A Smoking Cessation Induction Intervention Via Virtual Reality Headset During a Dental Cleaning: Randomized Controlled Trial

Protocol Number*: H-40368

National Clinical Trial (NCT) Identified Number:

NCT04524533

Principal Investigator: Belinda Borrelli Ph.D.

Sponsor: Boston University

Grant Title: Delivery of a Smoking Cessation Induction Intervention Via Virtual Reality Headset During a Dental Cleaning

Grant Number*: 4UH3DE028866-02

Funded by: National Institute of Dental & Craniofacial Research

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Version Number: 1.12

12 September 2024

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
5.5	Added information regarding saliva sample retention procedures.	This information was not included in previous versions, so it was added to improve clarity.
1.1, 1.2, 2.1, 9.2, 10.1.5	Updated total recruitment goal. Updated key roles and study governance	Recruitment goal increase from 376 to 455 was approved to account for differences due to the addition of the Tufts recruitment site.

CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the NIH terms of award.

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STATEMENT OF COMPLIANCE

(1) The trial will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the National Institute of Dental & Craniofacial Research Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), and the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, if applicable, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator or Clinical Site Investigator:

Signed:  Date: May 26, 2020

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

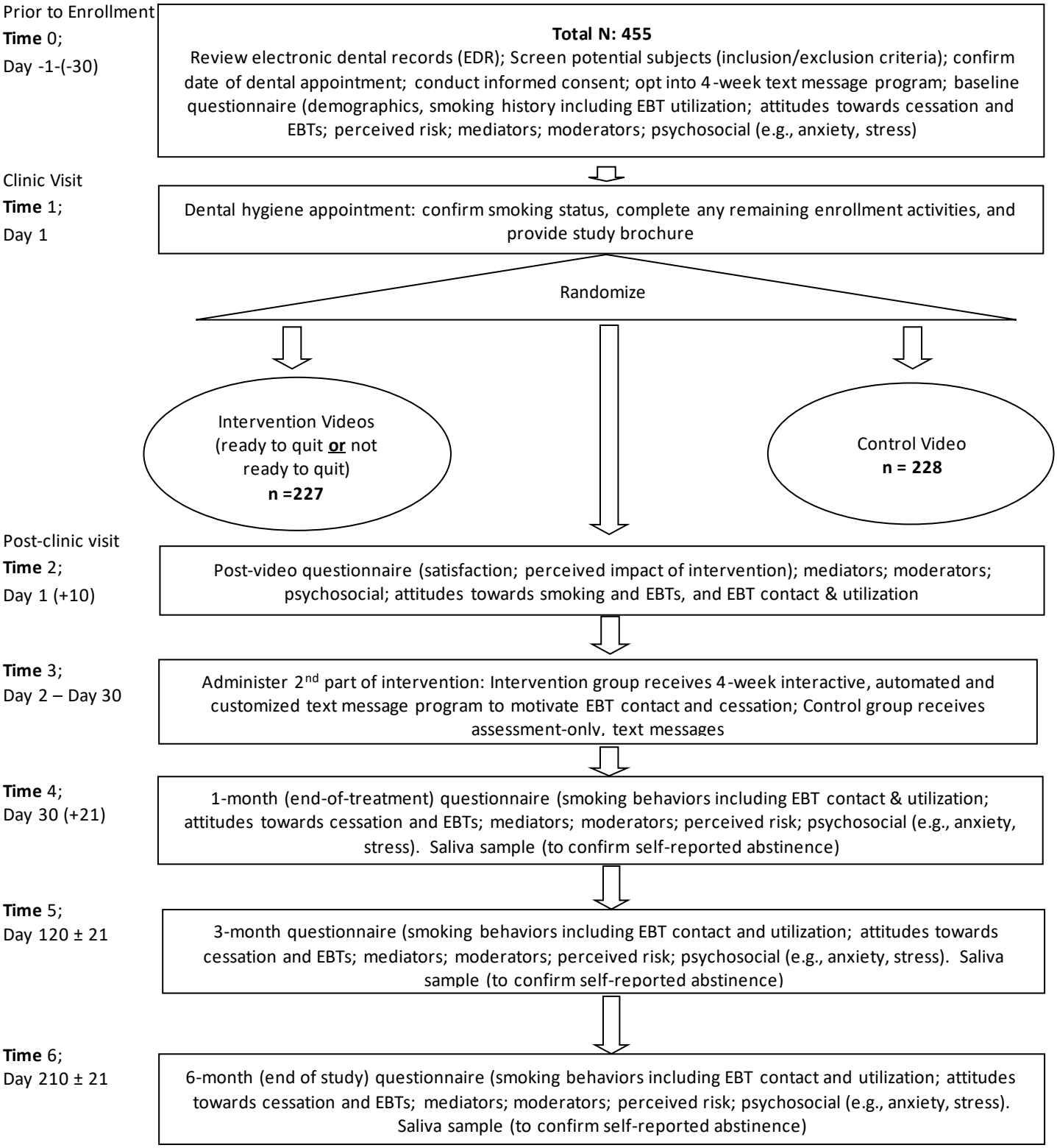
Title:	A Smoking Cessation Induction Intervention Via Virtual Reality Headset During a Dental Cleaning: Randomized Controlled Trial
Grant Number:	1UG3DE028866
Study Description:	The primary aim of the UH3 Stage III randomized efficacy trial is to test whether a video-based smoking cessation induction intervention delivered via virtual reality (VR) headset during part of a dental hygiene appointment increases dental patients' utilization of evidence-based treatments (EBTs) for smoking cessation (Massachusetts State quitline, clinic-based programs, NCI text message program [SmokefreeTXT], nicotine replacement products or other smoking cessation medications) within 7-months post-dental hygiene appointment. 437 cigarette smokers scheduled for dental prophylaxis or scaling and root planing at the Boston University Goldman School of Dental Medicine (BUGSDM) patient treatment center or Tufts University (TU) School of Dental Medicine Comprehensive Care Clinic or Periodontal Clinic will be randomized (1:1) to either the Intervention (smoking cessation video via VR headset, brochure about EBTs, and four-week of interactive, automated and tailored text message program to motivate EBT utilization) or Control group (control video on relaxation via VR headset, brochure about EBTs, and assessment-only text messages). The primary hypotheses are: Hypothesis 1.1: Participants in the Intervention will be more likely to contact and engage with EBTs and Hypothesis 1.2: Participants in the Intervention will have greater EBT utilization. The secondary hypotheses are: Hypothesis 2: Participants in the Intervention will have greater quit attempts and motivation to quit. Hypothesis 3: Participants in the Intervention will achieve higher biochemically confirmed smoking cessation rates at follow-up. Hypothesis 4: The Intervention will directly affect the putative mediators of intervention effect, which will in turn affect EBT utilization. The role of moderators will be exploratory.
Objectives*:	Primary Objective: To test the efficacy of the Intervention vs. Controls in increasing contact with, and utilization of, EBTs over a 7-month study period. Secondary Objectives: 1) To test the efficacy of the Intervention vs. Controls on quit attempts and on motivation to quit, 2) To test the efficacy of the Intervention vs. Controls on biochemically verified smoking abstinence, and 3) (exploratory) To assess the mechanisms through which the intervention effects occur (mediators) and to identify subpopulations for whom intervention effects differ (moderators).
Endpoints*:	Primary Endpoint: EBT utilization (any EBT contact, number of EBTs contacted, and duration of EBTs).

