TITLE: Augmented Reality as an Adjunct to Quitline Counseling for Smoking Cessation

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1. SPECIFIC AIMS

Smoking remains the leading preventable cause of mortality and morbidity, accounting for nearly 500,000 annual deaths in the United States alone. Developing effective cessation interventions remains a public health priority. mHealth offers the opportunity to reduce barriers to dissemination and implementation of cessation treatment and improve efficacy. Mobile technology offers the ability to conduct certain intervention components in the user's natural environment. Recent advances in augmented reality (AR) on smartphones provide opportunities for improving extinction-based therapies, including those for tobacco dependence.

AR inserts virtual, digitally-created objects into the real-world environment as viewed on a screen (i.e., smartphone or tablet) or headset. As such, AR provides the opportunity to conduct extinction-based treatment in the real-world. Cue-exposure treatments have demonstrated efficacy for decreasing tobacco craving in the laboratory or clinic, but these effects do not appear to generalize beyond the extinction setting. This "renewal effect" has been demonstrated in both animal and human studies. With AR, it is now possible to conduct extinction trials across multiple environments throughout smokers' own natural smoking settings.

The study team received R34 funding to develop and test AR stimuli, with the long-term goal of integrating this technology into a smartphone application for real-world use as an adjuvant to existing smoking cessation treatment. This research has shown that (1) AR smoking stimuli (e.g., cigarettes, lighter) produce substantial cue-provoked cravings to smoke, approximating in vivo stimuli, and (2) repeated exposure to these stimuli reduces craving responses, consistent with extinction. These proof-of-concept findings support the clinical use of AR for cue-exposure therapy to reduce the risk of smoking relapse in response to naturally-encountered "triggers."

The proposed study will test the efficacy of the AR app and assess key constructs related to optimizing future implementation. Utilizing a hybrid design in partnership with the Florida Tobacco Quitline, the study will test if the addition of extinction trials via the AR app improves cessation outcomes compared to quitline alone. Quitlines are a low-cost, easily scalable, standard of care treatment option for smoking cessation, employing both behavioral counseling and pharmacotherapy. Nonetheless, smoking abstinence via quitline treatment is modest (~15%) and would likely increase if paired with other theoretically-based treatment components.

Current smokers (N=2072) will be recruited via the quitline and randomized to one of two intervention arms: quitline only (QLO) or quitline plus the AR app (QL+AR). After achieving 48 hours of continuous self-reported abstinence, participants in the QL+AR condition will begin cue-exposure treatment. Although the AR app is designed to be sufficient, participants will have the option of contacting an App coach for app assistance. Abstinence, craving, and nicotine replacement therapy (NRT) will be monitored via daily diary across both conditions. The primary outcome is biochemically-confirmed abstinence at 6 months after baseline survey completion.

Aim 1. Update the existing AR app to be an engaging, user-friendly treatment tool, and verify user satisfaction.

Aim 2. Test efficacy of QL+AR over QLO & explore potential moderators and predictors of treatment effects.

a. Hypothesis: QL+AR participants will demonstrate higher tobacco abstinence rates six months post-baseline than will QLO participants.
b. Potential moderators of interest include sex, nicotine dependence, trait cue reactivity, smoking status during treatment, quitline use, and NRT use. Potential predictors within the QL+AR arm include initial cue reactivity, extinction magnitude and latency, indices of treatment engagement, and App coach use.

Aim 3. Evaluate treatment implementation to guide future quitline adoption, including:

a. Cost-assessment and incremental cost-effectiveness analyses comparing QL+AR with QLO.
b. Examine treatment engagement and acceptability among those in QL+AR. This will include evaluation of the App coach.
c. Identify facilitators and barriers to incorporating AR treatment into quitline services via qualitative interviews with quitline supervisors, App coaches, and participants.

If participants who receive the AR app demonstrate higher rates of tobacco abstinence than those in QLO, this would indicate that AR is a suitable adjunct to quitline treatment. Results of Aim 3 will guide implementation of the AR app into state quitlines and other smoking cessation services. This theoretically-based AR app has the potential to improve a range of existing treatments for dependence on tobacco as well as other substances.

2. BACKGROUND AND SIGNIFICANCE

Tobacco Use and Leveraging Scalable Smoking Cessation Treatment Options

Cigarette smoking is the leading preventable cause of morbidity and mortality in the U.S. (USDHHS, 2020). Smoking prevalence was 13.7% in the U.S. among adults in 2018 (Creamer et al., 2019). Whereas the majority of those who smoke report interest in quitting smoking, only 7.4% successfully quit each year (CDC, 2017; Fiore et al., 2000). Thus, improving the effectiveness and reach of cessation interventions remains a public health priority.

A significant advance in public health has been the development of evidence-based interventions for tobacco cessation, including those delivered via telephone quitlines (North American Quitline Consortium, 2016). Quitlines typically provide free smoking cessation counseling and nicotine replacement therapy (NRT). They have consistently demonstrated efficacy, cost-effectiveness, and high scalability, with quitlines now available in all 50 states, Puerto Rico, DC, and Guam (Abrams et al., 2010; Fiore, 2008; Glasgow et al., 2004; Matkin et al., 2019). However, abstinence rates via quitlines remain modest (10-15%; Fiore et al., 2008; Matkin et al., 2019; Pinerio et al., 2020) and would likely increase if paired with other, theory-based treatment components that maintain high scalability and low cost. Our study aims to leverage quitline services by pairing them with a novel theory-based, smartphone application that addresses a unique contributor, conditioned cue reactivity, to smoking cessation outcomes.

Mobile health (mHealth) interventions hold particular promise in reducing barriers to dissemination and implementation (Abroms et al., 2012; Free et al., 2011; Rodgers et al., 2005; Vinci et al., 2018; Vinci et al., 2020a). The advantages of mHealth have been magnified by the COVID-19 pandemic, which has accentuated the need for remote treatment delivery. Moreover, harnessing recent advances in technology may increase the uptake of cessation treatment, while also targeting identified roadblocks to cessation. In 2019, 81% of Americans owned a smartphone, with 70% ownership among low-income populations (PEW Research, 2019). Thus, novel interventions that leverage advances in technology hold great potential for improving the reach and effectiveness of smoking cessation interventions.

Augmented reality (AR) is a recent and rapidly advancing mobile technology with potential utility for smoking cessation treatment. Through the display of virtual smoking cues superimposed upon smokers' natural environment, AR appears ideal for improving the long-term effects of extinction-based intervention strategies (i.e., cue exposure). Cue exposure typically consists of presenting a drug cue (e.g., cigarette, glass of beer) to individuals multiple times, while not allowing them to engage in the typical drug behavior (smoking, drinking), so as to extinguish the cravings. As described in more detail below, cue-exposure treatments have demonstrated efficacy for decreasing craving in the clinic/laboratory, but these effects are short-lived, and have not generalized well beyond the extinction setting (e.g., clinic) into the real world (Bouton, 2000). AR allows the entire cue-exposure session to take place in the real world, which should greatly enhance the efficacy of cue-exposure treatment. The current proposal aims to capitalize upon emerging AR technology to test a novel treatment adjuvant for smoking cessation in conjunction with quitline services.

Augmented Reality (AR)

AR inserts virtual, digitally-created objects into the real-world environment as viewed on a screen (i.e., smartphone or tablet; see Figure 1 for AR smoking image developed and tested by our team), with emerging options for head-mounted displays. AR is similar to virtual reality (VR) in that the user is immersed in a digitally-enhanced environment. However, whereas VR attempts to insert the user fully into an artificial, computer-generated environment, AR inserts digital objects into the user's actual environment in real-time. To be considered AR, a system must (1) combine real and virtual objects in a real environment; (2) run interactively, and in real-time; and (3) align real and virtual objects with each other (Azuma et al., 2001; Baus & Bouchard, 2014).

Figure 1. AR Smoking-Related Image

Rudimentary forms of AR have been developed long before the term "augmented reality" was coined in 1990. However, with the exponential increase in computer power in mobile devices, AR hardware and software have advanced particularly fast over the past decade (Baus & Bouchard, 2014). The first mass awareness of AR occurred with the Pokémon Go gaming app, released in 2016, which used smartphones' GPS, gyroscopes,

compass, and camera to superimpose primitive (by today's standards) AR "creatures" in the users' natural environment. In the five years since, the technology has improved dramatically and has developed more mainstream uses in education, entertainment, architecture, and retail. For instance, many furniture retailers now have apps that allow the user to place and view digital depictions of products within the user's own home. Once a digital AR object has been placed within a user's natural environment, the digital object closely approximates the perceptual qualities of a real object in that location (e.g., the user can view the object from any direction, distance, or angle while maintaining a realistic perspective). Motion can also be included; for example, an AR cigarette can have smoke actively rising from it (as shown in Figure 1). Both Apple and Android devices support AR capabilities, and they continue to advance as AR becomes a more integral part of day-to-day life. For instance, the Apple iPhone 12 has a 3D triple lens camera system that includes a laser to enhance AR capabilities. Importantly, Apple's ARKit is a mobile platform that allows for simplifying the development of AR apps for iOS, and Google's ARCore platform is available for development of AR apps on Android and iOS.

