Early-phase Studies of a Tailored Evidence-Based Smoking Cessation mHealth App for Persons Living with HIV (PLWH)

Phase 2: Pilot RCT of LTQ-H
Study Protocol

NCT04609514

7/1/2020

1.0. Significance

PLWH are more likely to die from tobacco use than from HIV itself. Scalable and evidence-based smoking cessation interventions in line with current health consumer trends are highly needed in order to improve quality of life and curb mortality rates among PLWH. Moreover, the incorporation of state-of-the-art technology to improve access to hard-to-reach populations and settings has been identified as a high-priority research opportunity in the Trans-NIH Plan for HIV-Related Research. mHealth apps tailored to the specific needs of PLWH hold promise for reducing tobacco dependence among PLWH and HIV-related health disparities. However, despite promising initial evidence supporting the use of smoking cessation apps, there is a shortage of rigorous early-phase research developing and testing smoking cessation apps in general, and among PLWH specifically. The central premise of this research is that LTQ can be tailored using rigorous research methodology to meet the needs of PLWH smokers. This phase of the project will capitalize on background analytics and qualitative methods to evaluate the acceptability and preliminary efficacy of LTQ-H, a smoking cessation app iteratively designed for smokers with HIV by smokers living with HIV.

2.0. Goals and Aims

2.1. Aims

The overarching goals of this phase of the research are to evaluate the feasibility, acceptability, and preliminary efficacy of a tailored smoking cessation app for PLWH, “Learn to Quit-HIV” or “LTQ-H” for short, which was iteratively developed in the first phase of research. Specifically, we propose to conduct a feasibility, acceptability, and preliminary efficacy trial comparing LTQ-H (n=30) to an app based on U.S. Clinical Practice Guidelines only (NCI QuitGuide; n=30) among HIV-positive smokers. NCI QuitGuide will match LTQ-H’s format of delivery, dose, and duration. Both apps will be integrated with NRT and ongoing HIV clinical care. Primary outcomes: feasibility (i.e., recruitment rates, retention, app engagement); acceptability (i.e., usability, user experience, perceived utility). Secondary outcomes: cigarettes smoked per day, quit attempts, biochemically verified abstinence, NRT adherence and participant safety. Successful execution of this aim will indicate the feasibility, acceptability, and preliminary efficacy of LTQ-H.

2.2. Outcomes

Primary Outcomes:

(1) Recruitment rates and participant retention, which will be collected and monitored throughout study duration
(2) App engagement, which will be evaluated from background analytics data consisting of frequency and duration of app use, objective background analytics measures used in our previous work. We will use Google Analytics and our Data Transfer Agreement with smokefree.gov to gather this metric
(3) App usability measured with the Systems Usability Scale
(4) User Experience, extracted via thematic analysis of transcripts of semi-structured interviews. As in previous early-phase research by Dr. Vilardaga, these interviews will occur at the end of treatment (Week 12)

Secondary Outcomes:

(1) Cigarettes per day (CPD) will be measured daily with the tracking feature embedded within each app. LTQ contains a feature that allows users to enter how many cigarettes they smoked at the end of the day
(2) Quit attempts defined as self-reported no smoking at all for 24 hours, and time to 7-day relapse will assessed via a Timeline Follow Back interview at Weeks 4, 8 and 12
(3) 7-day point prevalence abstinence will be determined by responses to a standard self-report item (i.e., not smoking even a puff of a cigarette within the last 7 days) and breath CO<5 ppm at Week 12
(4) Adherence to NRT will be measured daily with the app tracking feature, as well as brief interviewer-administered questionnaires at Weeks 4, 8, and 12
(5) Participant Safety will be assessed by monitoring all adverse events during the 12-week period and in close collaboration with their medical providers

3.0. Participants

3.1. Inclusion Criteria

The inclusion criteria are meant to be broad enough to capture a wide swatch of smokers with HIV. However, there are medical requirements as we will be giving participants a study drug (NRT). Also, participants will have to want to quit smoking. Therefore, the inclusion criteria are as follows:

(1) HIV-positive
(2) Currently engaged with an HIV care provider
(3) Self-report smoking 5 cigarettes or more per day during the past 30 days
(4) Age 18 years or older
(5) Current interest in quitting smoking
(6) Currently own a functioning Apple or Android smartphone