	Secondary Endpoints: Quit smoking attempts, motivation to quit smoking, and biochemically verified smoking abstinence (7-day point prevalence). Exploratory Endpoints: Use of a combination of medications and counseling; mediators of the intervention effect, and moderators.
Study Population:	Participants will be 437 men and women (≥ 18 years of age) who are patients at Boston University GSDM pre-doctoral, or post-doctoral periodontal, treatment center, or TU Comprehensive Care Clinic or Periodontal Clinic, and smoke cigarettes, and are scheduled for dental prophylaxis or scaling and root planing at either dental clinic. The GSDM pre-doctoral and post-doctoral periodontal treatment centers are located in Boston, Massachusetts. Equal numbers of males and females receive treatment at the clinic, the average age is 46 years, and 25% are uninsured. Pilot data showed that, among smokers attending the clinic, 74% were unemployed and 57% were from minority groups.
Phase* or Stage:	Phase III.
Description of Sites/Facilities Enrolling Participants:	The GSDM dental clinic is in an urban area of Boston and focuses on serving underserved and indigent populations. The clinic has 72 treatment rooms. The treatment center employs the group practice model of care, with 18 full-time faculty serving as group practice leaders, and an additional 60 faculty serving as supervisors for the 300 clinically active dental students. The TU Comprehensive Care Clinic is a large dental clinic affiliated with Tufts University School of Dental Medicine and is also located in Boston.
Description of Study Intervention/Experimental Manipulation:	Eligible participants who provide informed consent will be asked to opt into the 4-week text message program and complete the baseline questionnaire before the start of their dental hygiene appointment. On the day of the dental hygiene appointment, all participants will receive a study brochure about EBTs for smoking cessation and will be subsequently randomized to either the Intervention or the Control group. Participants randomized to the Intervention will watch one of two educational videos, one for those who are ready to quit within the next 30 days and one for those who are not ready, as assessed on the baseline questionnaire and verified at the time of the clinic appointment. Participants in the Control group will watch a relaxation video of the same duration, so that providers are masked to treatment group. All participants will watch the video during their dental cleaning, and all videos last approximately 10-minutes. Shortly after their dental cleaning, all participants will receive a post-video questionnaire to complete within 10 days of the appointment. Within 24 hours post-randomization, participants in the Intervention group will begin receiving the 4-week text message program to motivate contact with EBTs for smoking cessation, whereas those in the Control group will receive only a limited number of text messages ('assessment only' text messages). Intervention text messages will be delivered approximately twice per day, and include two content 'tracks,' one for those who are motivated to quit and one for those who are not motivated to quit.

	Text message content will focus on addressing myths about stop smoking medications, motivating contact with EBTs, re-emphasizing some of the concepts in the educational video, resolving ambivalence, information about EBTs and what to expect, and specific help to connect to an EBT. With regard to the latter, this will include embedded web links and phone numbers for the quitline, information about how to procure nicotine replacement at no cost, contact information for local smoking cessation clinics, and a direct opt-in link to the National Cancer Institute's text message program (SmokefreeTXT). Intervention text message content will be geared towards enhancing putative mediators (motivation, self-efficacy, outcome expectations). Text message engagement strategies include customization, tailoring, interactivity and polls/quizzes.
Study Duration*:	60 months (08/01/2020 – 07/31/2025).
Participant Duration:	07 months.

1.2 SCHEMA

Flow Diagram: A Smoking Cessation Induction Intervention Via Virtual Reality Headset During a Dental Cleaning: Randomized Controlled Trial



1.3 SCHEDULE OF ACTIVITIES

	Prior to enrollment Time 0; Day -1 (-30)	Clinic Visit Time 1; Day 1	Post-clinic Time 2; Day 1 (+10)	Time 3; Day 2 – Day 30	Time 4; Day 30 (+21)	Time 5; Day 120 ± 21	Time 6; Day 210 ± 21
Electronic Record Review	X						
Informed Consent	X						
'Opt-in' 4-week text message program	X						
Baseline Questionnaire (e.g., past EBT utilization, smoking behavior, mediators, moderators)	X						
Study brochure		X					
Randomization		X					
Control & Intervention Videos		X					
Text Messages-Control				X			
Text Message-Intervention				X	X	X	X
Outcome Evaluation							
Satisfaction with intervention/post video questionnaire			X				
Follow-up Questionnaires (e.g., mediators, self-reported EBT contact and utilization, quit attempts)					X	X	X
Objective confirmation of contact and utilization of EBT resources				X	X	X	X
Biochemical validation of self-reported smoking abstinence					X	X	X
Adverse Events Reporting		X	X	X	X	X	X

2 INTRODUCTION

2.1 STUDY RATIONALE

Rationale for targeting smoking: Smoking is the top cause of preventable, premature death in the US. [1] Aside from the general effects of smoking on health, smoking has detrimental effects on oral health (oral squamous cell carcinoma and pre-cancers, impaired post-procedure healing, periodontal disease, mucosal lesions, gingival recession, dental implant failure). [2,3] The prevalence of smoking is substantially higher among adults of low socioeconomic status (SES), and the gap has widened between 2005 and 2015 whether measured by education, income or insurance status. [4] Only 30% of ever smokers with incomes below poverty level have quit compared to 53% with incomes at or above poverty level. [5,6] Despite evidence that low-income smokers have similar motivation to quit as the general population, cessation interventions such as quitlines and clinic based programs are *underutilized* by disadvantaged smokers. [7-9]

Rationale for targeting smokers in a dental setting: Research supports the effectiveness of smoking cessation counseling in dental settings. [10] However, several barriers exist preventing consistent implementation (provider lack of time and training, and lack of provision of counseling to smokers who are unmotivated to quit), [11-15] and there are limitations to existing research (lack of treatment fidelity, lack of biochemical verification). [10,16] Using technology could provide a cost-effective and time-efficient way of delivering evidenced-based smoking cessation in dental settings with a high degree of treatment fidelity. Because effective cessation programs already exist, innovations are needed to drive smokers to engage with smoking cessation resources. Additionally, because 40-80%[17] of smokers are not ready to quit within 30 days, efforts are needed to reach smokers with motivational interventions in their natural settings, such as when they visit a dental clinic. Incorporating smoking cessation into a dental visit and focusing on all smokers, not only those who are motivated to quit, provides proactive reach to smokers who otherwise may not seek treatment for smoking. Watching a video during their teeth cleaning is a clinically efficient use of time and the novelty is appealing to smokers who are not motivated to quit, as we have discovered from our pilot studies. Although Clinical Practice Guidelines [18] confirm the efficacy of medication and counseling for smokers, these treatments are underutilized, especially by smokers of low socioeconomic status. [19,20] We chose to implement the study in academically affiliated dental clinics because such clinics are more likely to encounter underserved patients.[21] If the intervention is successful in this setting, it is likely to be successful in other clinics as well. Because the vast majority of the providers at the GSDM treatment center have outside clinical practices, this will help build an intervention that is generalizable.

Rationale for video-based intervention: Video-based interventions are effective at delivering health behavior interventions to low-literacy populations. It is not our intention to minimize the role of the dental provider in smoking cessation, but rather our intervention is a way to provide information without incurring extra time for both patients and providers. Research has shown that smoking cessation counseling is effective in dental settings, but requires time and training, and counseling practices are reduced after the research has ended.[22] While providers may feel comfortable delivering smoking cessation to smokers who are ready to quit, the vast majority are reticent to counsel those who are not motivated to quit. This has been substantiated by provider interviews in preparatory research.

Rationale for Using Text messaging as an intervention component: Over 95% of US adults regularly use a mobile phone, and of those, 97% use text messaging, with no disparities in race, ethnicity and income. [23,24] Texting can be performed on various devices (e.g., iPad) without phone plans (e.g., iChat, Skype), making delivery inexpensive and with broad reach. All major cell phone plans now include unlimited

texting. Text messaging has been found to be effective for smoking cessation, with odds ratios ranging from 1.36 (95% CI=1.23. 1.51) [25] to 1.63 (95% CI=1.19, 2.24) [26] at 6-months follow-up. A Cochrane review examined six month sustained abstinence in text messaging trials and found a RR of 1.67 (95%CI=1.46, 1.90) which increased to 1.83 (95%CI=1.54, 2.19) in the subset (n=6) of trials that biochemically verified abstinence. [27] Text messaging programs can be tailored, provide real-time strategies in everyday settings, have few barriers to participation, are low burden, have interactive functionality in real-time, can reduce costs for health care systems, provide instant support, and has potential for dissemination. [28,29] [30] To our knowledge, no studies have used text messaging to drive smokers to utilize evidence-based treatments (EBTs).

Rationale for Using Social Cognitive Theory (SCT) [31] SCT posits reciprocal and dynamic person, behavior, and environmental interactions, which is key to examining health behavior change in underserved populations. SCT constructs include self-efficacy (perceived capability of performing the behavior), motivation, and outcome expectations (belief that performing the behavior will result in a positive outcome). These constructs form critical pathways to behavior change, and facilitate health behavior outcomes at both individual and population levels. [32-34] Motivation is important for the initial decision to change, as well as carrying out the steps necessary to complete behavior change. Tailoring treatment to smokers' cognitions that reflect their current motivational level increases change, [35] and providing treatment inconsistent with their motivational level can increase resistance to change. Self-efficacy not only determines choice of activities, but also how much effort is expended and how long one will persist in the face of adversity. Self-efficacy, in combination with specific and challenging goals, can enhance motivation. [36] Dr. Borrelli has shown that social cognitive constructs act as mediators in smoking cessation [34,37] and has built two previous interventions that operationalize SCT, [38,39] one of which uses text messaging. [38] We have used intervention mapping [40,41] in preparatory research to ensure SCT constructs are incorporated into the text message program. In preparatory research, we also created assessment of mediators via text message.