Aside from retail and entertainment, the vast majority of AR application has been in healthcare (e.g., surgical training; Barsom et al., 2016). In contrast, a systematic review identified only 13 published studies of AR within the domain of mental health (Giglioli et al., 2015). Perhaps ARs greatest potential is to advance extinction-based cue-exposure therapies, which have primarily been used to treat disorders conceptualized as originating from or maintained through conditioning processes, most notably substance use and anxiety disorders. We believe that AR will improve the efficacy of cue-exposure therapies for addictive behaviors, including tobacco use. Although the potential of AR for cue-exposure therapies has been recognized (Baus & Bouchard, 2014), research has been mostly limited to small animal phobias—cockroaches, in particular (e.g., Botella et al., 2016). AR was successful in such studies in reducing anxiety and avoidance behaviors.

Cue-Reactivity and Cue-Exposure Therapy

Most theories of addiction include a prominent role for conditioned cue reactivity—the idea, based on Pavlovian conditioning, that during substance self-administration otherwise neutral stimuli become paired or associated with the unconditioned, pharmacological effects of the drug (e.g., tachycardia or euphoria). Over time, the previously neutral conditioned stimuli (CSs) develop the capacity to elicit physiological conditioned responses (CRs) in the absence of drug ingestion (Stewart et al., 1984; Siegel, 1983; Wikler, 1965). Data have consistently shown that environmental CSs (e.g., drug paraphernalia) can cause cue reactivity in those addicted to alcohol, opioids, and cigarettes (Brandon et al., 1995a; Rohsenow et al., 1992), and these CRs are subjectively experienced as cravings to use the drug. In fact, as described below, our team recently demonstrated that smoking-related AR cues produce significantly greater cue reactivity than neutral AR cues with very large effect sizes (Brandon et al., 2020). CRs (craving in particular) contribute to drug use maintenance and relapse, and cue reactivity is predictive of future smoking cessation (Brandon et al., 2007; Conklin et al., 2012; Ditre et al., 2012). The role of conditioned cue reactivity in addictive behaviors has been incorporated into most of the major contemporary influential models of addiction, including models with primary perspectives that are psychosocial (e.g., Witkiewitz & Marlatt, 2004), cognitive (Tiffany, 1990), and neurological (Kalivas & Volkow, 2005; Robinson & Berridge, 1993).

The logical clinical implication of cue-reactivity theory and research is that cue reactivity can be extinguished through the repeated presentation of drug-related cues (CSs) in the absence of the unconditioned stimulus (UCS; the ingested drug). To the extent that post-cessation relapse is initiated by conditioned craving, this treatment—called cue-exposure with response prevention, or cue-exposure therapy—should have clinical efficacy (Monti & Rohsenow, 1999).

Although cue-exposure treatments produce declines in drug cravings or consumption (Childress et al., 1986; Drummond et al., 1994; McLellan et al., 1986; Monti et al., 1993; Sitharthan et al., 1997; Unrod et al., 2014), long-term clinical outcomes are modest. A meta-analysis of cue-exposure treatments for addictions found that their overall effect size was small (d=0.09; Conklin & Tiffany, 2002). Learning and addiction theorists have argued that the limited efficacy of cue-exposure therapies can be attributed to the minimal attention paid to context effects (Bouton, 2000; Brandon, 2001; Brandon et al., 1995a; Childress et al., 1986; Conklin & Tiffany, 2002; Powell, 1995; Rodriguez et al., 1999). That is, cue-exposure therapy is typically provided via

extinction trials that occur in either a laboratory or clinic. Based on extensive animal and human research, extinction that occurs in these contexts does not appear to generalize to contexts in the participant's natural environment (i.e., the "renewal effect"; Bouton, 2002; Collins & Brandon, 2002). Thus, considerable effort has been spent testing alternative approaches for expanding the context of extinction to smoking cues.

Expanding the Extinction Context

The most straight-forward approach to overcome the renewal effect would be to provide cue-exposure therapy in multiple contexts within the smoker's natural environment. However, smoking takes place in a multitude of locations, and it is not feasible for a smoking cessation counselor to accompany the smoker throughout his/her naturalistic environments to conduct cue-exposure sessions. Consequently, researchers have developed ways to expand the context of cue reactivity, which could then be used to expand the context and generalizability of cue-exposure therapies. These include (1) increasing the realism of the laboratory/clinic context via large-scale projections of photos taken by smokers of their natural environment (Conklin et al., 2010); (2) having smokers bring video images of smoking cues into their natural environment (Wray et al., 2011); and (3) providing smokers with "extinction cues" for them to bring into their natural environment (Unrod et al., 2014; Collins & Brandon, 2002). More recently, researchers have attempted to harness advances in VR (Pericot-Valverde et al., 2015), and although this approach has been effective at provoking cravings, limitations of VR environments include being (1) costly to produce, limiting availability; (2) graphically unrealistic, although this is improving; and (3) unrepresentative of individuals' unique smoking environments.

The Potential of Augmented Reality

In contrast to VR, AR requires the development of only the specific smoking cues (e.g., cigarettes, lighters, ashtrays), not the entire smoking environment. These cues are then inserted into the smoker's actual, naturalistic environments via smartphone (e.g., different locations in the home, work, outdoors). Our team has already developed and tested an initial set of AR smoking stimuli.

AR has the potential to extend the short-term gains produced in the laboratory. Importantly, cue exposure via AR can occur entirely in the smoker's natural environment, circumventing limitations of existing cue-exposure treatments. This should dramatically increase the sustained efficacy of cue-exposure therapy, based on contemporary models of extinction described above. AR also offers stimulus control and safety advantages over in vivo exposure for clinical use (i.e., the user is not exposed to the actual substance). Theoretical and therapeutic advantages aside, the value of conducting interventions remotely has been amplified by COVID-19 and the need to minimize direct social contact.

The Current Study

We conceptualize AR-based cue exposure as an extinction-based *adjuvant* to a more comprehensive smoking cessation intervention. Thus, we are not proposing AR-based cue exposure per se as a *stand-alone* intervention for treating tobacco dependence. However, because cue reactivity appears to be a proximal determinant of smoking maintenance and post-cessation relapse, cue exposure is a logical, theory-based treatment component aimed at improving cessation and reducing risk of relapse. Moreover, AR has the potential to break through the contextual barrier associated with previous extinction-based therapies for treating addiction—i.e., the renewal effect—because of its portability and presentation of stimuli in the users' natural environments. After demonstrating that AR cues elicit both cue reactivity and extinction in controlled experiments, the ideal next step is to test an AR app in conjunction with a telephone quitline. Not only do quitlines provide broad reach with validated counseling and pharmacotherapy, but cue exposure via AR should complement the potent elements of quitline counseling (e.g., general coping skills for managing craving, social support). If demonstrated as an effective adjuvant to quitlines, AR would likely be similarly effective with a variety of smoking cessation interventions, including traditional cessation counseling, online cessation websites, text messaging (SMS) interventions, other mobile cessation apps, and/or pharmacotherapy.

The proposed research represents a systematic and **scientifically rigorous** process in the evaluation of an evidence-based adjunctive therapy to quitline treatment. Indeed, it represents a hybrid type-I design (Curran et al., 2012), such that we aim to test the efficacy of AR when combined with quitline treatment, while also considering key questions relevant to future implementation. We will build off our team's preliminary data and initial app development to test the efficacy of the quitline plus the AR app (QL+AR) against usual care,

quitline only (QLO). To address implementation questions, we will determine the cost-effectiveness of the intervention, as well as measure indices of treatment engagement and acceptability. We will also collect feedback from quitline supervisors, study staff, and participants regarding potential barriers to implementation and dissemination. Although the AR app is designed to be self-contained (i.e., to not require additional explanation or assistance from live operators), we will also monitor the degree to which such live assistance is sought. Importantly, the proposed research is not driven solely by the availability of new technology, but by a sound **scientific premise** derived from both the theory-based and empirically-supported role of cue reactivity in the maintenance and cessation of addictive behaviors, and consequently, the potential value of extinction-based cue-exposure approaches in the treatment of addiction.

INNOVATION

The proposed research is innovative in numerous ways, capitalizing on advances in AR technology. Searches on NIH Reporter and PubMed revealed that AR has begun to be utilized for training purposes (e.g., for training physicians), but there is little literature and no ongoing grants utilizing AR psychotherapeutically aside from the work conducted by our team. Although there is a small literature on AR for extinction-based treatment of phobias, our team is the only group that has published on AR for the treatment of addictive behaviors. The only uses of AR for tobacco we could find include a British AR tool for physicians that illustrates organ damage caused by smoking, and a phone app by the British Health Foundation that, when pointed at a cigarette pack, illustrates how the smoker could spend money saved by quitting. Aside from the app itself, we are leveraging quitline treatment, an existing evidence-based treatment for tobacco cessation, and will examine implementation questions that will be key to future quitline adoption. Thus, adding such a novel, scalable adjuvant therapy to the quitline in and of itself is innovative. In sum, our proposed research appears to be among the first to use established scientific methods to capitalize upon AR technology to: (a) develop therapeutic uses of any kind; (b) including extinction-based approaches; (c) particularly for treating addictive behaviors; (d) notably tobacco dependence. AR provides a new opportunity to solve the therapeutic dilemma of the renewal effect that limits the real-world efficacy of cue-exposure therapy, and our team is uniquely situated to advance this innovative approach to smoking cessation treatment.

