent one of the above outcomes

Anticipated Events

Given that many people with serious mental illness and smokers have higher medical needs than the general population, we do anticipate subjects will report a higher rate of Adverse Events (AEs) to us as an inherent characteristic of this population. These include such events as COPD, lung cancer, pneumonia, psychiatric symptoms, psychiatric medication side effects, hospitalizations.

Some anticipated AEs resulting from the study interventions include study drug side effects. The study drug (i.e. NRT) does have some common side effects that we expect subjects will occasionally report including dizziness, headaches, rapid heart rate, increased blood pressure, nausea and diarrhea. For the nicotine patch, some common side effects include skin irritation and/or itching where the patch is placed, insomnia, and vivid dreaming. Nicotine lozenges may cause hiccups, cough, sore through, or heartburn.

There may be some risks associated with smartphone and app usage. Events that we anticipate subjects may report to us around using the study smartphone include sleep disturbances (from high frequency use), eye strain (from viewing the screen), and data breaches (if subjects enter their personal information in the phone).

Collecting & Recording Adverse Events

We will be tracking all adverse events (AEs) and serious adverse events (SAE) that a participant may experience once starting the study intervention. We will be doing this throughout the study, regardless of whether or not we think they are related to the study. We start asking about AEs at the second Coaching session, continuing to assess and track them at each subsequent study visits throughout the duration of the study. AEs will be documented by research personnel during these visits, or at any other time during the clinical trial that they have contact with or about the subject. The PI is responsible for oversight on AEs.

We will document each AE with details such as:

- Start and stop dates (if applicable)
- Severity: mild, moderate, severe
- Possible relation to study protocol
- Outcome: is it ongoing or resolved (e.g. did they get treatment)?
- Possible causes
- Any other pertinent details

Collected AEs will be documented and recorded with the information above on AE forms

On a weekly basis, the PI will review each AE to determine its relation to the study procedures; deciding what course of action should be taken to address the AE. The PI may consult with the study physician if needed.

If the participant reports a SAE, the same collection and recording procedures will take place as with AEs. However, research staff will alert the PI to the SAE as soon as possible (within 24 hours of a reported SAE). The PI will review the reported SAE within 24 hours of becoming aware of it. SAEs will have a separate form completed for each one reported.

Reporting Adverse Events

Standard reporting requirements, according to the IRB, will apply for all reportable AEs. Expedited reporting (within 24 hours of its occurrence or site's knowledge of the event) for reportable SAEs will be done with the IRB, to the appropriate program officer of the National Institute on Drug Abuse (NIDA) and the Food and Drug Administration (FDA). This initial report will be followed by a final report that will be sent to the IRB, NIDA, and FDA.

In the case of a reportable SAE we will submit the SAE form, summary, and any other relevant documentation along with the follow-up report. We may need to gather more information to evaluate the SAE, which may include obtaining hospital discharge reports, physician records, autopsy records or any other type of records or information necessary to provide a complete and clear picture of the SAE and events preceding and following the event.

Data & Safety Monitoring

Trial Stopping Rules
The intervention being studied—Learn to Quit—pose minimal safety risks to study participants. In the case of a SAE, the study will be stopped and no further enrollment will take place until the PI has conducted an investigation of the event. Appropriate modification of the protocol will be executed if an association is suspected. If protocol modifications to ensure the safety of future study participants cannot be executed, the study will be terminated. A decision to stop the study will be determined by the PI and his

mentors, in consultation with the National Institute on Drug Abuse, the Institutional Review Board.

Disclosure of any conflict of interest
The researchers involved in this study do not have any known conflict of interest issues in this Data and Safety Monitoring Plan.

Trial feasibility
We will conduct an interim analysis of the feasibility trial after 40 individuals are recruited to the study (likely at year 1 of the R00 Phase). Information on trial feasibility will be provided to NIDA on a yearly basis after this threshold of recruitment is met.

DSM Plan Administration

Responsibility for Data and Safety Monitoring
The primary responsibility for monitoring the data and safety of the study will be of the PI with the assistance of the research coordinator.