Rationale for Study Design and Innovation. Previous studies of smoking cessation in dental settings have relied on provider-based counseling, which can be costly in terms of provider training time, time spent delivering the intervention, and monitoring ongoing treatment fidelity. Prior studies suffer from dissipation of treatment effects over time; lack of objective verification of major outcome variables; recruiting only smokers who are ready to quit; and lack of "Arranging follow-up" as recommended by the NCI 5 As. Furthermore, few studies have specifically targeted settings that serve urban and low income smokers. The proposed study will fill in the gaps by: 1) testing the intervention in a fully powered, longitudinal trial, 2) using objective measurement for primary outcomes and for smoking cessation, 3) delivering an intervention that has minimal provider and patient burden, increasing the likelihood that it will be disseminated, 4) using a novel method of delivering an intervention while clinical care is being provided and without a loss of treatment fidelity, 5) targeting all smokers—not only those who are ready to quit, and 6) testing mechanisms of change. This study attempts to bridge the gap between dentistry and cessation services.

Study Design: The aim of the study is to test whether a video-based smoking cessation induction intervention delivered through a VR headset during dental cleanings increases utilization of EBTs for smoking cessation. Specifically, we will assess utilization of the following EBTs: the Massachusetts State quitline (operated by National Jewish Health), clinic-based programs (e.g., community health centers, hospital smoking cessation clinics), National Cancer institute's (NCI) text message program (SmokefreeTXT), nicotine replacement therapy (NRT) products, and non-NRT smoking cessation medications. 437 smokers will be randomized to either the Intervention consisting of: 1) smoking

cessation video intervention via VR headset during teeth cleaning, 2) print materials about the EBTs, and 3) two text messages per day for 4-weeks and periodically throughout the study period to motivate engagement with EBTs; or Control group, consisting of: 1) relaxation video via the VR headset (to maintain provider masking) during teeth cleaning, 2) receipt of the same print materials about the EBTs as the Intervention group, and 3) assessment only text messages. Our primary outcome is contact with, and utilization of, EBTs. Secondary outcomes are quit attempts, biochemically verified point-prevalence abstinence from smoking, and motivation to quit. We will also assess mediators of the intervention effect (self-efficacy, motivation, outcome expectations) and moderators of intervention effects (e.g., gender, readiness to quit). Assessments will occur at baseline, immediately post-appointment, weekly during the 4-week text message program (via text message) and at follow-up (one-month post-appointment, and 3- and 6-months later).

Because we are proactively reaching patients, they may or may not be ready to quit smoking. Therefore, quit rates would be expected to be low if we were focusing on cessation, necessitating a very large sample to be able to compute power. The goal of the study is to test whether a clinic-based intervention that reduces provider burden and has minimal patient burden can drive patients to make contact with EBTs. Our prior research has shown that smokers who are not motivated to quit either lack knowledge about the EBTs, do not know how to access EBTs, and/or have myths about EBTs. [42] The video-based intervention and subsequent four-week text message program addresses these barriers, and provides motivational strategies to make contact with EBTs.

2.2 BACKGROUND

Meta-analytic evidence has shown that smoking cessation interventions delivered in dental clinics increase the odds of tobacco abstinence at six-month follow-up or longer (n=5; OR=2.38).[10] A recent study using brief (5 minute) counseling based on the 5 A's vs usual care did not find significant between-group differences in cessation. [43] These studies have several limitations, such as recruiting only smokers who are ready to quit, lack of biochemical verification of smoking status, inability to mask clinicians to treatment condition, and inconsistent intervention delivery. [43-49] Almost no studies had clear methods of ensuring treatment fidelity, which is crucial for the interpretation of treatment outcomes. [16] Only two studies included treatment components delivered after patients left the clinic to sustain intervention effects. [48,49] One study had previously used an educational video as part of a smoking cessation intervention but it was not integrated into the dental visit. [50] The vast majority of the above studies used dental providers to deliver the intervention, but barriers to consistent counseling exist (concern about patient resistance, lack of knowledge, lack of time, lack of financial reimbursement).

Adults prefer to use mass media, rather than professional resources, for health information. [51] Videos are especially useful for patients of low SES. [52-56] In one study, patients with low levels of education were able to assimilate and recall information in videos and rated them even more useful and informative than more educated groups. [57] Videos are amenable to tailoring to the needs of specific populations and to the delivery of information in an entertaining audiovisual format that can be effective even for individuals with low literacy skills. [58] Videos increase learner interest and retention, and alleviate the problem of lengthy training of providers. [59-62] Use of video assures a standard and consistent intervention not subject to the varying abilities or opinions of different providers. Videos provide accurate health information, demonstrate skills, and model behaviors and coping strategies through both verbal and visual example. [63-65] Video has been used to successfully treat alcohol abuse, [66] diet and

weight management, [67-69] nutrition, [70] and diabetes. [71] Five randomized controlled trials have shown that videos are effective for smoking cessation, [72-76] but none have been implemented in dental settings.

Clinical Practice Guidelines for Treating Tobacco Use and Dependence confirms the efficacy of medication and counseling (including telephone quitlines) for smoking cessation, [18] and the combination is more effective than either one alone. The length of utilization of both medication and counseling is associated with a greater likelihood of initial and sustained abstinence. [18] Low-SES smokers, Blacks and Hispanics, and persons with inadequate insurance all are less likely to use EBTs [7,20,77-81] to quit smoking, due to misconceptions about effectiveness and safety, [80-87] and lack of awareness of resources and insurance coverage. Only 36%-46% of Medicaid-enrolled smokers are aware that their state covers cessation treatment. [88] Our study aims to address these misconceptions through an engaging video delivered via VR headset during teeth cleaning, and through follow-up text messages, to provide an easy and seamless transition to connect smokers to EBTs.

Quitlines provide evidence-based counseling and support to individuals trying to quit smoking. Since 2005, all states have quitlines and conduct multiple counseling sessions at no cost and many provide free or low-cost NRT. Quitlines have demonstrated both efficacy and real-world effectiveness and is cited as an EBT in clinical practice guidelines. Quitline counseling alone significantly increases abstinence rates (OR=1.6) and when combined with medication use, and abstinence rates reach 28.1%, [18,89] even for smokers who are not motivated to quit (RR= 1.30). [89] The Massachusetts quitline provides nicotine replacement for up to 8-weeks, and it attracts a diverse population of smokers who may face barriers accessing other cessation programs. [90] One study compared the demographics of Massachusetts quitline callers to that of smokers who did not contact the quitline and found little difference in education and other relevant demographics. [90,91] Counseling, whether clinic-based or through a quitline has been shown to be effective, [18] with a clear dose-response effect. Four studies have supported the effect of brief counseling on EBT utilization in non-treatment-seeking populations (ORs range from 1.8 to 2.4). [44,92-94] Smokers did not have to be motivated to quit to be eligible for these studies. One of these studies [44] found positive effects in a dental setting (the intervention group was more likely to contact the quitline) but the sample was small and there was no verification of quitline contact.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The study presents no more than minimal risk of harm to human subjects. There are no long-term risks to subjects related to the procedures described in the protocol. Immediate risks to subjects may include:

- The loss of privacy and confidentiality.
- Some aspects of the assessments (e.g. completing the questionnaires) may be uncomfortable because of questions regarding health habits and demographics.
- Possible discomfort wearing the virtual reality headset.
- Fatigue and injury related to the text message program.

2.3.2 KNOWN POTENTIAL BENEFITS

Immediate potential benefits to subjects include:

- Regardless of motivation to quit, participants will receive information about local and national smoking cessation resources (online resources, tobacco cessation quitline, clinic-based programs, and text message programs). The information can be acted upon immediately or when the participant is ready to quit smoking.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Although this study poses no more than minimal risk of harm to subjects, potential risks include loss of confidentiality, discomfort wearing the VR headset, and participants may feel uncomfortable answering some questionnaire items.

To minimize risk of loss of confidentiality, study data, documents, case report forms (CRFs), and other documents and files will be identified with a unique study ID number. The study ID number will be linked to a mastercode list that contains all study ID numbers and direct subject identifiers (e.g., name, address, telephone number, etc.). The mastercode list will be maintained in a secure, protected and HIPAA compliant drive separately from other study files, and access will be limited to members of the research team. Additionally, study data will be collected electronically using tablets or laptops through secure web-based application software REDCap managed by the Boston University Biostatistics and Epidemiology Data Analytics Center (BEDAC) at the Boston University (BU) School of Public Health. Electronic CRFs (eCRFs), provide for consistent data collection within the REDCap study management system. Data will be securely stored according to BU policy. Electronic devices for data collection (e.g., tablets or laptops) are password protected and kept in a locked filing cabinet when not being used. Data collected from research participants will be stored in a secured, password-protected computer file that is separate from identifiers. Any paper data will be placed in a locked file cabinet. Participant information will be accessible only to research staff. All research data, including a copy of the mastercode, will be kept for 7 years after completion of the project to allow for reidentification in case of an audit or other review, and in compliance with BU policy #FA-002.