3.2. Exclusion Criteria

(1) General Exclusion Criteria
    a. No desire to quit smoking
    b. Inability to provide informed consent
    c. Any medical condition or concomitant medication that could compromise subject safety or treatment, as determined by the Principal Investigators and/or Study Physician
(2) Medication Exclusion Criteria
    a. Presence of contraindications for nicotine patch
    b. Previous allergic reaction or hypersensitivity to nicotine patch (lifetime)
    c. Current use of nicotine replacement therapy or other smoking cessation treatment (e.g., bupropion, varenicline)
(3) Medical Exclusion Criteria
    a. Uncontrolled high blood pressure/hypertension
    b. Pregnant, planning to become pregnant, nursing, or becoming pregnant during the study
(4) Alcohol/Drug Exclusion Criteria
    a. Current untreated and unstable diagnosis of alcohol/substance abuse or dependence (eligible if past abuse/dependence and if receiving treatment and stable for >30 days)

3.3. Target Population Distribution

Inclusion of Women and Minorities: The study will be open to males and females, and all ethnic groups. The population of Durham County, North Carolina is approximately 52% female and 48% male. According to U.S. census 2013 data, the racial/ethnic composition of Durham County, NC is 53.1% Caucasian, 38.5% African-American, and 4.8% Asian, with 13.5% reporting Hispanic ethnicity. We plan to recruit a sample that is representative of the Durham County area with respect to gender and race/ethnicity.

4.0. Study Overview

1. **Eligibility and Consent:** PLWH who provisionally qualify based on a phone screen will be invited to attend a remote Zoom screening visit. Informed consent will be obtained, and participants' interest in quitting, HIV and smoking statuses will be evaluated. Individuals will be screened to ensure that they own an Apple or Android smartphone, are not pregnant (if female), and are medically eligible to use NRT. Our study physician will evaluate their medical eligibility. In addition, we will obtain a signed Release of Information from potential participants to closely work with their own medical providers to monitor adverse events, dispensing of NRT, and overall participant safety.
2. **Randomization:** Participants will be allocated to conditions using 1:1 randomization.
3. **Interventions:** Participants will be assigned to LTQ-H or NCI QuitGuide. All participants will receive a standard 8-week course of NRT (transdermal nicotine patches starting at 21mg/24h) following recommendations contained in the U.S. Clinical Practice Guidelines.
4. **Background Analytics:** Research staff will instruct participants on how to install the study app onto their personal smartphones and will tell them how to add a study ID in the app that will be used to retrieve background analytics information (Google Analytics) from both the LTQ-H and NCI QuitGuide apps.
5. **Follow-Up Visits:** Visits will occur at 4, 8 and 12 weeks post-randomization. During these visits we will assess smoking and smoking abstinence, new or changes in existing adverse events and user experience with the assigned app. We will biochemically verify self-reported smoking abstinence at week 12.

4.1. Timeline

	Sep 2019 - Aug 2020												Sep 2020 - Aug 2021											
	YEAR 1												YEAR 2											
	SEP	OCT	NOV	DEC	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG
Aim 2: Pilot Randomized Controlled Trial of LTQ-H App																								
Obtain human subjects approval (full board, medical oversight and health outcomes)				X	X	X	X																	
Recruitment through Duke MyChart and community advertisement								X	X	X	X	X	X	X	X									
Data collection for pilot randomized controlled trial (n = 60)								X	X	X	X	X	X	X	X	X	X	X	X					
Complete data analysis and prepare article for publication																				X	X	X	X	
Prepare NIH submission for R01 randomized controlled trial																					X	X	X	X

Participants who are enrolled in Phase 2 of the study will participate over the course of 12 weeks, which includes a screening visit, randomization visit, plus 3 monthly follow-up visits.

5.0. Interventions and Measures

5.1. Interventions

Learn to Quit-HIV (LTQ-H)

Learn to Quit (LTQ) is an Android/iOS smoking cessation app developed by Dr. Vilardaga. It was originally developed for persons with serious mental illness (SMI). However, in this study we will be using a new version of LTQ called LTQ-H. LTQ-H was iteratively designed through a user-centered design study in persons living with HIV to evaluate key usability barriers and design requirements for this population. LTQ is based on Acceptance and Commitment Therapy (ACT), a mindfulness-based intervention with promising results for smoking cessation in several clinical trials. LTQ includes 28 Modules that encourage the learning and practice of three processes of change (e.g., awareness of urges to smoke, openness to experiencing urges, and commitment to specific values for quitting), as well as adherence to U.S. Clinical Practice Guidelines (e.g., use of medications). The app also includes ecological momentary assessments (e.g., self-tracking) of mood, nicotine replacement therapy (NRT) use, cravings to smoke, acceptance of cravings, and cigarettes smoked daily.