The PI will follow and monitor reportable AEs/SAEs until resolution, stabilization or study end. Any serious and study-related AEs will be followed until resolution or stabilization (even if beyond the end of the study).

Frequency of DSM Reviews
The data will be reviewed annually over the course of the study.

Content of the DSM Report
The DSM report, to be submitted with the annual progress report, will include information organized into the following sections: study description, socio-demographic characteristics of the accumulated participants at baseline, data on the status of study participants, quality assurance issues, and regulatory issues, data on Adverse Events and Serious Adverse Events, and feasibility outcomes.

Data Management & Analysis

Data Management Plan

We will collect data of various types in a variety of ways for this project. Included in the data to be collected are quantitative and qualitative types including psychometric (tasks and self-report), biometric, observational (automated user analytics from investigational apps), and audio recordings of user interviews. Quantitative data collected will be formatted into CSV files: Qualitative data will be initially collected using the MP3 format, and (.txt) files created from these. We will require around 1 TB of data storage for this purpose.

Much of the psychometric and biometric data will be collected during study visits with subjects, sometimes on paper, but ultimately in electronic data capture systems (i.e. REDCap) unless otherwise specified. Research staff will collect biometric data to verify smoking status from subjects via a Carbon Monoxide (CO) breath test during study appointments. We will collect two types of psychological task data – cognitive functioning and Theory of Mind. Trained research staff will administer cognitive tasks on an app via an electronic tablet device. The app records the subject's responses into a third-party web portal and downloaded as a CSV file. Research staff will administer and record Theory of Mind tasks on pen and paper, then entered into the electronic data capture system. Self-report data will either be asked by research staff or provided by the subject via survey response, which will be entered into the electronic data capture system. Audio recordings will be collected via USB microphones onto study laptops during study visits: Transcribers will then translate these recordings into text files. Observational user analytic data will be automatically collected via Google Analytics in real-time while subjects use the investigational app. With the exception of aggregated data sets from the electronic data capture system, all of these data files will be organized by the subject level and type. The data files will be labelled with subject ID, date collected (if applicable), time point, and randomization assignment. We will maintain version control by adding consecutive integers to the end of file names for any new versions beyond the original. CSV files will then be imported into a SQL relational database with the primary key being subject ID.

Tracking participants' app usage will be done automatically and continuously through Google Analytics for Mobile Apps. A unique tracking ID will be entered into the app to track the individual user as a study subject in the reports obtained from Google Analytics. Once the subject completes the study, research staff will remove the tracking ID from the study app so as to stop any new data coming in. For Learn to Quit users, the app will be deleted from the study phone after they complete the study. The data from the apps is stored on Google servers, which are located in various data centers around the world, and regularly backed up to prevent data loss. Any data at rest or in transit are encrypted. The analytic data will be labeled with their subject ID, and will not contain any identifying information other than user time stamps. Subjects will use phones provided to them by research staff.

Both the research team and the vendor of the QuitGuilde app (National Cancer Institute) will have access to this analytic data. NCI normally collects app usage data on all users of QuitGuide. They have agreed to share our participants' data (using QuitGuide) with us.

The developer of Learn to Quit, and its current owner, the University of Washington will not have access to our participant's data.

Data from the Brief Assessment of Cognition (BAC) will be collected through the BAC app (cognitive assessment battery mentioned earlier), and accessed through a web portal. Subjects are only identified through study ID and time stamp of assessment. Any

data collected from the assessment is stored locally in an encrypted database on the device. Audio files collected during test administration are stored in an unencrypted form, though staff and participants are instructed not to record direct identifiers while audio recording. Data is only transmitted to NeuroCog Trials (NCT) when authorized by both NCT and the site. These data are transferred over an encrypted HTTPS secure internet connection. Data stored at NCT are protected using physical and technical security and administrative safeguards. The research team will download this data to our shared drive as well.