“Agile Health” (AH) is the company that will be programming and delivering our 4-week text message curriculum. Their database will contain the text messages including information on what text messages each participant has received, which texts participants have responded to, their actual responses, and feedback about individual messages. This database is HIPAA secure. Agile Health will not have access to the link between participant contact information and survey data. To ensure the highest level of data confidentiality, secure data transfer will occur through REDCap managed by the Boston University Biostatistics and Epidemiology Data Analytics Center (BEDAC) at the School of Public Health. Following a discussion with the BU director of health privacy and compliance, a BAA for this study is not required. Following a discussion with BUMC Information Security, study's co-investigator Dr Romano Endrighi is the appointed coordinator who will conduct quarterly access audits in consultation with Agile Health.

In order to verify that study participant have connected with the quitline, we need to share subject identifiers with National Jewish Health, which is the contracted vendor for the Massachusetts State quitline. The participants’ information we share includes: 1) participant’s name, 2) participant’s telephone number, 3) participant's date of birth, and 4) participant’s home address. We will also need to share the study enrollment date.

These identifiers constitute the minimum necessary data requested by National Jewish Health to enable them to verify in their database:
1. whether the participant made contact with the quitline; 2. whether the participant elected to start counseling; 3. the type of counseling the participant requested (e.g., phone, web or text message); 4. the number of counseling session the participant received; 5. whether the participant set a date to quit smoking; 6. whether the participant requested nicotine replacement products; and 7. whether nicotine replacement products were sent to the participant. Data sharing between the study team and National Jewish Health will only occur through a secure encrypted email system.

It is possible that some aspects of the assessments (e.g., answering questions about health habits and demographics) may be uncomfortable for some participants. However, participants will be informed that they may choose not to answer any questions that make them uncomfortable.

Participants will watch the videos through a VR headset during their teeth cleaning. The VR headset we used during the UG3 usability study (Viotek Spectre) was rated highly comfortable by participants. However, if a participant feels uncomfortable wearing the headset during the video, he or she may remove it. In this case, we will terminate participation and compensate the participant accordingly.

There are two potential risks of text messaging: accidents, thumb, and joint pain. Frequent texting may increase the risk of thumb and joint pain. The number of texts involved in this study is not likely to result in thumb and joint pain. To prevent text message-related injury, we will inform participants that text messages should not be attended to while driving or walking. In a previous pilot study that included a similar text message curriculum participants received for two months, [38] there were no issues related to fatigue interacting with text messages, and the text message program was well received by participants.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary			
To test the efficacy of the Intervention vs. Controls in increasing contact with, and utilization of, EBTs over a 7-month study period.	-Any EBT contact over the 7-month study period. -Total number of EBTs contacted – ranging 0 to 4 – over the 7-month study period -EBT utilization index score over the 7-month study period	Because effective cessation programs already exist, innovations are needed to drive smokers to engage with them. 40-80% of smokers are not ready to quit within 30 days, and efforts are needed to reach smokers with motivational interventions in their natural settings. Because we are proactively reaching patients, they may or may not be ready to quit smoking. Therefore, quit rates would be expected to be low if we were focusing on cessation, necessitating a very large sample to be able to compute power. The goal of the study is to test whether a clinic-based intervention that reduces provider burden and has minimal patient burden can drive patients to make contact with EBTs. Our prior research has shown that smokers who are not motivated to quit either lack knowledge about the EBTs, do not know how to access EBTs, and/or have myths about EBTs. The video-based intervention and subsequent 4-week text message program addresses these barriers, and provides motivational strategies to make contact with EBTs.	The VR video intervention including the subsequent 4-week text message program target social cognitive theory constructs (e.g., motivation, self-efficacy, outcome expectations) which are the hypothesized mechanisms that mediate the effect of the intervention on the primary study endpoints.
Secondary			
To test the efficacy of the Intervention vs. Controls in motivating smokers to use a combination of medication and counseling.	-Combination of at least one form of counseling EBTs (state quitline counseling, clinic-based counseling, text messaging) and at least one form of medication (nicotine replacement	Participants may utilize more than one EBT and will be encouraged to do so. Evidence shows that a combination of counseling and medication is more effective that either treatment alone.	

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
	therapy or tablet medication) over the 7-month study period.		
To test the efficacy of the Intervention vs. Controls on quit attempts and on motivation to quit.	-The number of quit smoking attempts, since last contact, that lasted 24 hours or more, not due to hospitalization or illness over the 7-month study period. -Participants' motivation to quit smoking within 30-days over the 7-month study period.	Quit attempts and motivation to quit are robust interim predictors of smoking cessation. [97]	
To test the efficacy of the Intervention vs. Controls on biochemically verified smoking abstinence.	-Biochemically verified 7-day point prevalence abstinence as indexed by salivary cotinine level < 15 ng/mL measured at 1- 3- and 6-months post treatment	Biochemically confirmed self-report of 7-day point prevalence abstinence is best practice in smoking cessation induction clinical trials. [98]	

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
To assess the mechanisms through which the intervention effects occur (mediators) and to identify subpopulations for whom intervention effects differ (moderators)	-Mediators include the social cognitive theory constructs of motivation, self-efficacy, outcome expectations, measured over the 7-month study period. -Moderators include perceived stress, readiness to quit smoking, gender and race/ethnicity.	-Social cognitive theory's theoretical constructs are the hypothesized mechanisms of action (targeted by the intervention) that mediate the effect of the intervention on study's endpoints. -The role of moderators will be exploratory.	

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study is a 2-arm, stage III randomized controlled efficacy trial. Three hundred seventy-six patients will be recruited at Boston University GSDM patient treatment center or TU comprehensive care (or Periodontal) clinic, and randomized to the Intervention group or the Control group. To account for participants who become ineligible post-informed consent (e.g., do not complete baseline activities, do not show up to dental visit) and thus are not randomized, we estimate that approximately 700 subjects will be enrolled. Our aim is to test whether the Intervention administered to dental patients during teeth cleaning increases contact with, and utilization of, EBTs. Smokers randomized to the Intervention group will receive: 1) the smoking cessation video intervention via VR headset during their teeth cleaning, 2) brochure about EBTs, and 3) 4-weeks of tailored, interactive, and automated text messages to motivate engagement with EBTs plus periodic text message reminders throughout the study. The Control group will watch a relaxation video through the VR headset during their teeth cleaning, receive a brochure about EBTs, and receive assessment-only text messages. We chose a 'relaxation video' because this topic is at least somewhat connected to the teeth cleaning experience (e.g., to ease dental anxiety and discomfort), rather than watching a video on general health and wellness, for example.

The Primary Objective is to test the efficacy of the Intervention vs. Controls in increasing contact with, and utilization of, EBTs over a 7-month period. Hypothesis 1.1 states: Participants randomized to the Intervention will be more likely to engage (make contact with) EBTs. Hypothesis 1.2 states: Participants randomized to the Intervention will have greater EBT utilization (e.g., more quitline counseling sessions, more days in the text message program).

The Secondary Objectives are: 1) To test the effect of the Intervention vs. Controls on quit attempts and on motivation to quit. Hypothesis 2 states: Participants in the Intervention will make more quit

attempts and increase their motivation to quit; 2) To test the efficacy of the Intervention vs. Controls on biochemically verified smoking abstinence. Hypothesis 3 states: Participants in the Intervention will achieve higher rates of point-prevalence abstinence at follow-up; 3) To assess the mechanisms through which intervention effects occur (mediators such as self-efficacy, motivation, and outcome expectations) and to identify subpopulations for whom intervention effects differ (moderators such as gender and motivation to quit). Hypothesis 4 states: The Intervention will directly affect the putative mediators of intervention effect, which will in turn affect EBT engagement (contact) and utilization. The role of moderators will be exploratory.

Participants will be randomized (1:1) at the dental clinic, after receiving the study brochure and before watching the videos during their teeth cleaning. Randomization will be implemented by employing a stratified block procedure with small, random size blocks and will be stratified by motivation to quit (ready to quit smoking in 30 days vs. not ready to quit within 30 days). To avoid randomization errors, randomization will be configured within REDCap, the secure web application used to build and manage the questionnaires and study forms which is programmed and managed by the BU Biostatistics and Epidemiology Data Analytics Center (BEDAC). A biostatistician will build the randomization program. The study RA will trigger randomization by pressing the feature on the REDCap eCRF form using an iPad. All dental providers will be masked to treatment condition because both the Intervention group and the Control group will be watching a video through the VR headset. Only the PI, project director, statistician, and study RA who is in the clinic will be unmasked to treatment condition.