3. PARTICIPANT SELECTION

3.1 AIM 1: For Aim 1, we will recruit 10 adult participants who have quit smoking within the last 3 months and are currently abstaining from smoking for usability testing. Inclusion criteria will be: ≥ 18 years of age; were daily smokers that have quit smoking within the past 3 months; functioning telephone number; owns a smartphone capable of supporting AR and willing to download the study app (94% of Android phones and >99% of iPhones in the U.S. have operating systems that support AR; Statcounter, 2021); and can speak, read, and write in English. Exclusion criteria for both aims will include another household member already enrolled in the study.

Recruitment and Consent

The primary goal of recruiting participants for Aim 1 is to conduct field-based usability testing on the enhanced AR app with respect to the new smoking cues and general app functionality, building upon the lab-based data collected on the basic app via our preliminary research. This approach permits identification of major issues by participants or staff, while preparing staff to problem-solve in real time in preparation for Aim 2.

All Aim 1 procedures will be conducted remotely. Recruitment will take place on social media and other websites, as our team has successfully used this approach to recruit large samples of smokers (Martinez et al., in press). Interested individuals will either directly call the study phone line or complete online contact forms and be called back, and additional information about the study will be provided. Interested participants will be screened for eligibility and complete the verbal informed consent process, with a waiver of written consent. Once consented, participants are enrolled in the study. Recruitment will take place over 3 months. Participants may withdraw at any time for any reason by contacting the staff and informing staff of their desire to withdraw from the study. Participants will be removed from the study if they do not download the app within one week.

3.2 AIM 2: Participants and Recruitment

For Aim 2, inclusion criteria include: ≥ 18 years of age; currently smoking ≥ 3 cigarettes per day for the past year; functioning telephone number; owns a smartphone capable of supporting AR and willing to download the study app; and can speak, read, and write in English. The smoking criteria were selected to obtain a wide range of smokers who would have developed both sufficient cue reactivity and cessation motivation (Shiffman et al., 2014). Recruitment (N=2072) will take place via Tobacco Free Florida's Quitline. Upon calling the quitline and enrolling in quitline services, participants will be provided with information about the study by quitline enrollment agents to determine initial interest. A brief eligibility screening will be conducted (e.g., confirm English-speaking, smoking status); eligible callers will be asked for their consent for the quitline to send their contact information to the study team. Enrollment agents will send referrals to study staff daily either via a secure email or secure file transfer protocol. Upon referral receipt, study staff will call participants to complete eligibility screening and conduct the full informed consent process. Then, participants will be randomized to one of the two study conditions. A baseline survey will be sent to participants and study staff will textlinks to participants to download the study app after survey completion, provided the participant reports not being currently abstinent for more than 7 days. Participants are considered enrolled in the study following app download. Participants may withdraw at any time for any reason by contacting the staff and informing staff of their desire to withdraw from the study. These procedures have already been developed in conjunction with the Tobacco Free Florida Quitline. We have allotted 29 months for recruitment, which requires consenting an average of 17 participants per week. Figure 5 presents the expected flow of participants. Thus, the recruitment process is feasible with respect to sample size, quitline burden, research staff burden, and funding duration.

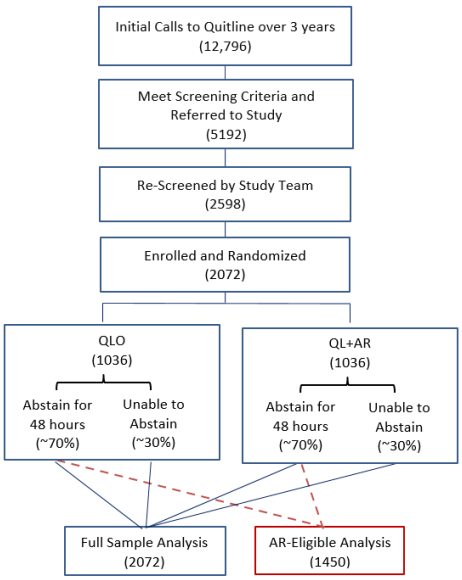

Figure 5. Participant Flow Through Study

4. STUDY DESIGN AND METHODS

4.1 Design

The proposed study will test the efficacy of the AR app while also assessing key constructs related to optimizing future implementation. Utilizing a hybrid design in partnership with the Florida Tobacco Quitline, we will recruit and randomize participants to one of two treatment arms: (1) quitline only (QLO) or (2) quitline plus the AR app (QL+AR).

4.2 Intervention

Participants in the QL + AR condition will download and use a smoking cue extinction app that includes the features outlined in Table 1.

Table 1. AR App Features

FEATURE	DESCRIPTION	RATIONALE
Situation Menu	Participants will choose what situations/times of day are most appropriate for their AR sessions, although the app will provide general recommendations.	Tailoring treatment content to the individual and supporting choice;[1] supporting autonomy.[2]
Tutorials	Video tutorial on correct app use (e.g., placing AR stimuli), with unlimited interactive practice sessions.	Supporting competence; identified as a needed feature in preliminary work by the investigative team.
Rationale for Cue Exposure	Rationale for cue exposure to help quit smoking/support participant goals (video).	Supporting autonomy;[2] providing purpose of the app and improving knowledge of benefits.[1]
Best Practices for AR Sessions	Specific guidelines for using the app (e.g., no smoking during sessions; no use of nicotine products before sessions, patch use ok).	"Expert advice" is an ideal feature for quit smoking apps.[3]
Reminder Notifications	Participants will select frequency of reminder notifications to complete AR sessions.	Supporting autonomy;[2] participants prefer to choose timing of reminders.[3]
Progress Tracker	Participants will be able to view 1) their progress through the program overall, 2) changes in urge ratings over time, 3) daily cigarette use, and 4) use of NRT.	Supporting competence;[2] consistent with mHealth frameworks;[1] preferred feature in quit smoking apps.[3,4]

Troubleshooting	Available any time to support use of the app.	Quick access for app support.
Rewards	Linked app engagement and progress towards quitting (e.g., visual presentation of money saved by not smoking).	Rewards for quitting smoking commonly requested feature.[3]
App Coach	Link to live App coaching by phone call.	Offers additional explanation of extinction goals as well as technical assistance for app.

[1]Floryan et al., 2016; [2]Ryan & Deci, 2000; [3]Hartzler et al., 2016; [4]McClure et al., 2016

App Use

Initial use of the app will occur in stages: Assess, Setup, Recommendations for Use, and Extras. Once users complete the stages, they will be able to use the app as needed on a daily basis. We describe all aspects of the app below, including those only relevant to Aim 2.

Assess. Each morning, participants will be prompted to complete a daily diary to assess the following from the previous day: number of cigarettes smoked, NRT use, and tobacco craving. Because ongoing smoking during cue-exposure sessions will be counter-productive to extinction of urges, participants will need to self-report 48 hours of abstinence to advance to Setup. Achieving such short-term abstinence with quitline support/NRT should be feasible for at least 70% of participants (Shiffman et al., 1996; Shiffman et al., 2007).

Setup. Once the abstinence requirement is met, participants will personalize the app, learn the purpose of the app, and practice using AR. First, they will watch a video tutorial explaining the use of cue exposure. They will select their most relevant AR cues and situations in which they most commonly smoke and/or experience high cravings (e.g., upon waking, after meals, when stressed, with alcohol, with coffee, celebrating). They will receive a list of "best practices" for completing AR sessions (e.g., no smoking during sessions). Participants will next receive instruction on using the app for cue-exposure sessions, comprising a short video describing how to place the AR objects, followed by an interactive tutorial with real-time practice.

Recommendations for Use. Recommendations for daily use will be proactively provided, but also available for later review on demand. The app will recommend that participants complete 2-5 AR sessions per day. It will emphasize that the more often they use the app when experiencing craving, the more successful they will likely be in maintaining abstinence.

Extras. Participants will be introduced to all other features of the app: setting up reminder notifications, accessing the progress tracker, access to the App coach, and viewing of rewards.

Details of AR Sessions. Participants will be encouraged and reminded to complete 2-5 AR sessions per day. Each session will present 3-8 cues, and each cue will be presented for 20-40 seconds (average amount of extinction per day will be about 10 minutes). We have included variability in the number and length of cue presentations to decrease predictability and maintain general interest in the sessions. Participants will be encouraged to conduct the AR sessions when high cravings are expected. Before beginning an AR session, participants will indicate their current situation/environment (e.g., after meal), and current urge to smoke and then a series of AR cues will be presented. Participants will rate their urge to smoke following the first and last cue in the session. Data will be automatically uploaded to the cloud.