Audio recordings will be collected through lab-owned devices with encryption, and saved onto the study's IRB folder on Duke Medicine's secured network drive. Any transmission of audio files and transcriptions outside of Duke Medicine will be done through Duke's secured internet connection and entrusted to a contracted third-party. The text files transcribed from the audio recordings will then be stored on the Duke Medicine servers where they will be analyzed. Once the transcriptions are completed, the audio files will be deleted from any temporary storage locations (e.g. Duke Box, third-party database).

The metadata accompanying the study data includes codebooks, the questionnaires and measures themselves, along with this study's protocol.

Regardless of where data collection originates, all study data will eventually be stored on the secured Duke Medicine servers.

Data Flow

Study Laptop

User metrics (e.g. app openings,
time on app, features used

Study Smartphone

Statistical Analyses

Study iPad

Data Monitoring & Quality Assurance

We will maintain quality assurance by reviewing and cleaning study data on a regular basis before it is imported into the main database. Duke's Psychiatry and Behavioral Sciences Clinical Research Unit (CRU) will also provide periodic monitoring of the study. Data quality will be maintained by entering most measures directly into a REDCap database, minimizing errors in data entry. In addition, all data will be double-checked by trained research assistants as entered. On a monthly basis the project manager will review the study database for the accuracy of data. When data quality issues arise they will be immediately addressed. The PI will intermittently observe clinical interviews conducted by research staff. Data quality issues will also be reviewed weekly at the study team meeting, which will include all research staff. Trained research staff will double-check all data before data analysis. For ensuring accurate and reliable biometric carbon monoxide results, we will be calibrating the piCO+ smokerlyzer device per package instructions.

Privacy, Data Storage & Confidentiality

Recording Direct Subject Identifiers

Research materials obtained from subject will include personal data and audio-recorded data derived from interviews. Research materials obtained from subjects will include data shared by them during study visits using REDCap and the Brief Assessment of Cognition (BAC) app, app usage data extracted from Google Analytics, and transcripts of audio-recorded data derived from interviews. Names and contact information (i.e. telephone number, email address, living/mailing address, alternative contacts) are needed for subject tracking during the duration of the study in order to solve potential technical problems with the mobile device, and scheduling follow-ups and the return of the device.

All forms with information concerning an individual subject will be marked with a unique code and not their name. The link between the code and the name will be stored on a user managed database that is only accessible by research staff, and our database developer (only on a required basis to assist in managing the database). This database will contain the subject's identifiable information and subject ID number.

Retaining link between study code numbers and direct identifiers after collection

After the study is closed, we will destroy the link between (a) the subject's name and the ID number and (b) the ID number and subject's contact information.

Protecting against data disclosure to the public or non-researchers

Records and materials generated by the study will only be available to authorized study staff members who have signed a confidentiality agreement with our research lab (with the exception of those contracted by the research lab to perform certain tasks – mentioned elsewhere in the protocol). Any transmission and storage of electronic data will be done as securely as possible, and through encrypted means whenever possible. Paper files will be kept in locked filing cabinets located in locked offices on a restricted access suite.

Staff will be trained to be sensitive to issues surrounding confidentiality and other forms of participant risk. Agencies, such as the NIH and the Duke University, may request access to this data for auditing purposes.

To the extent possible, any information about a participant will never be released to outsiders without his/her explicit written consent, except that, in the event of a medical emergency, pertinent medical information will be given to the medical personnel caring for the participant, or as required by law.

Some of the data subjects provide as part of the study will be shared with third-party vendors of the apps used in the study. This data will not include subjects' name, but may include other identifiers as indicated below, such as timestamps of app usage activity. All vendors are required to comply with HIPAA regulations surrounding the confidentiality of the information you provide to us, but this cannot be guaranteed by Duke.

App usage data will be managed through Google servers via Google Analytics and saved securely at DUHS. More information on Google's data security and privacy

policies relating to analytics data can be found at https://support.google.com/analytics/topic/2919631. The data collected from the apps do not contain personally identifiable information other than time stamps of app usage. This data will be labeled with a subject ID number.