QuitGuide (QG)

QG is an app developed by the National Cancer Institute (NCI) based on US Clinical Practice Guidelines. The app encourages users to pick a quit date upon starting the app. The app also contains mood and cigarette craving tracking, and tracking of number of days that the user was smoke-free or slipped. It also contains a journaling feature and the option to opt-in to location- or time-based notifications.

Nicotine Replacement Therapy (NRT) Patches

All participants will receive an 8-week course of NRT patches regardless of app assignment. Based on the number of cigarettes-per-day (CPD) reported, they will receive either a standard or adjusted course for the first 4 weeks of patch use.

	Standard	Adjusted
CPD at baseline	≥ 10	< 10
Starting dose	21 mg/24 hours	14 mg/24 hours

Following the first 4 weeks of use, participants will use 14 mg/24 hour patches for 2 weeks, followed by 7 mg/24 hour patches for the last 2 weeks (regardless of starting dosage).

5.2. Measures

- **Carbon Monoxide Breath Test:** The coVita iCO Smokerlyzer® breath carbon monoxide monitor will be used to obtain biochemical verification of smoking abstinence at the Week 12 visit (cutoff: CO < 5 ppm = abstinent). Only participants who self-report abstinence will be sent these devices. 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.

- **Demographics:** A series of questions assessing common demographic information such as sex, race/ethnicity, income, etc. We administer this measure to subjects at the screening session only. This measure takes approximately 5 minutes to complete.
- **Brief Medical History and Brief Medical History Follow-Up Questionnaire:** This questionnaire asks about multiple aspects of the participant's medical history including questions about chronic diseases and medications. The Follow-Up questionnaire goes into more detail about any conditions that the participant endorsed, including their specific diagnosis and what medications they are taking to treat the condition. These two questionnaires take approximately 20 minutes to complete.
- **Drug Abuse Screening Test (DAST):** 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. It takes approximately 2 minutes to complete.
- **Drug Use Questionnaire (12+1 Month and 1 Month):** This questionnaire asks about past drug use. The questionnaires asks participants about 15 different types of drugs, plus a 16th type for "Other." The 12+1 Month questionnaires asks about drug use in the past year AND the past 30 days, whereas the 1 Month version asks only about the past 30 days of use. This questionnaire captures whether or not someone used the drug in question, and how often it was used (number of days). This measure takes approximately 3 minutes to complete.
- **Mini International Neuropsychiatric Inventory, Version 5.0 (MINI):** A brief standardized structured interview for the major Axis I psychiatric disorders in the ICD-10 with good reliability and validity. This measure will help determine if the participant is experiencing any psychiatric symptoms. This measure takes approximately 20 minutes to complete.
- **Columbia-Suicide Severity Rating Scale (CSSRS):** This 6-item survey provides prompts to assess any suicidal ideation and behavior that the participant may be exhibiting, with higher scores indicating a more frequent presence of suicidal ideations and/or behaviors. This measure takes approximately 5 minutes to complete.
- **Depression Anxiety Stress Scale-21 (DASS-21):** This 21-item symptom scale assesses symptoms of depression, anxiety, and stress that occurred in the past week. Each item is rated on a Likert-style scale from 0-3 with higher scores indicating a more frequent occurrence of symptoms. This measure takes around 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.
- **Stigma Mechanisms Scale:** This scale is broken down into 3 sections, each measuring a different type of stigma related to HIV status: internalized, anticipated, and enacted forms of stigma. There are 24 items which participants rate on a Likert-style scale from 1-5 with higher scores indicating greater stigma.
- **Everyday Discrimination Scale:** This short 6-item measure asks about self-reported discrimination experienced by participants in their day-to-day lives. The first section asks about the frequency of this discrimination using a Likert-style scale from 1-6 with lower scores indicating a higher frequency of discrimination. The second section asks participants to think about the reasons why they may be experiencing this discrimination. This measure takes about 3 minutes to complete.
- **Tobacco Use History Questionnaire:** This questionnaire assesses a variety of current and past smoking behaviors, including periods of non-smoking. It also assesses other tobacco/nicotine product use besides cigarettes. This measure takes approximately 10 minutes to complete.