4.3 Procedure

Aim 1: AR App Updates and Usability Testing

Aim 1 Overview

Aim 1 will include updates/modifications to the AR app, along with participant usability testing to finalize the product for use in Aim 2. In collaboration with Haneke Design, we will develop additional AR smoking-related stimuli, totaling 12 to 20 AR images. Given our previous experience developing smoking and neutral AR stimuli, we believe this process will take relatively little time to complete. We will also update the AR app with additional content for Aim 2 (e.g., menu options) and make the app functional for both Apple and Android devices. We will field-test the revised app with 10 participants, and adjust software and methodology as needed prior to Aim 2. Concurrently, Dr. Vickerman will work with her team at RVO Health to modify the existing software of the Tobacco Free Florida Quitline to facilitate recruitment for Aim 2, and train quitline enrollment agents on caller screening and study referral. Aim 1 will take 12 months to complete (see attached Timeline).

Development of Additional Stimuli and App-based Content

Figure 4. Existing AR Smoking Cues

Currently, the AR app is only available on iOS, Apple's operating system, so Aim 1 will update the app to be compatible with both Apple and Android operating systems. We already developed 6 AR smoking cues (Figure 4), and we will create 6-14 additional images. We anticipate a subset of these cues to include motion (e.g., smoke rising) and some combined cues (e.g., lighter, ashtray, and pack of cigarettes). The process for developing these cues will mimic the procedures from our R34 project.

Although the app will function as an adjuvant to quitline phone counseling, we will include specific functionality and features within the app that complement the AR sessions. These features are based on: (1) current recommendations for mHealth interventions, guided by both self-determination theory (SDT) and the behavioral intervention technologies (BIT) model (Floryan et al., 2016; Mohr et al., 2014); (2) recommendations for smoking cessation apps (Hartzler et al., 2016; Heffner et al., 2015; McClure et al., 2016; Ortis et al., 2020); and (3) our experience developing the first iteration of the app. To increase intrinsic motivation and engagement, we utilized SDT as a guiding framework when deciding on features to include, with a primary focus on supporting autonomy and competence (Deci et al., 1994; Ryan & Deci, 2000; Williams et al., 2006). Given modest rates of treatment adherence for existing smoking cessation apps (Abroms et al., 2013), it is important to integrate features that enhance engagement. Social support is often recommended for smoking cessation apps (e.g., Hartzler et al., 2016; Heffner et al., 2015), but because this app will be an adjuvant to quitline counseling, we will not include a comprehensive support feature. That said, we are interested in knowing whether participants require additional support for the AR and cue-exposure components, and we have incorporated the option of utilizing an App coach via two routes.

Table 1 (above) includes primary app features and rationale for inclusion. Consistent with SDT and general recommendations for mHealth apps (e.g., Floryan et al., 2016), we have incorporated participant choice into the features whenever possible. We expand on those features that require additional rationale here. First, "Rationale for Cue Exposure" will provide a foundation for the use of cue exposure to aid in quitting smoking and will offer information on why cue exposure is important for their personal goal to quit. Second, "Best Practices for AR Sessions" will provide guidelines for using the app that are specific to tobacco (e.g., no smoking during cue-exposure sessions; no use of acute-delivery nicotine products before the sessions). Content from "experts" has been identified as a desirable app feature (Hartzler et al., 2016).

Participants (see 3.1 above)

Informed Consent and Assent

All consenting procedures described here apply to both smokers and quitline supervisors. Prior to enrolling in the study, interested participants will speak with study staff at TRIP to learn more about the study. At that time they will be provided with a detailed overview of the study. Potential participants will be screened for inclusion/exclusion criteria. If eligible, the informed consent process will take place, which includes study personnel providing a detailed description of the study, answering questions, and obtaining verbal consent to participate. We will apply for a waiver of written consent from our IRB. If this is not approved, we are prepared to collect electronic consent via REDCap, which our institution has setup to be a secure, HIPAA-compliant way to document consent from participants. Participants will be given as much time as needed to ask questions during the consenting process, prior to agreeing to participate. Assent is not applicable to our study, as all participants must be over the age of 18.

Recruitment and Procedures

All Aim 1 procedures will be conducted remotely. Recruitment will take place on social media and other websites. Interested individuals will either directly call the study phone line or complete online contact forms and be called back, and additional information about the study will be provided. Interested participants will be screened for eligibility and complete the informed consent process. Staff will provide an overview of general issues about which we will seek feedback (e.g., functionality). Participants will be sent a REDCap survey to

complete when the call is over. When the survey has been completed, participants will then be texted a link to download the app onto their personal device and use the app in their natural environments for 1 week. A second survey will be sent at the end of the week, followed by a phone interview. Participants will be paid $10 for completing the baseline survey, $20 for the follow-up survey and $15 for completing the phone interview.

App Use (see 4.2 above)

Aims 2 and 3: Randomized Controlled Trial

Project Overview

The primary goal of Aim 2 is to test the incremental efficacy of the AR app when added to standard tobacco quitline services. We will recruit and randomize participants to one of two treatment arms: (1) quitline only (QLO) or (2) quitline plus the AR app (QL+AR). In the interest of rapid dissemination and implementation pending positive findings, we have designed procedures with future scalability in mind. Participants will be recruited via the Tobacco Free Florida Quitline and referred to the study team via quitline enrollment agents. Participants who return a baseline questionnaire will be directed to download the app on their personal device and will complete the study. The primary outcome will be biochemically-confirmed tobacco abstinence assessed at around 6 months in a subset of participants.

Participants and Recruitment (see 3.2 above)

Randomization

Block randomization (block sizes=8) will be used to assign 2072 enrolled participants to one of the two conditions. The randomization order will be generated by Dr. Sutton and implemented within REDCap.

Quitline Services

All study procedures have been developed in close coordination with Tobacco Free Florida, the Florida Department of Health, and RVO Health, the quitline contractor will oversee all aspects of the quitline, including supervising staff to coordinate project activities, modification of quitline software to support the screening and referral of callers, and management of data collection by quitline staff.

The Florida Tobacco Quitline is operated by RVO Health, the largest provider of tobacco cessation quitlines in the U.S. RVO Health's Quit For Life® program is an evidence-based tobacco cessation treatment delivered over phone, web, and text, and is grounded in social cognitive theory and the U.S. Public Health Service clinical guidelines (PHS Guideline, 2008). Quitline coaches use cognitive behavioral therapy, reinforcement, and principles of self-efficacy to promote effective behavior change. The quitline approach includes 5 key elements: setting a quit date, coping with triggers, effectively using medications, tobacco proofing, and social support. Phone counseling for cessation has been evaluated in randomized trials and effectiveness studies (Hollis et al., 2007; Orleans et al., 1991; Stead et al., 2013; Zhu et al., 2002). Individuals who enroll in the quitline's multi-call program receive three phone calls. They are mailed two weeks of NRT after the first phone call, to begin using on their quit date (coinciding with the second call). Participants will be provided with information about the study during their first phone call, and study staff will reach out to enroll participants in the study after receiving their contact information from the Quitline.

Study Arms

Quitline Only (QLO). Participants randomized to the QLO condition will receive an app that administers the daily diary questions for 5 weeks and shows their app and abstinence related progress. They will not receive any treatment via the app. Thus, they will receive usual care via the quitline and complete minimal daily assessments.

Quitline plus AR (QL+AR). Participants randomized to QL+AR will receive the AR app described in Aim 1. Initially, the app will only administer the daily diary questions. Once 48 hours of self-reported tobacco abstinence is achieved, the AR elements of the app will become available (see 4.2). Daily diary questions will continue for 5 weeks. AR extinction trials will occur daily until (1) the participant reports 3 consecutive days of smoking, in which case the AR trials will be suspended until another smoke-free 48 hours are reported, or (2) a

total of 5 weeks have elapsed since the start of app use.

The integration of cue exposure and quitline treatment is important. Quitline coaches encourage removing all smoking paraphernalia prior to the quit date, which will facilitate tobacco-free AR sessions and reduce risk of post-AR relapse. Notably, the use of AR stimuli for exposure sessions is completely consistent with the instructions to avoid in vivo cues to smoke. Other aspects of quitline treatment (setting a quit date, coping with triggers, using NRT, social support) are well-established tobacco treatment components and should facilitate abstinence.

Although the app is designed to be self-contained, it will include access to an App coach who can provide additional instruction and explanation of the extinction goals and process, as well as technical assistance with the app. App coaching can be initiated through two routes: *on demand* and *triggered*. The *on demand* route allows participants to contact an App coach at any time (9am – 6pm, 7 days/week) via a selection within the app. The *triggered route* is activated based on non-engagement with the app within the first 48-hour post-abstinence period. If AR trials have not been initiated within this period, the app will first send reminder notifications. If these do not yield AR usage within 24 hours, the app will send a notification offering the option of immediate or scheduled connection to an App coach (opt-in). If this is declined and AR disuse continues for another 24 hours, the app will send a notification that an App coach will reach out to them that day. This process may be repeated one additional time. App coaching sessions will focus on the following topics: reinforcing the rationale for cue exposure; addressing any issues related to smoking or NRT use before/during/after cue-exposure sessions; guidance on how to be fully immersed in the exposure sessions; and encouragement to maintain connection with the stimuli during exposures (vs use of any avoidance strategies). Technology-related assistance will also be provided as needed, along with any other concerns brought up by the participant. It should be noted that these topics will be available to view in the app itself. We will monitor the frequency, content, and time required of App coaching to guide future implementation. Data may inform improvements to the app and whether App coaches should be retained—perhaps via specialized training of quitline coaches.