At the teeth cleaning appointment, all participants will receive a Viotek Spectre virtual reality and earbuds with volume control. A study smartphone (iPhone) will be inserted into the headset and programmed to show either the intervention or the control video, depending upon the patient's randomization. Both videos will be the same duration (10 minutes). Participants randomized to the Intervention group will watch one of two videos dependent upon their latest assessment of motivation to quit (assessed at the dental clinic appointment). If the participant is motivated to quit within 30 days, they will watch the "Ready to Quit" video; those not motivated to quit within 30 days will watch the "Not Ready to Quit" video. The RA will help the participant adjust the headset for comfort and use the audio control on the earbuds to ensure the volume is set at a level where the participant is able to hear the practitioner while watching the video. Participants will be advised to raise their hand to signal for adjustments, removal of the headset, or the conclusion of the video.

Shortly after participants complete watching the assigned video, the RA will trigger the post-video questionnaire in REDCap. The post-video questionnaire will be delivered as e-link through text message and email to all participants. Participants will be required to complete this questionnaire in their own time within 10 days of receiving the e-link invitation.

Within 24 hours of randomization, the Intervention group will begin the 4-week text message curriculum program that has been designed in preparatory research to: a) motivate EBT contact and utilization, b) facilitate transition to EBTs, c) dispel myths and misinformation about EBTs, and d) measure mediators weekly. There are two different tracks of text messages to motivate EBT contact and utilization: one for those who are motivated to quit and one those who are not motivated to quit. The Control group will receive assessment-only text messages, and will follow the same schedule as the assessment text messages in the intervention group (e.g., one text message to assess motivation, one to assess self-efficacy, and one to assess outcome expectancies each week for three weeks). All participants will be able to connect to, and access the services of, one or more EBT resources at any point during the study: both groups receive this information at the dental clinic visit via brochure, and the Intervention group

will receive additional information via text messaging. At the conclusion of both text message programs (Intervention text messages and Control group assessment-only text messages), participants will complete an end-of-treatment assessment (*Time 4*, immediately after the end of the text message program 4-weeks post-randomization). Follow-up assessments will occur at *Time 5* (3-months post end-of-treatment assessment), and at *Time 6* (6-months post end-of-treatment assessment). Participants who self-report quitting smoking at any of these assessments will be asked to provide a saliva sample for biochemical verification of smoking abstinence. Samples will be assayed for cotinine; smoking abstinence is defined as cotinine values < 15 ng/mL. [98]

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Effective smoking cessation programs exist but are underutilized by smokers, particularly underserved smokers. Innovations are needed to increase engagement with these cessation programs. Incorporating smoking cessation into a dental clinic visit and targeting all smokers, regardless of motivation to quit, provides proactive reach to cigarette smokers who otherwise may not seek treatment for smoking. Our study measures EBTs contact and utilization as the study outcome rather than smoking cessation because not all participants may be ready to quit at the time of their dental appointment. Smokers who are not motivated to quit are also less likely to participate in intensive interventions. The video-based intervention serves as a low burden platform suitable for smokers who are unmotivated to quit because it is given during their teeth cleaning (e.g., doesn't require extra time).

Participants who are randomized to the control group will also watch a video of the same length as the intervention group (10 minutes), through the VR headset, while getting their teeth cleaned. The video was created in our previous NIH-funded study and uses guided imagery for relaxation. This video depicts a country setting and a voice-over helps viewers simulate perception of sounds, tastes, smells, movements, texture, temperature, and pressure. The country scene slowly changes (e.g., more flowers are grown, a bird flies by) to keep viewer's attention. Guided imagery has been extensively documented in the literature. [99] We chose to use a 'guided relaxation video' because it is somewhat related to the teeth cleaning experience regarding easing dental anxiety and discomfort as opposed to showing a video on a neutral topic. We considered having the control group receive the same amount of text messages on a different topic but rejected this idea for several reasons: 1. Cost to build an equivalent "control" text message program with same features (customization, personalization, interactivity) to achieve equivalency with the intervention group, 2. Given that the control group will be receiving weekly assessments via texts, we did not feel the extra cost to have exact equivalency would be justified, and 3. Difficulty finding a control topic that would be engaging to unmotivated smokers, risking low program usage.

We decided to use two academically affiliated dental clinics because these clinics are more likely to encounter underserved patients.[21] Underserved smokers are our target population because they are less likely to utilize EBTs. If the intervention is successful in this setting, it is likely to be successful in other clinics as well. Because the vast majority of the providers have outside clinical practices, this will help build an intervention that is generalizable.

We will encourage providers to implement best practice guidelines for smoking cessation. However, because it is not part of the research question, we will not be providing intensive trainings and

treatment fidelity checks on whether or not they are providing counseling. We will, however, ask patients if they received advice to quit from their provider.

4.3 JUSTIFICATION FOR INTERVENTION

Overview of the Intervention: The Intervention consists of: 1) smoking cessation video intervention via VR headset during teeth cleaning (one tailored for those who are ready to quit and one tailored for those who are not ready to quit; both are 10-minutes in length), 2) print materials about the EBTs, and 3) text message program for 4-weeks to motivate engagement with EBTs and reminder texts throughout the study period.

Content of the intervention video: Videos were created using a professional video company. Videos are a mix of narration, interviews, b-roll (video images related to the topic), graphics, and animations, and include a combination of personal anecdotes from smokers (some who are motivated to quit and some who are ambivalent) and guidance from health professionals. The tone of the videos are optimistic (it can be done), empathic (doing it is difficult) and collaborative (vs. prescriptive). We followed key principles for designing videos for low literacy populations and for facilitating attention, comprehension, recall and adherence. [100-102] The "not motivated to quit" video focused on motivational interviewing (MI) principles (and also features Bill Miller, the founder of MI) empathizing that quitting is a difficult decision, reasons why people want to quit but delay quitting, how to resolve ambivalence about quitting, how smoking facilitates and hinders their values and goals, strategies for taking small steps towards quitting, dispelling myths about smoking cessation medications and emphasizing personal choice. The "motivated to quit" video provided greater detail on pharmacotherapy options, strategies to cope with triggers and withdrawal symptoms, benefits of quitting, creating new habits, avoiding slips, and sustaining motivation for abstinence. Both videos present information on EBT options, and how to seamlessly connect to them when ready to quit. Both videos also feature a dentist who narrates a 3D animation of the effects of smoking and quitting smoking on oral health.

Content of text message program: The text messages help to bridge the intervention video shown during the dental appointment and their 'landing' at an EBT. The text messages begin within one day of their dental appointment. Participants receive approximately two text messages per day for 4 weeks. The program is automated, interactive, and tailored and includes two different content tracks: one that is tailored for those who are motivated to quit within 30 days and one for those who are not motivated to quit within 30 days. Intervention text messages were explicitly written to target our mediators and we ensured that at least one message per week targets each of the three mediators, using an intervention mapping process that we have used in prior studies. Other message content includes debunking myths about nicotine replacement and tablet medication options, providing information about EBTs and what to expect, motivating utilization of EBTs, providing information about how to get reduced or no-cost pharmacological treatment for cessation, weekly assessments of hypothesized mediators, and connecting smokers to EBTs.

Rationale for content and platform: Our prior research has shown that smokers who are not motivated to quit either lack knowledge about the EBTs, do not know how to access EBTs, and/or have myths about EBTs. [42] The video-based intervention and subsequent four-week text message program addresses these barriers, and provides motivational strategies to make contact with EBTs. Videos were not filmed in virtual reality because we believed that it would not have a differential effect on attitudes and

behavior (vs. a traditionally filmed video), that it would distract viewers from our core intervention messages, and that the head movement resulting from engaging with VR would interfere with clinical care. Watching a traditionally filmed video through a headset, however, enables continuous viewing of the video despite practitioner request for patients to turn their head, and it also enables a more immersive experience (increasing attention and possibly retention) vs. watching a projected video. Video-based interventions are effective at delivering health behavior interventions to low-literacy populations. We do not propose minimizing the role of the dental provider in smoking cessation, but rather provide a way to augment information without incurring extra time for both patients and providers. Research has shown that smoking cessation counseling is effective in dental settings, but requires time and training, and counseling practices are reduced after the research has ended.[22] While providers may feel comfortable delivering smoking cessation to smokers who are ready to quit, the vast majority are reticent to counsel those who are not motivated to quit.