- **Fagerström Test for Nicotine Dependence (FTND):** A scaled 6-item measure for assessing the severity of nicotine dependence. We will complete this at baseline and at monthly follow-ups. This measure takes approximately 2 minutes to complete.
- **Smoking Cessation Therapies Questionnaire:** This questionnaire asks about past and current (past 30 days) use of smoking cessation therapies such as NRT and medications. This measure takes about 2 minutes to complete.
- **Stages of Change Questionnaire:** Also known as “The Contemplation Ladder,” this brief survey assesses the participant’s readiness to quit smoking and their confidence in quitting. It takes approximately 2 minutes to complete.
- **Barriers to Study Participation Survey:** This 15-item survey asks about participants’ barriers to participating in research studies. It takes approximately 5 minutes to complete.
- **Health Changes Questionnaire:** This questionnaire is designed to assess any changes in health since the participants’ last study visit. It assesses changes in health condition, medications, and asks if there have been any adverse events. It takes approximately 3 minutes to complete.
- **Internet/Smartphone 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.
- **Timeline Follow-Back:** This measure quantifies the substances a subject has used in a certain period of time. It utilizes a calendar format and key events to record substance use. In our trial, we will specifically be asking about cigarette consumption, smoking abstinence, NRT usage, and Antiretroviral Therapy (ART) adherence. Depending on the timeframe of the assessment, the measure takes about 10 minutes to complete.
- **Smoking Abstinence Survey:** This is a brief 12-item questionnaire designed to assess current smoking or non-smoking behavior, including quit attempts and periods of abstinence. It also includes questions about NRT use. This measure takes approximately 3 minutes to complete.
- **Systems Usability Scale:** 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.
- **Research Participant Perception Survey:** 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.

6.0. Study Procedures

6.1. Recruitment

Participants (n=60) will be recruited through similar channels as those from the user-centered design study: patient referrals from other HIV research studies and from Duke clinics (i.e., infectious disease clinic). Participants will be instructed to contact the lab phone or email to learn more about the study. We will also recruit potential participants through Duke's electronic health record (EHR) in order to expand our recruitment pool. We will use Maestro Care and DEDUCE to identify potentially eligible Duke patients that meet the age, smoking, and HIV inclusion criteria.

In addition, we will recruit participants from other external community clinics in the Triangle area. We will provide clinics with advertising materials such as flyers and handouts to give to potentially interested patients. Patients will be instructed to contact the research team for more information. As this is a completely remote study, we may also recruit through online advertisements (e.g. Facebook, Craigslist). Finally, we may also use research study repositories such as ResearchMatch.org to recruit potentially eligible candidates.

Research staff will phone screen each potential participant to see if they meet primary eligibility for the study (*see section 2.1 "Inclusion Criteria"*). If participants are eligible after the phone screen, they will be invited to attend a remote screening session via Zoom video call. If they are not eligible following the phone screen, they will be transferred to other C*f*AST studies for which they may be eligible (if they desire), or directed towards local quitting resources. If potential participants are unsure about whether or not they'd like to participate after the screening phone call, they will be encouraged to take as much time as they need to think it over before getting back to research staff about participation. However, they will need to be re-phone screened if there is a substantial amount of time (i.e., greater than 1 month) between the original phone screen and the participant's contact as their eligibility to participate may have changed.

6.2. Screening Visit

Participants will receive a Zoom video call via email link prior to their visit. We will also send instructions on how to join the Zoom call, and tell participants to call research staff if they are experiencing any technical difficulties. They will be instructed to join the call at the time of their visit. Once on the call, staff will give the participant a brief reminder of the study purpose. Then, staff will email a REDCap survey link to the participant to read and sign an electronic consent form. After reviewing the form, and before signing, the research staff member will display a PowerPoint presentation that outlines everything in the consent form (responsibilities, risks, benefits, compensation, etc.). After the presentation, the participant will electronically sign and complete the consent form if they choose to participate. They will be officially enrolled in the study, and will be assigned a subject ID number. If they do not want to participate anymore after going through the consent form or presentation, they will be thanked for their time and be given quitting resources.