End of Treatment and Follow-up

Follow-up questionnaires will be sent to all participants via REDCap around 5 weeks and 6 months after-baseline completion. A subset of participants (40%, approximately 100) who self-report cigarette smoking abstinence at around 6 months will be mailed a saliva collection kit for cotinine-based biochemical confirmation of abstinence. A subset of participants (n=40) from QL+AR will complete a phone interview at the end of treatment, as will a subset of quitline supervisors (n=10) and all App coaches.

Compensation and Retention

For completion of measures at baseline, and around 5 weeks and 6 months after baseline survey completion, participants will receive a $20 gift card (up to $60 total). For each week they complete at least 70% of the daily diary questions (5 days), they will receive a $10 gift card (up to $50 total). Thus, most participants will be compensated up to $110. Participants who complete the interview, will be compensated $20. Participants who return a saliva sample will be compensated $25.

To aid in retention, the following procedures will take place: collection of full contact information; text reminders and phone calls to follow-up on incomplete surveys; and collection of names and contact information of at least 2 collaterals (i.e., relatives, friends) who can help us reach lost participants.

Treatment Delivery and Fidelity for AR and Quitline Coaching

Although we expect minimal use of App coaches based on the comprehensive app content, we will monitor and assess coaching fidelity. App coaches will be part of the study team. With an eye toward scalability, qualifications will mimic those of quitline coaches (e.g., Bachelor's degree, tobacco abstinent). Training will be manualized and conducted by Drs. Vinci and Brandon, given their experience with exposure-based treatments. Training (8-10 hours) will be a combination of reading, didactics, and role playing. We will develop a measure to assess adherence and competence to be used during the training period. Weekly supervision will occur to ensure App coaching is delivered consistently. Coaches falling below performance

criteria will receive additional training. To monitor treatment adherence, sessions will be recorded and a random sample of 50% will be rated by the investigators using the measure developed during the training period. Fidelity of the screening and referral process will be conducted by Dr. Vickerman's team on a weekly basis by reviewing a subset of call recordings of the study offer and screening, and providing regular feedback to enrollment agents.

4.4 Measures

AIM 1 Measures

Baseline Measures. Participants will complete a series of baseline measures, administered via REDCap link, to assess demographics, experience with AR, and smoking history.

Daily Diary Questions. Each morning, participants will report via the app: number of cigarettes smoked from previous day; previous day's use of NRT, e-cigarettes, and other tobacco products; and current urge to smoke, assessed on a 10-point Likert scale (see appendices).

Urge and Situation during AR Sessions. Participants will rate their urge (craving) to smoke on a single 10-point Likert scale. Single-item scales reduce participant burden when multiple ratings are required, and they have been found to be reliable and valid in assessing urge to smoke (Kozlowski et al., 1996). The circumstances surrounding app use (e.g., at home, alone, with alcohol, etc.) will be assessed.

Feedback and App Usage. The System Usability Scale (SUS) measures participants' perception of usability and learnability (Brooke et al., 1996; Lewis & Sauro, 2009). We will develop a questionnaire with Likert scale items to capture the following areas: reality/co-existence of the AR images (e.g., How realistic did the AR images appear?), usefulness (e.g., How useful was this app for smoking craving this past week?), ease of use (e.g., How easy/difficult did you find using the app?); ease of learning (e.g., How many days did it take to get comfortable using the app?); and satisfaction (e.g., Would you recommend this app to a friend or family member to help them quit smoking?; Overall, how satisfied were you with the app?). During the phone interview, participants will be asked open-ended questions on their perceptions of the app. Interviews will be tailored to participants' app use to understand challenges and barriers among those with low app use (completed <5 AR sessions) and to receive feedback from those with high app use (completed 5 or more AR session). Examples of questions include: "What changes would you make to the app to increase the likelihood of using it, or, to make it more enjoyable?; What was the easiest part of using the app?; What was most difficult?; What was most interesting? (see appendices). We will also have access to the real-time app use metadata, including proportion of sessions started, completed, etc.; number of unfinished sessions; time spent in the app; days of use; engagement with app features (e.g., tracking, rewards). We will query during the phone interview why any app feature was not used.

AIM 2 Measures

Measures assessed via the app were described for Aim 1. Additional measures unique to Aims 2 and 3 are described below. REDCap will be programmed to email and text participants a survey link to complete measures at baseline, around 5 weeks post initial app engagement, and around 6 months post-baseline.

Questionnaires. Demographics and Smoking History will collect data on variables including gender, age, race, marital status, income, education, and smoking history (e.g., number of quit attempts, years smoked). Heaviness of Smoking Indiex (HSI; Heatherton et al., 1989) is a widely used measure of nicotine dependence. We will also administer the subscales of Automaticity and Affective Engagement of the Brief Wisconsin Inventory of Smoking Dependence Motives (WISDM-38), a multidimensional assessment of motivational factors associated with smoking behavior (Smith et al., 2010). We are particularly interested in the Cue-Exposure/Associative Processes scale, which assesses the degree to which smoking is driven by cue reactivity. Therefore, we will include the full subscale from the original WISDM-68 (Piper et al., 2004), due to its superior psychometrics (Smith et al., 2010). We will use the Self-efficacy Scale – Smoking to assess level of confidence for not smoking in various situations (Velicer et al., 1990). Positive and Negative Affect Schedule short form (PANAS; Thomson, 2007) will assess affect. Aside from their descriptive value, these measures will allow for testing moderators of the study outcomes. These measures will be administered at each assessment.

App Use, Evaluation, and Extinction. Similar to Aim 1, we will collect metadata on app use as an

indicator of treatment engagement. Primary treatment engagement variables of interest that are linked to our theoretical model of extinction and that are related to increased abstinence include: greater completion of the AR sessions (e.g., multiple times per day over several days), conducting the AR sessions in several different locations (to increase generalizability of extinction), and less use of avoidance strategies during the AR sessions (e.g., using distraction or other behaviors to avoid experiencing craving). Avoidance strategies will be assessed at the 5 week survey via a checklist of avoidance strategies and the frequency that they occurred during AR sessions. We will also collect self-reported treatment satisfaction using a modified version of the Client Satisfaction Questionnaire (Attkisson & Greenfield, 1994), the SUS (Brooke et al., 1996; Lewis & Sauro, 2009), and unique items to assess features and functions of the app and the AR experience, including the App coach. Extinction magnitude (degree of craving reduction over time) and latency (time to meeting extinction criteria) will also be derived. For participants who never achieved abstinence during the 5 weeks of app use, thus, never completed AR sessions, versions of the follow-up surveys will omit items specifically related to AR use. For participants who achieved abstinence, but did not complete more than 4 AR sessions, there will be questions at the 5-week survey regarding barriers to completing the AR sessions.

Quitline Usage and App Coaching. Basic information on participant interactions will be provided to the study team from the quitline, including call completion dates, quit status (planned and actual quit dates), and NRT that was shipped. For those in QL+AR, we will track calls completed with an App coach.

Tobacco Abstinence. The primary outcome measure will be 7-day point prevalence abstinence (defined as self-report of no combustible tobacco use in the past 7 days; Piper et al., 2020) around 6 months post-baseline. Reported abstinence will be confirmed in approximately 40% of self-reported abstinent participants using a saliva cotinine level cut-off of <10 ng/ml (Benowitz et al., 2020). Cotinine analysis using ELISA assay will be conducted by Salimetrics (Carlsbad, CA).

Cost-assessment and Cost-effectiveness. An important step in evaluating feasibility of interventions is showing that the intervention can be performed at a (relatively) low cost while improving outcomes. We will assess the resource utilization associated with both arms of the intervention, allowing us to determine the relative costs and cost-effectiveness of the arms. Our cost-assessment methodology will be done initially from the perspective of the health care system and based on collecting information on all resources used in the intervention and affixing a standardized “price” to those resources. This approach, long recommended as the most appropriate means of calculating true resource costs (Sanders et al., 2016; Dranove, 1996; Weinstein et al., 1996), results in “costs” that are comparable both among participants within an intervention and between interventions. We have successfully used this methodology in previous studies (e.g., Byrne et al., 2006; 2014; Martinez et al., in press; Medina-Ramirez et al., 2019; 2020; Morgan et al., 2008).

Quality of Life. To assess potential improvements in quality of life, we will assess smoking-related health items from the Tobacco Quality Of Life Impact Tool™ (TQOLIT v.1; Ware JE; Gandek B; Kulasekaran A; Guyer R, 2015) which includes 8 items that measure the frequency of smoking-related symptoms (e.g., bad breath, difficulty breathing). We will also use the EQ-5D-5L which consists of the EQ-5D descriptive system that measures health using five levels of severity in five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) and the EQ visual analogue scale (EQ VAS) that records the individual’s self-rated health on a vertical visual analogue scale, where the endpoints are labelled ‘The best health you can imagine’ and ‘the worst health you can imagine (Herdman, et al. 2011). Each of these measures will be included in the Baseline and 6 Month surveys.