Rationale for Intervention content and frequency: The video intervention during the teeth cleaning is a clinically efficient use of time and low burden on patients and care providers. The 4-week text message curriculum program also requires low effort activity making it suitable for unmotivated smokers and low-income smokers. The program length is sufficient to provide information about EBTs, and motivate and facilitate patient's connection to EBT resources. A longer intervention may result in program disengagement. The end of treatment (4-week post-randomization), and the 3- and 6-months follow-up assessments allow the study team to assess the sustainability of EBT engagement. The vast majority of participants in both of our pilot studies indicated that the length of the video was 'just about right" (vs. too long or too short). Smokers who are unmotivated to quit are not likely to participate in intensive interventions that have a high amount of burden. Therefore, a video-based intervention that does not require additional time (it is shown during their teeth cleaning) and receipt of one month of text messages (a low effort activity) is a nice fit for unmotivated smokers. The length of the one-month text message program is appropriate for the goal: providing information about EBTs and motivating the smoker's connection to them. A longer program would be warranted if the text messages were focused on smoking cessation. We view the video as having a 'priming effect' to motivate smokers to make contact with the EBTs. Reminders of how to connect with EBTs will be sent via text message to the intervention group throughout the 7-month intervention period.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all baseline activities, watched the video through the VR headset during their teeth cleaning, complete the post-visit questionnaire, complete the 4-week text message program, complete the end-of-treatment questionnaire, and complete the two follow-up assessments (3-and 6 months after the end of treatment). The end of the study is defined as completion of the final assessment (6-months post end-of-treatment assessment) shown in the SoA, **Section 1.3**.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

To be eligible to participate in this study, human subjects must meet all of the following criteria, as applicable:

1. Provision of verbal consent to be screened (brief screening agreement).
2. Provision of verbal (or electronic) and dated informed consent to participate.
3. Patient of the Boston University, Henry M Goldman School of Dental Medicine, or the Tufts University, School of Dental Medicine with an upcoming dental hygiene appointment (dental prophylaxis or scaling and root planing) at the pre-doctoral, or the post-doctoral periodontal, patient treatment center for Boston University patients, or the comprehensive care clinics or the periodontal clinic for Tufts University patients, as indicated in EDR.
4. Male or female, 18 years of age or older.
5. Self-reported smoking 100 cigarettes or more in lifetime (not including e-cigarettes or vaping).
6. Self-reported smoking ≥ 1 cigarette in the preceding week (not including e-cigarettes or vaping).
7. Self-reported smoking cigarettes (not including e-cigarettes or vaping) 'some days', 'most days' or 'every day' in the preceding week.
8. Is able to understand written and spoken study materials.
9. Score of 'Never', 'Rarely' or 'Sometimes' on the validated single-item literacy screener ("How often do you need to have someone help you when you read instructions, pamphlets, or other written material from your doctor, dentist, or pharmacy?").
10. Self-reported visual capacity to watch a video as indicated by the score 'Some difficulty' or 'No difficulty' to: "How much difficulty do you have with your vision, even when wearing glasses?").
11. Self-reported ability to wear headphones that are inserted partially inside the ear.
12. Self-reported use of text messaging at least once in the preceding month.
13. Self-reported access to necessary resources for intervention: Cell phone capable of text messaging.
14. Live in Massachusetts.
15. Stated willingness to comply with text message program procedures (receive and respond to text messages for 4-weeks).

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Participation in another treatment or intervention study for smoking cessation or research involving text messaging.
2. Current use of medications for smoking cessation or smoking reduction (nicotine replacement product, or non-nicotine medications) whether prescribed or not.
3. Failure to complete the pre-dental clinic appointment procedure before the start of the dental appointment (e.g., informed consent, opt-into the text message program and complete the baseline questionnaire).
4. Failure to show up to the scheduled dental appointment at the BU or TU clinic.
5. Previous participation in the UG3 Usability study or pre-award pilot study.

6. Inability to watch the video with the VR headset during the dental appointment.

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Examples include participants who do not complete baseline activities before their dental appointment (e.g., opting-into the 4-week text message program; completing the baseline questionnaire), do not show for or complete their dental visit, or who reschedule their dental appointment outside of the study period. Participants will be rescreened and required to complete the baseline questionnaire again if their new appointment is scheduled 45 days after the date the screening form was completed. On the day of the scheduled dental appointment, we will reassess participants' smoking status to confirm that participants who had been screened during the pre-enrollment phase are still eligible. Participants who self-report no cigarette smoking in the preceding week will be terminated.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The study target population includes patients (≥ 18 years of age) at the GSDM patient treatment center or at the TU comprehensive care clinic, or periodontal clinic. The primary recruitment method of GSDM patients will be study RAs identifying patients through EDRs review who have upcoming dental hygiene appointments (dental prophylaxis or scaling and root planing) at the pre-doctoral, or the post-doctoral periodontal, treatment center. The Director of Clinical Operations at BUGSDM will coordinate with study RAs and set up a database query to identify patients who have a positive indication of tobacco use and upcoming dental appointments scheduled within the following two to four weeks.

Database queries will return a list that includes the patient's first and last name, home address and email address, appointment date, and telephone number. Study RAs will approach these patients by phone in reference to their upcoming dental hygiene appointment to determine interest in the study (patients will have the option to opt out). Patients who demonstrate an interest in the study will be screened for eligibility.

In the event that the study team is unable to reach the patient by phone, we will mail a recruitment letter that states basic information about the study and a recruitment brochure (e.g., study requirements, participant compensation, and study contact information) to the patient's home address. The letter will also state that the patient was contacted because he or she is scheduled for dental hygiene at the GSDM treatment center.

The primary recruitment method of TU dental patients will be similar to GSDM's. The main difference pertains to the procedure to identify patients with upcoming dental hygiene appointments. The IT department of the TU clinic will provide study RAs a list of patients (name, address, telephone number, medical record number, and dental appointment date) with a positive indication of cigarette smoking who have upcoming dental hygiene appointments (dental prophylaxis or scaling and root planing) at the

comprehensive care clinic or at the periodontal clinic scheduled within the following two to four weeks. This list will be generated once a week of more frequently depending on work load and patients' availability, and will be transferred to the BU study team via secure, encrypted email. Study RAs will approach these patients by phone in reference to their upcoming dental hygiene appointment at TU to determine interest in the study (patients will have the option to opt out). Patients who demonstrate an interest in the study will be screened for eligibility. In the event that the study team is unable to reach patients by phone, we will email similar recruitment letters and brochures.

Additional strategies to identify and contact potential participants include:

(1) Distribution of recruitment brochures in the patient waiting rooms of the GSDM treatment center and at TU comprehensive care clinic.
(2) A digital study ad will be displayed on screen in the patient treatment center waiting areas at the GSDM clinic.
(3) Recruitment text messages will be sent to patients after at least one voicemail has been made and/or if a voicemail is unable to be left due to patient's not having a voicemail box set up or the voicemail box is full.
(4) TU site only: To boost recruitment, the IT department will run a query to identify patients with a positive history of smoking who had not had a dental hygiene appointment within the past year. When we obtain this list, we will mail a revised recruitment letter and the recruitment brochure to these patients. The purpose of the letter is to make them aware that the study is conducted during a routine dental hygiene appointment at the TU clinic. In case a patient decides to schedule an appointment with the dental clinic, this appointment will show up in the database query run by the IT department that we receive on a weekly basis. We will then reach out to the patient using the standard procedure described above.

For GSDM patients, recruitment may also take place in the patient waiting area at the GSDM treatment center. Study RAs will approach patients in the waiting area and briefly introduce the study. Patients who express an interest in the study and provide verbal consent will be screened for eligibility. Patients who meet study eligibility criteria and are willing to participate, and have adequate time to complete baseline study activities before the start of their dental appointment will be consented and enrolled in the study.

Study RAs will screen and consent potential participants over the phone, with the exception of those recruited solely at the GSDM treatment center. Those unable to complete the screening process will be informed that their contact information are kept for 45 days while the study team arranges to continue screening at a later, more convenient time.

For patients who meet the study eligibility criteria and wish to take part in the study, informed consent to participate may be obtained in the following ways:

1) Verbally during the screening call (and documented on the appropriate eCRF).
2) Electronically by emailing the informed consent document as an electronic link to patients' email address.
3) In-person at the GSDM clinic (for GSDM patients recruited at the GSDM treatment center only).

During the screening call, we will provide participants who have a valid email address the option of having the informed consent document emailed as an electronic link. Participants may choose to follow along as the study RA reads the informed consent document, and ask any question. Informed consent may then be obtained verbally by the RA during the screening call, or those who requested the consent document as electronic link can provide informed consent to participate in their own time by clicking on

the “I Agree” radio button and by inserting the date consent is provided on the “today’s date” box on the electronic consent document. Study staff will regularly reach out to eligible patients who have not completed informed consent.