After signing the consent form, participants will complete the following measures:

(1) Demographics and Identifying Information Form
(2) Medical eligibility to participate
    a. Brief Medical History Questionnaire and BMHQ Follow-Up (if applicable) to assess medical compatibility with NRT treatment and involvement with HIV treatment
    b. Filling out Concomitant Medications ("con meds") form (if applicable)

c. Completing Release of Information Form to communicate with providers
d. COVID-19 & Quitting Smoking Questionnaire – Screening Version

(3) Psychiatric assessment
a. Drug Abuse Screening Test (DAST) and Alcohol Use Disorders Identification Test (AUDIT) to assess current problematic behaviors related to drug and alcohol use
b. Drug Use Questionnaire (12+1 Month) to assess current and past drug use
c. Mini International Neuropsychiatric Interview (MINI)
d. Columbia Suicide Severity Rating Scale (C-SSRS) to assess any current suicidality

(4) HIV-related stigma
a. Stigma Mechanisms Scale and Everyday Discrimination Scale to determine perceived HIV- and smoking-related stigma

(5) Smoking status
a. Tobacco Use History and Exposure questionnaire to evaluate smoking status and past and current tobacco use
b. Smoking Cessation Therapies questionnaire
c. Stages of Change questionnaire (Contemplation Ladder) to evaluate interest in quitting smoking

(6) Barriers to Study Participation survey

At the end of the session, participants will be compensated for their time and told that we will review their eligibility with the PI and study doctor, and get back to them to schedule their baseline session. All participants are compensated regardless of final eligibility. The baseline session will occur within 30 days of consent, otherwise we will have to re-screen the participant.

Following the screening session, all information will be given to the study doctor to determine medical eligibility to participate (i.e., medical compatibility with NRT). The PI will then make the final decision about the participant's eligibility. If not eligible, participants will be notified and referred to other research studies and/or quitting resources. If deemed eligible, research staff will reach out to schedule a baseline session during which the participant will be randomized to the intervention.

6.3. Baseline Visit

Participants will attend a Zoom baseline session following their eligibility determination to be randomized to the intervention. A few measures will be completed prior to randomizing the participant:

(1) Health Changes questionnaire (adverse event and con med forms filled out if applicable)
(2) COVID-19 & Quitting smoking Questionnaire (Adapted)
(3) Assessing psychiatric functioning
a. Depression Anxiety Stress Scale-21 (DASS-21)
b. C-SSRS
c. Brief Symptom Inventory (BSI)
(4) Fagerström Test for Nicotine Dependence (FTND)
(5) Timeline Follow-Back (TLFB) Questionnaire
(6) Drug Use Questionnaire (1 Month)
(7) Internet/Smartphone Access and Use survey

After completing these measures, the participant will be randomized. They will receive either the LTQ-H app, or a standard-of-care app called QuitGuide developed by the National Cancer Institute (NCI). The RA will instruct

the participant on how to download their assigned app from the App Store/Google Play Store. The RA will give a brief overview of the assigned app to discuss the main functions and troubleshoot any major issues that may arise. They will also instruct the participant to enter their unique tracking code (similar to their subject ID) to allow us to track their background analytics data.

Following the baseline visit, we will mail 8 weeks of NRT patches to participants. We will tell participants to call/email the study team to confirm that they received their NRT. We will then instruct participants to start using the patches on the day of their quit date, which will be within 4 weeks of the baseline visit. Participants will be oriented on the best practices of using NRT based on the package instructions. There will be a brief compliance review session following the instructions in order to ensure that patients understand how to use the medication.

6.4. Follow-Up Visits

Participants will complete monthly follow-up (FU) visits at Weeks 4, 8, and 12 weeks post-randomization. All visits will be conducted via zoom video calling.

At each visit, participants will complete surveys to assess their smoking behavior, changes in physical or mental health (which will prompt staff to assess for adverse events), and user experience with their assigned study app. See table below for a list of all the measures.

At each visit, research staff will conduct an interview with the participant to ask about their experience using their assigned app. This interview will be audio recorded for later review. Each FU visit is expected to last between 45-60 minutes, depending on the assessment burden.

Measure	Week 4	Week 8	Week 12
Biochemical Verification (CO)			x
Health Changes Questionnaire	x	x	x
Adverse Events and Con Meds (if applicable)	x	x	x
COVID-19 & Quitting Smoking Questionnaire (Follow-up)	x	x	x
Drug Use Questionnaire (1 Month)	x	x	x
Timeline Follow-Back	x	x	x
DASS-21	x	x	x
BSI	x	x	x
Systems Usability Scale (SUS)	x		x
Qualitative user experience interview	x		x
Research Participant Perception Survey (RPPS)			x

Participants who self-report smoking abstinence by the final follow-up visit (FU3) will be mailed an iCO smokerlyzer device to do a breath test in order to biochemically verify abstinence. We will mail these to participants following their FU3 session. Once they receive the device, we will set up a short Zoom call to walk them through the CO breath test process. Staff will be on the call in order to ensure that it is the participant

who is doing the test, and that they are doing the test properly. Once the participant completes the test, we will ask them to email the result of their test to our lab email. Participants will keep these devices once they are completed in the study. The stop date for these participants will be the date of this breath test instead of the date of the FU3 visit.