Implementation Barriers and Facilitators. To identify barriers and facilitators of incorporating AR treatment into the quitline, interviews will be conducted with a subset of quitline supervisors, all App coaches, and a subset of participants. The interview guide will be structured around the Consolidated Framework for Implementation Research and assess multi-level barriers and facilitators for implementation. For example, the guide will assess information about *intervention characteristics* (e.g., technical challenges with AR app), *organizational characteristics* (e.g., compatibility of the app with quitline workflow), individual characteristics (e.g., beliefs about the AR app, self-efficacy for app use), *process* (e.g., sufficiency of training and engagement strategy), and *external context* (e.g., how well the app fits with quitline external incentives and policies).). A brief survey will capture demographic information.

Questions will be asked to quitline supervisors (e.g., What training is needed to train quitline coaches to train callers in using the AR app?; What concerns do you have about quitline callers using the app?) and App coaches (e.g., What additional training would be useful as an App coach?; What were some common issues participants reported having and do you have any thoughts on how to resolve those more effectively?; What challenges did you encounter as a coach?). A small subset of 20 participants who used the AR app feature (AR use = 10+ times) will be randomly selected and asked about their experiences (e.g., What features of the AR app could be improved?; What challenges did you encounter with the app?; How might we improve the App coaching you received?). To learn how to improve engagement, we will also contact 10 participants who failed to engage with the AR app feature (AR use = 0 times), and 10 who engaged but prematurely discontinued using the AR app feature (AR use = 1-4 times). Thus, a total of 40 participants will be included.

Data Safety and Monitoring Plan

The data and safety monitoring plan development for this project is commensurate with the expected minimal risks posed by the project. Data and safety monitoring will be ongoing by the Principal Investigators, Moffitt Cancer Center's Protocol Review and Monitoring Committee, the Data and Safety Monitoring Board (DSMB), and the Institutional Review Board (IRB). Overall, the plan for monitoring includes: 1) Monitoring the progress of the studies and safety of participants; 2) Assuring compliance with the requirements for reporting adverse events that may occur during the study; 3) Assuring any action resulting in a temporary or permanent suspension of a study is reported to the NIH official who is responsible for the grant; and 4) assuring data accuracy and protocol compliance. Participant data will be associated with participant study ID and not directly associable with names or other identifying information. Questionnaire/interview data will be collected and recorded via computer and will only be identified with the participant's study ID. The PIs will keep the codes that link the name of the participant and the study ID confidential in a password protected electronic file. Data accuracy will be subject to random audit. Monthly data management reports will be made by the project manager (with oversight by the study statistician), including data entry progress, error rates, range checks, and general descriptive statistics. The investigators and research staff will conduct all data analyses using primarily SPSS and SAS software. Participants who elect to be informed of study findings will be sent summaries of the research findings upon the completion of data analysis.

Research staff will report any potential AEs immediately to the PIs. Any SAEs will be reported within two days to the IRB and NIH using the required reporting format. We will use the FDA definitions of AE (any untoward medical occurrence associated with the [intervention] in humans, whether or not considered [intervention] related) and SAE (an AE that results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect). Given the very low-risk nature of our behavioral intervention, the likelihood of suspected SAEs is extremely low. Any IRB actions in relation to this protocol will also be reported to NIH.

As noted above, this project will have a DSMB comprised of individuals with expertise in the necessary content areas (e.g., mHealth, tobacco, statistics). We have already identified three individuals with expertise in these areas who have agreed to serve on the DSMB, assuming we receive funding – Michael Sayette, Ph.D. (University of Pittsburgh; tobacco use and cue exposure), Michael Businelle, Ph.D. (University of Oklahoma; smoking cessation interventions and mHealth), and Brent Small, Ph.D. (University of South Florida; statistician with expertise in longitudinal data analysis). The primary role of the DSMB will be to evaluate the safety and efficacy of the study as it is ongoing, and to provide recommendations as needed on the protocol. Data on participant progress through the study (e.g., recruitment, retention), protocol compliance, and any protocol deviations and AEs/SAEs will be monitored. DSMB meetings will occur twice per year, with a report provided to the committee in advance of the meeting for review. A final report will be drafted following the meeting and will

be forwarded to the necessary stakeholders (e.g., NIDA, IRB). Additional meetings, phone calls, and emails will be exchanged between meetings as needed.

Drs. Vinci and Brandon will implement standardized procedures for each Aim. This will include weekly meetings to discuss any issues related to the progression of the project and factors that may affect the outcome, including a review of data quality and security, recruitment, and retention. For any problems that may arise, including adverse events, a discussion among the investigators will be conducted.

4.5 Adverse Reactions

Minimal risks are anticipated for this study and are described below. Risk mitigation strategies are described in the Adequacy of Protection Against Risks. This study involves no investigational drugs or devices.

- Data including self-report, interview (psychological and medical), and/or biological samples (e.g., saliva) involve risk of breaches in confidentiality. Participants will always be given the option to refuse to answer any questions on the measures that may be distressing. This is the only risk that also applies to quitline supervisors.
- For data collected via smartphone, there are always risks associated with privacy when collecting data in this format.
- There may also be an increased risk of using cigarettes due to increased craving experienced during some of the AR sessions.
- Successful abstinence may cause irritability, anxiety, general distress, and difficulty concentrating.
- Nicotine replacement therapy (NRT) will be provided via the quitline per their usual treatment procedures and will be the appropriate dose based on level of smoking and should aid in the management of withdrawal symptoms. NRT and smoking cessation counseling have been shown to be safe and effective for smokers attempting to quit (e.g., NRT is available over-the-counter). However, side effects of NRT may occur and include skin irritation/ rash (for the patch), nausea, dizziness, dry mouth, diarrhea, nervousness, headache, vivid dreams or sleep disturbances, irritability, and irregular heartbeat.

5. STATISTICAL CONSIDERATIONS

Data Management and Statistical Considerations for Aim 1

Compliance will be calculated for the completion of AR urge and daily diary questions. We will also observe the use of various features to determine general use/engagement. The SUS will be scored according to scale instructions, with an expected mean above 68. Interview responses will be reviewed for common themes. Modifications to the app will be made based on these findings. In the unlikely event that major changes need to be made based on participant feedback, we will repeat the procedures for this aim to gather additional feedback on the revised app. Any major changes will field tested in a similar manner prior to the onset of the RCT in Aim 2.

Data Management and Statistical Considerations for Aims 2 and 3

Overview of Data Management and Statistical Considerations for Aim 2

Based on abstinence rates from quitline/telephone counseling (Fiore et al., 2008; Matkin et al., 2019; Pinerio et al., 2020), the estimated abstinence rate around 6 months for the QLO condition is 10%. With 1036 randomized to each condition, power was calculated for the 725 participants expected to achieve 48-hours of abstinence in each condition (to activate the AR app). Power ≥ .80 to detect an abstinence rate of at least 15% (OR = 1.59) in the QL+AR condition using alpha = .05, a 2-sided test, and allowing 5% of variance in abstinence rates to be accounted for by other variables. Treatment group differences in baseline measures will be assessed and any variable with a group difference of $p < .10$ will be incorporated into analyses focusing on

intervention effects. To manage missing data, multiple imputation under the Missing at Random assumption will be applied using a Markov Chain Monte Carlo method. The primary statistical analysis for Aim 2 will use logistic regression to compare biochemically-confirmed abstinence rates at the 6-month assessment between conditions. A parallel analysis will be performed to evaluate efficacy for all enrolled (N=2072; i.e., beyond those who exhibit the required 48-hour abstinence to engage the AR intervention). A second test of effectiveness will use generalized estimating equations (GEE) with both the 5-week and 6-month abstinence as the outcomes. Please see the Statistical Design and Power attachment for additional details on our statistical approach.

Data Management. Baseline, 5-week, and 6-month survey data will be exported from REDCap as .CSV files, which will be read into SAS version 9.4 (SAS Institute, Cary, NC) on a weekly basis during data collection. Data review and primary data analyses will be performed using SAS version 9.4. Dr. Sutton will oversee the data management, provide the PIs with reports and summaries on a regular basis, and perform the final analyses.

Sample Size and Study Power Analysis. The primary statistical analysis for Aim 2 will use logistic regression to compare abstinence rates at the 6-month assessment between QL+AR and QLO conditions. Preliminary analyses will be used to identify demographics and tobacco history variables that predict either missing surveys or abstinence around 5 weeks and 6 months. These variables will be used in a multiple imputationmodel to manage missing data. Based on abstinence rates from quitline/telephone counseling (Fiore et al., 2008; Matkin et al., 2019; Pinerio et al., 2020), the estimated 7-day point prevalence abstinence rate around 6 months for the QLO condition is 10%. With 1036 randomized to each condition, power was calculated for the 725 participants expected to achieve 48-hours of abstinence in each condition (to activate the AR app). Power ≥ .80 to detect an abstinence rate of at least 15% (OR = 1.59) in the QL+AR condition using alpha = .05, a 2-sided test, and allowing 5% of variance in abstinence rates to be accounted for by other variables. A comparable analysis using all 2072 randomized participants (the 1450 who do achieve 48-hours of abstinence plus the 622 who do not) will have lower expected abstinence rates. Estimating that 7% of all QLO participants will be abstinent, power > .80 to detect an abstinence rate of at least 10.6% for QL+AR (OR = 1.57)using alpha = .05, a 2-sided test, and allowing 5% of variance in abstinence rates to be accounted for by other variables.