If the participant does not have adequate time for consent, they will be given the following alternatives:

(1) The study RA will arrange a more convenient time to call the participant to complete consent.
(2) For GSDM patients only: The participant may provide consent in person at the GSDM clinic. The study RA will inform the participant that if they would like to provide consent in person, they will need to arrive to their dental appointment one hour early to ensure adequate time to complete all required study activities before the start of their appointment. Every effort will be made to complete the consent process before the scheduled dental clinic visit.

Those eligible to participate and who have consented to study participation will then be asked to provide basic contact information, opt-in to the text message program, and complete a baseline questionnaire before the start of their dental appointment. This questionnaire will be emailed and sent by text message as electronic link. Questionnaire assessments may be completed by the participant either online or on their mobile phones.

Because there is often a lag (e.g., one to two weeks) between screening/consenting and the dental appointment visit (and as retention strategy), after participants give consent to be in the study we will mail them a welcome letter to provide additional information about the study activities, and confirmation of date and time of the dental appointment visit (where participants will be randomized and watch the video with the VR headset).

Retention During Text Message Program: We adhered to best practices to prevent drop out during the 4-week text message program in our preparatory research and there were no dropouts. Specifically, we created personalized and customized texts, two tracks of messages (one for those who are motivated to quit and one for those who are not motivated to quit), avoided message redundancy, varied the content and frequency of messages, and used participants’ first name. We also asked participants questions that have a "$" sign. Each time they provided an answer to these questions, they were entered into a monthly raffle for a $50 gift card. In UH3, we will continue these strategies and also deploy fun quizzes about relevant topics with the answers provided the following day. Participants will also be able to re-watch the video they saw at their appointment. Intervention participants will additionally be able to watch the video that was not shown to them at their appointment. For example, if they watched the ‘not ready to quit’ video they will be able to watch the ‘ready to quit’ video. These links will be sent via the 4-week text message program.

Retention for Follow-up Surveys. We will use various cohort maintenance procedures to enhance retention, including text messages and email reminders for follow-up questionnaires (automated through REDCap supplemented with manual reach-outs), phone calls, letters, designation of a staff member as their ‘primary contact’ person to enhance relationship with our study, sending birthday cards, establishing regular contact with participants to update/verify contact info for themselves and their designated ‘alternative contact’ person, and using web-based paid “people search” finders. We also have weekly team meeting to review retention of each participant who is in the follow-up window and number and types of attempts to develop a tailored reach-out strategy for each participant. With

regard to compensation, participants will receive $50 for completing baseline assessment activities ($30 for baseline assessment, given at the end of the appointment; $20 for the post-appointment satisfaction questionnaire to be completed via e-link), and $30 for each completed follow-up (1 month-end of text message, and 3-and 6-months later) as well as a $10 bonus if they complete each assessment within two weeks of the deadline. We will send participants a 'compensation chart' so they can be reminded of the various points at which they will receive compensation for completing the surveys.

The retention schedule for each survey is detailed below:

Survey	REDCap reminders	Manual reach outs frequency	Type of contact
Baseline	Email: Days 2, 4, 6 from survey invitation **as long as dental appointment is still pending**	Day 8 from survey invitation **as long as dental appointment is still pending**	Phone call and voicemail
	Text: Days 2,4,6 from survey invitation **as long as dental appointment is still pending**	Two days before dental appointment	Text message only
		Day before dental appointment	Phone call, voicemail, and text message
Post-video	Email: Days 2, 4, 6 from survey invitation	**Day 8** from survey invitation	Phone call and voicemail
	Text: Days 2,4,6 from survey invitation	**Day 10** from survey invitation (final day)	Phone call, voicemail, and text message
1 month, 3 month, and 6 month	Email: Days 3, 6, 9, 12 from survey invitation	**Day 1** from survey invitation	Retention letter
		Day 8 from survey invitation	Phone call and voicemail

	Text: Days 3, 6, 12 from survey invitation	**Day 13** from survey invitation (last chance to earn $40 before 2 weeks is over!!)	Phone call, voicemail, and text message
		Day 18 from survey invitation	Text message including hyperlink to REDCap survey only
		Day 20 from survey invitation (last chance to earn $30 before 3 weeks!!)	Phone call, voicemail, and text message

Retention for Saliva Samples. Participants who self-report smoking abstinence (7-day point-prevalence abstinence) at any assessment between Time 4 and Time 6 will be asked to provide a saliva sample for cotinine analysis to verify smoking abstinence (as referenced in Section 6.1.2). Study staff will be notified of a participant's reported smoking abstinence via an automated email from REDCap. We will utilize phone calls, voicemails, and text messages to contact participants who qualify to provide a saliva sample. Participant contact will begin as soon as possible following participant report of smoking abstinence. Participants will be contacted by study staff at various times of day and days of the week. Retention for saliva sample collection will cease after a period of about two weeks of contact, if a collection appointment is scheduled, or if the participant declines to provide a sample. For participants who agree to provide a sample, we will schedule a date, place, and time for collection to occur at the participant's earliest convenience. Each time a participant successfully provides a sample, they will receive $25.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

The intervention uses a VR headset to deliver an educational video on smoking cessation during a dental cleaning followed by a 4-week text message program, to motivate smokers to contact and access EBT resources for smoking cessation. Participants will be randomized to either the Intervention group (10-minute educational video on smoking cessation), or a control group (10-minute video on guided

relaxation techniques to maintain provider masking). Participants will complete questionnaires at baseline and end-of-treatment (one-month), and 3- and 6-month follow-ups.

One of two different 10-minute smoking induction cessation videos will be shown for those who are randomized to the intervention condition: one for smokers who are ready to quit in 30 days and one for smokers who are not yet ready to quit. Both videos feature current and former smokers, men and women, and people of different ages, races and ethnicities. Both videos use a combination of personal anecdotes from smokers and guidance from health professionals, have content on EBTs, and how EBTs help smokers successfully quit. Both videos emphasize that the combination of behavioral strategies and medication is the most effective way to quit. Smokers talk about their reasons for quitting (motivation), and how they have overcome cravings to smoke (promoting self-efficacy). Animations (2D and 3D) depict the short-and long-term effects of smoking on health with particular emphasis on oral health. In line with the social cognitive theoretical framework underpinning our intervention (see Table 1 below), the short- and long-term health benefits of quitting, particularly for oral health and disease risk reduction (outcome expectations), are illustrated through animations and narrated by a GSDM dentist faculty member. Former smokers discuss the medications that worked for them, as well as how they brought other activities in their lives to take the focus away from cigarettes and cravings. The video for smokers 'not ready to quit' treads more lightly so as not to elicit denial and defensiveness. Successful quitters admit that they had mixed feelings about quitting, and how they resolved their ambivalence. Issues common to unmotivated smokers are discussed (e.g., myths about stop smoking medications, getting stuck in ambivalence). Dr. Bill Miller, co-founder of Motivational Interviewing, [103] discusses ways to resolve ambivalence, such as building a discrepancy between smoking behavior and goals/values. Taking small steps are emphasized and EBTs are discussed.

The Intervention group will receive one to two text message per day for 4 weeks, focusing on building motivation, self-efficacy, and outcome expectations to contact and utilize one or more EBT resources for smoking cessation. Participants will be able to text key words for more information on any one of the EBTs. Participants will receive their first text message within 24 hours of their dental appointment. Message features include polls (text message questions that allow tailoring of subsequent messages), quizzes (interesting questions will be texted to them with answers given the next day), tailoring (e.g., readiness to make contact with an EBT) and interactivity (e.g., participants who requested more information about an EBT will be asked 48 hours later if they contacted the EBT and if not, the program will query the barriers and provide problem solving). There will be two text message curriculums: messages to motivate EBT utilization for those who are not ready to quit and messages to motivate EBT utilization for those who are ready to quit. For participants who are not ready to quit, the curriculum builds on our extensive work with unmotivated smokers. [42,104] Text messages will focus on addressing myths that surround NRT and other stop smoking medications (e.g., concerns about addiction), take small steps towards making the decision towards EBT utilization, re-emphasis of some of the motivational strategies and concepts used in the video, tips on not getting stuck in ambivalence, and enhancement of outcome expectations. For motivated smokers, we will provide information about the EBT and what to expect, advantages of the EBT (more chances of quitting, less cravings), preparing for cessation, and specific help to connect and facilitate access to EBT. Both text message curriculums will include information on how to contact the EBTs and procure NRT and other smoking cessation medications. After the 4-week text message program has ended, we will send occasional "reminder" text messages throughout the remaining study period (e.g., ending prior to the six-month follow-up questionnaire). These reminder text messages serve two purposes: to remind participants of the EBTs resources for smoking cessation, and as a retention strategy that "fills the gap" in communication during the remaining study period.