Background analytics will be collected throughout the 4 months of participation, and will be measuring some things such as CPD, mood ratings, NRT use, duration of app use, and number of interactions within the app.

At the final visit (Week 12), participants will be given quitting resources if they have not quit. They will also be referred to other research studies, if eligible and willing.

6.5. Compensation

Participants will be compensated for their participation in the trial. Participants can earn up to $130 for completing all study activities. Compensation amounts are determined based on the burden of the research activities at the time point, as well as the length of the visit. Compensation will be provided on a Duke ClinCard that will be given out at the screening visit. Any withdrawn participants will be compensated for any research activities that were completed. In addition to monetary compensation, participants will be given an 8-week supply of NRT patches free of charge.

Assessment Time Point	Compensation Amount
Screening	$15
Baseline	$15
Week 4	$20
Week 8 (Via telephone)	$30
Week 12	$50
Total	**$130**

7.0. Participant Safety

7.1. Risks & Benefits

Nature and degree of risk

The anticipated physical, psychological, social, or legal risks of this study are minimal. The possible side effects of using NRT 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. Dr. Vilardaga (one of the MPIs) is a licensed clinical psychologist and can use his clinical judgment to assess how much risk a participant may be put in by doing this interview. The participant could also experience discomfort or embarrassment related to their ability to use a mobile app or smartphone device.

Minimizing risk of harm and protecting participants' rights and welfare

To address the possible side effects from Nicotine Replacement Therapy (NRT) patches, we will have our study doctor, Dr. Paolo Mannelli, available to monitor and evaluate participants' use of NRT in addition to consulting with the research team. We will also emphasize the package instructions' directions of 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 review any reported changes in medications by the subject throughout the course of their participation.

Potential participants will be screened to eliminate candidates with disorders or conditions that are contraindicated with the intervention (see section 2.1), or those who are not able to provide informed consent. We will work to coordinate the subject's participation in the study with the medical/mental health care that they are already receiving by obtaining a written Release of Information (ROI) that will allow research staff to communicate with their providers throughout the study.

The research team will be sensitive to issues surrounding confidentiality and other forms of participant risk by 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), and any forms/data containing PII will be stored separate from research data. We will emphasize the confidential nature of the data collected in this trial, explaining our safeguarding procedures 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 necessary, we will contact patients' providers using a ROI to connect them with the patient in distress.

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 by quitting smoking. We will provide free nicotine replacement therapy patches to participants, and the monitored use of the smoking cessation apps may contribute to cessation.

Anticipated benefits of research on society, benefits outweighing risks

Smoking directly causes 480,000 deaths a year in the United States. The prevalence of smoking among PLWH is disproportionately high (42-43%) as compared to the U.S. general population (15%). Increased longevity among PLWH—due to the development of highly effective treatments for HIV infection—has resulted in PLWH losing more years to smoking than to HIV infection itself.

Information derived from the study could help improve the effectiveness and reach of smoking cessation treatments for PLWH. 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 PLWH in areas where there may be few or lacking smoking cessation services (e.g., rural areas). Therefore, the minimal risks to participants are reasonable in relation to the anticipated benefits.

7.2. Adverse Event Collection & Reporting

Anticipated events

Given that many people who are HIV+ and smokers have more medical needs than the general population, we do anticipate subjects will report a higher rate of Adverse Events (AEs) as an inherent characteristic of this population. These include such events as COPD, lung cancer, pneumonia, psychiatric symptoms, and Antiretroviral Therapy medication side effects.

Some anticipated AEs resulting from the study interventions include study drug side effects. The study drug (i.e. NRT) has some common side effects that we expect subjects to occasionally report, including: dizziness, headaches, rapid heart rate, increased blood pressure, nausea and diarrhea. For the nicotine patch in particular, common side effects include skin irritation and/or itching where the patch is placed, insomnia, and vivid dreaming.