If a subject is assigned to QuitGuide, the National Cancer Institute (developer of QuitGuide) will have access to their app usage data. More information on NCI's privacy policy can be found at https://www.smokefree.gov/privacy-policy as well as in their app menu. They collect this data for all users of the app as a common practice, though it is possible for the research team to receive a participant's specific usage data by adding a unique code to the app to tag it. We will use a combination of a subject ID and another code to identify our study to create this unique code for NCI to retrieve and send us this data. By adding this particular code combination identifying a subject in our study as such, they consent NCI to share this information with us.

For those using Learn to Quit, neither Smashing Ideas nor the University of Washington will have access to this data. The app's privacy policy and terms of use regarding this app are detailed on a sheet given to participants by research staff. It can also be found here https://duke.app.box.com/s/n1w3feedyzs8937r5wv31nj72q5nr4sy.

The data from the cognitive assessment performed on the BAC app will be send to the developer of the app, NeuroCog Trials (NCT).Subjects' assessment data will be combined with all other users, and will be aggregated and anonymized to understand and publish information regarding activities across the various studies using this app. This app will not collect any personally identifiable information other than the time stamp of the assessment. The privacy policy for NCT can be found at http://www.neurocogtrials.com/about/privacy-policy/.

Audio Recordings

Coaching sessions with participants will be audio-recorded for developing more refined protocols, as well as selected interviews for training purposes. Qualitative interviews will be audio recorded in order to gain a deeper insight into subject's experience with the smoking cessation app.

Audio-recordings will be done through encrypted study devices (e.g. laptop, tablet, smartphone, etc.). These will be marked with a unique subject ID number and not the subject's name. Audio-recordings will be stored on our Duke Medicine servers, and transmitted to our transcribers via Duke's Box service to be transcribed. Once we receive and store the transcription from them (into our Duke Medicine servers), the recording will be deleted from the Box.

Other Uses of Study Data

The research team may use a third party vendor to assist us in managing our study databases that contain personal health information (PHI) of participants. Anyone we

authorize to have access to our databases will be approved to do so by Duke (via an official agreement with ORC), and must agree to abide by all applicable HIPAA and IRB regulations when handling participant and patient data.

Other researchers and the public may have access to this study data, distributed through protected digital data repositories (e.g. NIDA Data Share, Duke Digital Repository). Any personal information that could identify subjects will be removed or changed to de-identify them before study files are shared with other researchers or results are made public.

Data Analysis & Statistical Considerations

The current study is a pilot trial with small sample size that may include design adjustments to maximize recruitment, retention and assessment quality. As such, we cannot test research hypotheses. Instead, the primary focus of study data is to inform the development of a fully powered RCT of Learn to Quit. Thorough descriptive statistics (e.g., M, SD, proportions) will be used to characterize feasibility outcomes. As a secondary analysis, regression models will be used to compare each arm's primary and secondary outcomes. An emphasis will be put on visual analytic strategies and hierarchical linear modeling (HLM) for continuous, binary and count data. When appropriate, multiple imputation techniques will be used to address data missingness

Qualitative data analysis will be through a thematic analysis of transcripts from the audio-recorded interviews. We will extract emerging themes coming out of participants' user experience with the apps and coaching protocol.

Appendix

List of Abbreviations

PI – Principal Investigator

CRC – Clinical Research Coordinator

CRS – Clinical Research Specialist

DUHS – Duke University Health System

NAMI – National Alliance on Mental Illness

NRT – Nicotine Replacement Therapy

ROI – Release of Information

SMI – Serious Mental Illnesss

UNC – University of North Carolina

PHI – Protected Health Information

RPR – Review Preparatory to Research

CSV – Comma Separated Variables

HCA – Health Care Administrator

PCP – Primary Care Provider

PCRC – Primary Care Research Consortium

DEDUCE – Duke Enterprise Data Unified Content Explorer

DISCERN – Duke Integrated Subject Cohort and Enrollment Research Network

AE – Adverse Event

SAE – Serious Adverse Event

IRB – Institutional Review Board

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