Data Analysis Overview. Descriptive statistics will be used to review all variables in the study prior to hypothesis testing. Data transformations will be made as needed. Treatment group differences in baseline measures will be assessed and any variable with a group difference of $p < .10$ will be incorporated into analyses focusing on intervention effects. All analyses described below will be performed for those who achieved 48 hours of self-reported abstinence (n=1450) as well as the full sample of those enrolled (N=3590). The former is relevant to assessing the efficacy of the app specifically, whereas the latter will reflect the overall incremental effectiveness of the app from the perspective of the quitline. Full-sample versus AR-sample differences in baseline measures will be evaluated.

To manage missing data, multiple imputation under the Missing at Random assumption will be applied using a Markov Chain Monte Carlo method (Schafer, 1997) via PROC MI in SAS, given the expected nonmonotonicmissing data patterns and the expected large number of auxiliary variables (e.g., baseline measuresthat predict smoking status at follow-up) to be determined by preliminary analyses. The imputation model will
include smoking status around 5 weeks, which is expected to be a primary predictor of smoking status around 6 months.
In addition, any other measures acquired around 5 weeks that are unique predictors of missingness or smokingstatus around 6 months will be included in the imputation model. Finally, a post hoc approach (Rubin, 1987) willaddress the possible influence of Missing Not at Random. As done in recent studies (e.g., Brandon et al.,
2016; Martinez et al., in press), the post hoc adjustment will be small-to-medium in size (akin to Cohen's d=0.35) in accordance with missing implies smoking. Twenty data sets will be generated. Therefore, all analyses of the primary outcome will be performed on complete data sets (i.e., intent-to-treat) following multiple imputation.

Analytic Plan for Addressing Specific Aims.

Aim 2a. The primary test of the efficacy of QL+AR over QLO will use logistic regression on biochemically-confirmed abstinence around 6 months after baseline survey completion. This will be performed on the 20 imputed data sets usingthose participants who exhibited 48 hours of abstinence (n=1450). The model will include demographics and
smoking-related variables that were found to uniquely predict self-reported abstinence at 6 months based on preliminary analyses. A parallel analysis will be performed to evaluate efficacy for all enrolled (N=2072; i.e., beyond those who exhibit the required 48-hour abstinence to engage the AR intervention). A second test of effectiveness will use generalized estimating equations (GEE) with both the 5-week and 6-month abstinence as the outcomes. This approach permits evaluation of a change in abstinence from around 5 weeks to 6 months andan assessment of the intervention at around 5 weeks in the context of the primary outcome (using a timespecificcontrast).

Aim 2b. Prospective moderators of the QL+AR intervention will be explored, separately, by extending the analyses described above through the inclusion of the moderator and the moderator x intervention as predictors of the dependent measure. A significant interaction term supports the variable as a moderator, which will be explored by assessing condition differences for each level of categorical moderators and for levels of continuous moderators created via median splits, tertiles, or quartiles. The following baseline measures will be evaluated: sex, nicotine dependence, trait cue reactivity, smoking status during treatment, quitline use, and NRT use.

Prospective predictors of the AR intervention will be evaluated using only participants from the QL+AR arm. Similar to the analyses described above, AR-related variables will be added to a logistic regression model of abstinence at around 6 months that includes demographics and baseline smoking-related variables found to bepredictors of abstinence among QL+AR participants. The following variables will be explored: initial cue reactivity, extinction magnitude and latency, indices of treatment engagement, and App coach use.

Aim 3a. Our preliminary cost-effectiveness assessment will use the primary trial endpoint of smoking abstinence at around 6 months as the main effectiveness/outcome measure. Using this outcome, we will calculate theincremental cost-effectiveness of the QL+AR arm compared to the QLO arm in increasing smoking abstinence
(e.g., cost per quitter). Finally, we will also use quality adjusted life years (QALYs) and lifetime medical costs to estimate more inclusive, life-long effect and cost-effectiveness of the intervention. We will use the most recent estimates in the literature (e.g., Feirman et al., 2016; Kaplan et al., 2007) to estimate QALYs and lifetime medical costs associated with smokers and smoking cessation. We will assess the robustness of incremental results between the two study arms using probabilistic sensitivity analysis. Cost-assessments and cost effectiveness will be calculated on the basis of both all enrolled participants as well as only those who qualified for the AR intervention by achieving 48 hours of abstinence.

Aims 3b and 3c. Descriptive statistics will be used to evaluate treatment engagement (measured via greater completion of the AR sessions, conducting the AR sessions in several different locations, and less use of avoidance strategies during the AR sessions), acceptability (measured via the Client Satisfaction Questionnaire, System Usability Scale, and unique items that assess app features, functions, and the AR experience including the App coach). Variables derived from engagement with the app will be explored as predictors in multivariable models that already include baseline predictors.
Qualitative methods will be used to identify facilitators and barriers to app usage. We will use thematic analysis to analyze the key stakeholder interviews (quitline supervisors, App coaches, subset of participants; Creswell, 2007). We will develop a list of a priori codes based on the domains identified in the interview guide to develop an initial codebook. Two trained qualitative analysts from Moffitt's Participant Research Interventions and Measurement Core will independently code an initial set of transcripts (n=5). After the first round of coding is complete, they will discuss their notes on possible new codes (e.g., themes that emerge from the data) and refine the codebook. The analysts will code another initial set of transcripts (n=5) and

compare coding through Kappa coefficients (the lines of text on a code transcript divided by the number of coding agreements between the two coders; Ulin et al., 2004). If k ≥ .80 is achieved, the analysts will continue coding the rest of the transcripts. If sufficient inter-rater agreement is not achieved, the analysts will refine the codebook and recode the transcripts. Coding and analyses will be conducted in NVivo qualitative software package. We anticipate 10 interviews with quitline supervisors and 40 participant interviews (20 high AR app users, 10 low AR app users
, and 10 no AR app users) will be sufficient to achieve data saturation or the point at which no new themes emerge (ensures minimum of 10 in each group; Guest et al., 2006). All App coaches will be interviewed, as we anticipate having fewer than 10 across the course of the study.

6. STUDY TIMELINE and ACCRUAL ESTIMATES

Aim 1 Timeline

	MONTH											
	1	2	3	4	5	6	7	8	9	10	11	12
Develop additional AR stimuli	•	•										
Update app with new content (e.g., menu options; embed new AR stimuli); staff testing		•	•	•	•	•	•					
Usability Testing (N=10)								•	•	•		
Update app based on usability testing										•	•	•
Ongoing app software updates (e.g., Android and iOS functionality) and staff testing as needed	•	•	•	•	•	•	•	•	•	•	•	•
Modification of Florida Tobacco Quitline database	•	•	•	•	•	•	•	•	•			
Training of quitline coaches										•	•	•

Full Study Timeline

MONTH	TASK
Months 1-12	• See Aim 1 timeline for specific details

Months 13-41	• Recruit, enroll, and run *N*=2072 participants for Aim 2 (recruitment goal: 23 participants per week)
	• Data collection programmed via REDCap and through app
	• Data download and initial reduction will be ongoing as participants finish study
	• Manuscripts:
	  ○ Aim 1 manuscript on app development and refinement
	  ○ Aim 2 protocol manuscript

Months 42-48	• Complete all follow-ups
	• Final data reduction and preparation
	• Data analysis
	• Begin Aim 2 primary outcomes manuscript
	• Begin Aim 2 secondary manuscripts:
	  ○ Report on theory-based mediating variables
	  ○ Analyze and report on qualitative outcomes
	  ○ Applied paper on remote cue-exposure therapy
	  ○ Update to 2020 conceptual paper on clinical applications of AR

Estimate for	AIM 1	AIM 2
25% Accrual	Month 8	Month 20
50% Accrual	Month 9	Month 27
75% Accrual	Month 10	Month 34
100% Accrual	Month 10	Month 41

7. REGULATORY AND REPORTING REMINDERS

7.1 Institutional Review Board

No subject is to be enrolled on this protocol until the Center's Institution Review Board has approved it.

7.2 Informed Consent

The investigators and the researchers associated with the study are responsible for obtaining consent by the participants in a manner approved by the Institutional Review Board.

7.3 Investigator Study Files

Research records are the responsibility of the investigator.

They will be available for review by the sponsors of the trial, health care personnel involved in this study, the IRB, and the SRC.

The Principal Investigator will maintain study files for a period of years.

8. DATA SHARING

Data obtained from interviews, including both audio recordings and transcripts, will be shared with other investigators and institutions as approved to facilitate data analysis. These data could contain PHI.

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Appendix of non-standard self-report surveys for AIM 1).

AIM 1 Augmented Reality Questions

1. Have you ever used any kind of augmented reality (AR) app before? (e.g., AR feature in Pokemon Go, IKEA or other furniture app, Snapchat filters, Google Sky Map, etc.)