In addition, quitting smoking can result in withdrawal symptoms that may be uncomfortable to the participant. Common withdrawal symptoms include: cravings for cigarettes; depressed or sad mood; insomnia or trouble sleeping; feeling irritable, on edge, or grouchy; trouble concentrating; restlessness; decreased heart rate; and increased appetite/weight gain.

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 and recording AEs

We will be tracking all AEs and serious adverse events (SAEs) that a participant may experience once starting the study intervention (from Baseline onward). We will be doing this throughout the study, regardless of whether or not we think they are related to the study intervention. AEs will be documented by research personnel during research assessments, or at any other time during the clinical trial that they have contact with or about the subject. The PIs and study doctor are responsible for oversight on AEs.

We will document each AE with details such as:

- Description of event;
- Start and stop dates (if applicable);
- Whether or not they are getting treated (e.g. medications or therapies);
- Whether or not it is considered an SAE;
- Any other pertinent details.

Collected AEs will be documented and recorded with the information above on AE forms and entered into an electronic database (i.e., REDCap). On a weekly basis, the PI will review each AE to determine the following:

- Relationship to the study intervention;
- Severity of the event;
- Outcome;
- Status: ongoing, closed, lost to follow-up;
- 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 that's reported.

8.0. Data Analysis and Sample Size

8.1. Determination of Sample Size

Given that this is primarily a feasibility and acceptability 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. A pilot study of LTQ and prior studies in the general population of ACT-based interventions for smoking cessation show 93% 6-month participant retention, and 70% for standard of care.

Further, with 30 participants per group, we calculated that we would have 70%, 75% and 80% power to detect abstinence rates of 0.32, 0.34, and 0.36 effect sizes, respectively.

8.2. Data Analysis

Primary feasibility outcomes include:

- Recruitment rates and participant retention;
- App engagement (frequency and duration of app use)

We will report on *recruitment rates and participant retention* descriptively. Trajectories of *app engagement* will be plotted to examine ongoing *interactions with the app* and *duration of app* use per day.

Primary acceptability outcomes include:

- App usability (System Usability Scale);
- User experience (semi-structured interviews);

Acceptability outcomes will be evaluated descriptively with summary scores of the SUS. Scores above the SUS threshold (>68) are considered optimal. User experience will be extracted via Thematic Analysis of transcripts of semi-structured interviews.

Secondary outcome measures include:

- Change in cigarettes smoked per day (CPD) (measured daily with the tracking feature embedded within each app)

- Quit attempts (self-reported no smoking at all for 24 hours—and *time to 7-day relapse* will assessed via a Timeline Follow Back interview at Weeks 4, 8, and 12)
- 7-day point prevalence abstinence (not smoking even a puff of a cigarette within the last 7 days) and breath CO<5 ppm at Weeks 4, 8, and12)
- Adherence to NRT (measured via app tracking feature and Timeline Follow-Back interview at Weeks 4, 8, and 12)
- Participant safety (adverse events)

Differences between treatment groups (LTQ-*H* vs. NCI QuitGuide) in terms of secondary outcomes will be assessed via chi-square tests and logistic regression or t-tests and linear regression, as appropriate:

Chi-square tests and logistic regression:

- Quit attempts (prevalence of any quit attempts, yes/no)
- 7-day point prevalence abstinence (prevalence of any verified abstinence, yes/no)
- Adherence to NRT (prevalence of use of optimal amount of NRT, yes/no)
- Participant safety (prevalence of any adverse events, yes/no)

t-tests and linear regression:

- Change in CPD (measured as a continuous variable)
- Quit attempts (total number of quit attempts, measured as a continuous variable)
- Adherence to NRT (overall % of NRT used as directed, measured as a continuous variable)
- Participant safety (total number of adverse events, measured as a continuous variable)

Appendix

List of Abbreviations

ROI – Release of information

ICF – Informed consent form

Con meds – Concomitant medications

AE – Adverse event

SAE – Serious adverse event

CO – Carbon monoxide

BAL – Breath alcohol level

BP – Blood pressure

HR – Heart rate

NRT – Nicotine replacement therapy

LTQ-H – Learn to Quit-HIV

QG – QuitGuide

NCI – National Cancer institute

RA – Research assistant

CPD – Cigarettes-per-day

UE – User engagement

UX – User experience

C*f*AST – Center for Addiction Science and Technology

PLWH – Persons living with HIV

RCT – Randomized controlled trial

PPM – Parts per million

PII – Personally Identifiable Information