- ○ Yes
- ○ No
- ○ Don't know

2. How frequently do you use augmented reality (AR) apps?

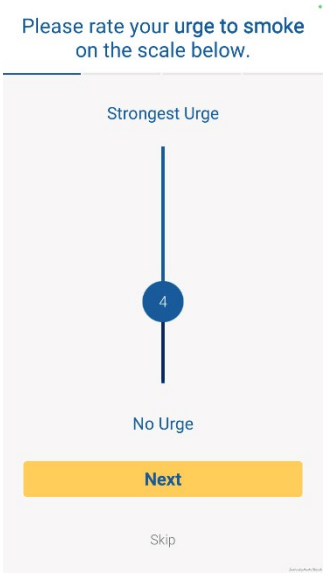
- ○ 7 days a week
- ○ 4-6 days a week
- ○ 1-3 days a week
- ○ 1-5 times a month
- ○ Less than once a month
- ○ Never
- ○ Don't know

3. How ***interested*** are you in using an augmented reality smartphone app?

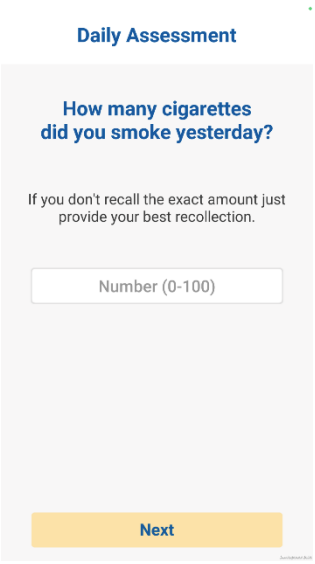
1	2	3	4	5	6	7	8	9	10
Not at All									Very Interested

IN App Daily Diary Questions:

URGE:



Cigarettes smoked prior day:



Did you use any of the following products yesterday? (check all that apply).

Nicotine Gum	O
Nicotine Patch	O
Nicotine Nasal Spray	O
Prescription Nicotine Inhaler	O
Nicotine Lozenge	O
Zyban or Wellbutrin	O
Chantix or Varenicline	O
E-cigarette (e.g., vape pen, personal vaporizer, etc.)	O
Other treatments or medications Specify: _____	O

AIM 1: Feedback and app usage self-report measures

Reality/Coexistence items

Instructions: Please **mark** the number from 1-10 that represents how you feel about each question.

1. **How real did the objects seem to you?**

1	2	3	4	5	6	7	8	9	10
Not at All									Very Real

2. **How well did the objects appear to be a part of the scene?**

1	2	3	4	5	6	7	8	9	10
Not at All									Very Well

3. **How much did you feel the objects were right there in front of you?**

1	2	3	4	5	6	7	8	9	10
Not at All									Very Much

App Usefullness/Ease of learning/Satisfaction

1. Would this app appeal to you if you were currently attempting to quit smoking?

1	2	3	4
No, definitely not	No, I don't think so	Yes, I think so	Yes, definitely

2. **At the beginning of the week,** how easy or difficult was it to use the app?

1	2	3	4	5
Very Difficult				Very Easy

3. **At the end of the week,** how easy or difficult was it to use the app?

1	2	3	4	5
Very Difficult				Very Easy

4. How many days did it take to get comfortable using the app?
   Choices are from 1day -7 days

5. Would you recommend this app to a friend or family member to help them quit smoking?

1	2	3	4
No, definitely not	No, I don't think so	Yes, I think so	Yes, definitely

6. Overall, how satisfied were you with the app?

1	2	3	4
Quite dissatisfied	Indifferent or mildly dissatisfied	Mostly satisfied	Very satisfied

ARC AIM 1 Follow-up Phone Interview (APP USE [AR ≥ 5])

"Hello, this is _____ from Project ARC. How are you today?"
"Thank you for setting time aside to give us feedback. I just have a few questions for you today."

General:

1. What did you think of the augmented reality smartphone app?
    a. [probe for specifics if give general answers,] e.g., "It was good/weird/frustrating".

Rationale:

2. What do you think is the purpose of this app?
3. [TAM – perceived usefulness] Based on your recent experience quitting smoking, how do you think viewing smoking related images might be used while someone is trying to quit smoking?

Ease of use:

4. "What were the issues you encountered when navigating the app (e.g., …)?"
5. [TAM – perceived ease of use] What was the easiest part of using the app?
6. [TAM – perceived ease of use] What was the most difficult part of using the app?
7. [TAM – attitude toward using] What was the most interesting part of using the app?
8. [TAM – behavioral intention to use] How would you tell your friends/family about this app if you were going to have them use the app to quit smoking?

New Features: I'm going to ask you about some specific features of the app.

9. In the app, there are three videos that explain how the AR sessions work, how they will help you stop smoking, and tips for the best AR experience. Did you watch these videos?
    a. If yes, What did you find most helpful after watching these videos? What aspects of the videos can be improved?
    b. If no, why did you not watch them? What recommendations may you have for improvement?
10. What are your thoughts on the instructions for doing the AR sessions?
    a. What would have been helpful to know about doing AR sessions?
11. [TAM – perceived usefulness] After the three videos, there was a Practice Tutorial with a Rubber Ducky and the chance to practice an AR session. Did you practice?
    a. If yes, what was helpful?
    b. If no, why did you not practice?
    c. What could we change to improve the practice experience? [Probe]
12. [TAM – perceived ease of use] When you started using the app, you had the chance to select 0, 1, or 2 reminder notifications. What did you select? Can you tell us why you choose this amount?
    a. [TAM – perceived usefulness] If > 0, How did you feel about that number of reminders? Did they help remind you to complete AR sessions?
    b. [TAM – perceived usefulness] If 0, Why did you opt out of reminder notifications?
    c. What would you change about the reminder notifications?
13. In the app, there is a feature to track your progress (e.g., money and time saved, days abstinent, number of AR sessions completed).
    a. I will list each progress feature, and I'd like you to tell me if you ever viewed it.
        i. Days Remaining / Weekly Streak

ii. # AR sessions Completed
iii. Days Abstinent
iv. Daily use of Nicotine Replacement Therapy
v. Change in Urge
vi. Money Saved
vii. Time Saved

b. [If Never used,] Why not?
c. [For <u>each</u> progress feature ask;]
    i. What about [feature] did you like?
    ii. What about [feature] didn't you like? Why?
d. [TAM – perceived usefulness] Did you find the progress feature useful as related to your quitting smoking?
e. [TAM – perceived usefulness] Did you find the progress feature useful for your continued use of the app? (if question unclear, rephrase: In other words, did it make you more likely to continue using the app?)

14. After completing a certain amount of AR sessions, you had the ability to receive a reward. Did you ever receive a reward (as a reminder, the first one was a flower pot)? If no, skip a-d.
    a. [TAM – attitude toward use] What did you like about the rewards?
    b. [TAM – attitude towards use] What did you NOT like about them?
    c. [TAM – perceived usefulness] How did the rewards motivate you to do more AR sessions?
    d. [TAM – perceived usefulness or attitude towards use] What aspects of the AR rewards could be improved?

Improvements:

15. [TAM – behavioral intention to use OR attitude toward using] What type of changes would you make to the app to increase the likelihood of using it, or, to make it more enjoyable to use?
16. [TAM – behavioral intention to use] What other features could we include in the app to help someone continue using the app for quitting smoking?
17. What aspects would you change about the app?
18. What are the key points that you think we should talk to smokers about when explaining this app for smoking cessation?

Study team/Support:

19. [TAM – perceived ease of use] Did you ever reach out to the study team for help with the app?
    If YES: What did you find helpful?
    IF NO: Why not?
    What other feedback do you have for us?

ARC AIM 1 Follow-up Phone Interview (NO/Little APP USE [AR < 5])

"Hello, this is _____ from Project ARC. How are you today?"
"Thank you for setting time aside to give us feedback. I just have a few questions for you today."

General:

1. We noticed that although you downloaded the app, you did not use the app/only used the app X times. It would help us to understand why you did not use the app (much). Can you tell me why you didn't use the app? Probe reasons.

2. What did you think about the description of the app during the study screening call and directions for use?
    a. Were the descriptions and directions clear?
        i. If not clear, what could have made it clearer?
    b. What do you wish you were told before starting the ARC app?
    c. When we first introduce this study to smokers in the future, what else should we tell them about the app to make sure they fully understand what they are being asked to do?

Rationale:

20. What do you think is the purpose of this app?

21. [TAM – perceived usefulness] How do you think viewing smoking related images might be used while someone is trying to quit smoking?

22. [TAM – behavioral intention to use] How would you tell your friends/family about this app if you were going to have them use the app to quit smoking?

Barriers:

23. [TAM – perceived ease of use] Can you tell me what made it difficult to use the app? (Probe all)
    a. What would make it easier to use the app

24. [TAM – behavioral intention to use] What kind of strategies do you think would help motivate someone to continue using the app to help them quit smoking?

Study team/Support:

25. Did you ever reach out to the study team for help with the app?
    a. If YES: Did you find it helpful? Why or why not?

26. Do you have any other feedback for the study team?