Table 1. Examples of mapping social cognitive theory onto the intervention

Social Cognitive Theory: Constructs	Definition	Video Content Example of Each Construct	Text Message Example of Each Construct
Behavioral capability/ Modeling	Promote mastery through skills training; show examples of behavior	Smokers discuss their struggles & how they overcame them. Alternative activities to smoking are demonstrated	Provide info on coping with cravings, & how smokers have success with the EBTs
Outcome Expectations	Belief that behavior change will lead to the desired outcome	Benefits of quitting in the short term and the long term	Cravings are reduced with NRT and other medications
Self-efficacy	Confidence in one's ability to take action and overcome barriers	Quitters discuss that they had mixed feelings about quitting but overcame them, and strategies for dealing with triggers and cravings	Assessment of barriers to making contact with EBTs, & strategies to overcome them
Motivation	Cognitions involved in proximal goal setting; important for initial change & long-term maintenance	Smokers discuss their values, how smoking hinders them & how they resolved their ambivalence about quitting	Address myths and misconceptions about EBTs
Goal setting	Setting realistic, proximal, and specific sub goals	Smokers discuss the small steps they've made toward quitting	Encourage taking small steps toward EBT utilization
Reinforcement & Feedback	Responses to a person's behavior that increase or decrease the likelihood of occurrence	Smokers discuss rewards they received from quitting and from using EBTs (less cravings)	Provide congrats for each small step taken towards EBT utilization

The text message curriculum will also include assessment text messages to measure putative mediators of intervention effect weekly.

Participants who are randomized to the control group will also watch a video of the same length as the Intervention group (10 minutes), through the VR headset, while getting their teeth cleaned. The video uses guided imagery for relaxation. This video depicts a country setting and a voice-over helps viewers simulate perception of sounds, tastes, smells, movements, texture, temperature, and pressure. The country scene slowly changes (e.g., more flowers are grown, a bird flies by) to keep viewer's attention. Guided imagery has been extensively documented in the literature. [99]
The control group will receive mediators assessment-only text messages that follow the same schedule as the intervention group. Both the control and the Intervention group will receive identical print materials on EBTs for smoking cessation, as consistent with standard clinical care. The study brochure about EBTs will be given after the baseline assessment and before randomization.

6.1.2 ADMINISTRATION AND/OR DOSING

The study has several phases. At Time 1 after receiving the study brochure, participants will be randomized to watch either the Intervention or Control videos using the VR headset and earbuds during part of their dental cleaning at the GSDM patient treatment center or at the TU comprehensive care (or periodontal) clinic. Before administration of the video intervention, a study RA will perform instrumentation (set up correct video according to randomization parameters and motivation to quit status, ensuring patient comfort and equipment functionality) while the patient is in the dental chair before the beginning of dental cleaning. Following the dental care provider signal to initiate dental cleaning procedure, the RA will start the video and patients will watch the video through the VR headset. All videos are approximately 10 minutes in length. Once the video has concluded, the RA will

remove the VR headset from the participant and exit the room. The Principal Investigator, project director, statistician, and the clinic study RA will be unmasked to treatment condition. Since all participants will be watching a video, dental providers remain masked to treatment condition.

With 24-hours of their dental appointment, the Intervention group will begin receiving the 4-week text message curriculum to motivate and facilitate utilization of EBT resources for smoking cessation. The text message program includes two tracks, one for those who are motivated to quit and one for those who are not motivated to quit. The administration and dosing of the program curriculum will be as follows:

- 'Introduction' text messages in Week 1.
- Approximately 1-2 intervention text messages per day (‘core messages’). These intervention texts target social cognitive mediators, motivate contact with EBTs, and also dispel myths about smoking cessation medications and other EBTs.
- Weekly 'Assessment' text messages each week (to measures social cognitive mediators).
- Weekly 'Transition' text messages beginning on day 7 (to facilitate participants’ transition to one or more EBT resources).
- 'Check-in' text messages in week 2 – 4, scheduled to be delivered approximately 5 days after the 'Transition' text message (to check in on participants’ transition to EBTs).

The control group will receive mediators ‘Assessment-only’ text messages.

All participants will complete questionnaires at baseline, post-video, end-of-treatment (Time 4), and 3- and 6-months post end-of-treatment (Time 5 and Time 6). Participants who self-report smoking abstinence (7-day point-prevalence abstinence) at any assessment between Time 4 and Time 6 will be asked to provide a saliva sample for cotinine analysis to verify smoking abstinence.

Intervention participants who have completed the Time 1 clinic visit assessment (watched the video with the VR headset and earbuds during dental cleaning) and the 4-week text message program (Time 3) are considered as having received the full intervention.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

We will adhere to NIH guidelines on treatment fidelity. [16,105] Failure of treatment fidelity is unlikely given that our program is video-based and delivered via text messages. Although we have not had technical problems in our prior studies, it is possible that they could occur in the future. We will bring a spare set of VR glasses and earbuds to the dental appointment to minimize this. In order to identify problems at the earliest point, we will continuously monitor outgoing and incoming texts from participants through a desktop dashboard that has this functionality. We will also document all technical problems on an eCRF. We have also created protocols to ensure that the active ingredients of the intervention are fully operationalized, ensured that the intervention components and measures are reflective of underlying theory, used feedback from preparatory research to refine adherence to the theoretical model and improve acceptability, feasibility, and potential effectiveness of the intervention; developed a plan to

record protocol deviations across both conditions; established a plan for implementation setbacks; assessed whether patients received smoking advice or intervention from providers, and ensured that written materials have appropriate health literacy.

Research staff will be trained in all aspects of study implementation which includes recruitment and enrollment (accessing electronic dental records, screening of potential study subjects using eCRF in REDCap, informed consent, text-message program opt-in procedures, and baseline questionnaire), intervention delivery (setting up materials and instrumentation, implementation of intervention or control video during teeth cleaning), and follow-up activities (sending questionnaires, tracking subject status, and retention). During the preparatory research phase, we have successfully piloted all relevant study procedures and developed a manual of procedures which will be adapted for this study. To ensure the highest standard of training and fidelity in the training of all study personnel, we will use the manual of procedures, conduct role plays, simulate clinic visit procedures, and conduct mock intervention delivery. A training checklist will be developed by the PI and Co-I and used during training sessions. All study personnel will be required to satisfy the checklist criteria before initiating any study procedure. Research staff training and quality control procedures regarding the collection and processing of saliva samples are described in detail in a separate protocol (Saliva sampling procedures – including remote sampling – 06.18.20).

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

We will conduct a stratified block randomization procedure with small, random size blocks. Participants will be randomized to one of two groups, Intervention or Control, after completing the baseline assessment, the in-clinic eligibility screener (to ensure that their smoking status has not changed since the screener), and receipt of brochure. Randomization will be stratified by motivation to quit (ready to quit smoking in 30 days vs. not ready to quit within 30 days). [18] Only the PI, the project director, the statistician, and the clinic RAs (RAs who are setting up the video for each patient) will be unmasked to treatment condition. These RAs will not be involved in the collection of any outcome data. Because both the Intervention and Control groups will be watching a video, all dental providers will be able to be masked to participant's treatment condition. The RA who performs follow-ups and collection of saliva cotinine will be masked to treatment condition.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Text message program. The Agile Health Platform keeps track of all text messages sent and received, including both unprompted responses and expected responses from participants. This includes responses to assessment questions, and responses to the interactive intervention features of the text message programs. In order to identify technical problems or problems of non-compliance at the earliest point, we will continuously monitor outgoing and incoming texts from participants through a desktop dashboard that has this functionality. The study team will also receive weekly reports from Agile Health on adherence indicator (e.g., percent of assessment texts responded to; percent of intervention texts responded to; non-responders) consistent with procedures tested in the preparatory research phase. We also meet with Agile Health once per week to monitor participant adherence. Any technical or adherence issue will be documented on an eCRF.

Intervention. Adherence to the VR video intervention component which takes place during dental cleaning will be monitored by the study RA who will be in the treatment room when the patient is in the dental chair watching the allocated video through the VR headset. The RA will bring a spare VR headset and earbuds in case of technical issues. Any technical or adherence issue will be documented on an eCRF.

6.5 CONCOMITANT THERAPY

N/A

6.5.1 RESCUE THERAPY

N/A

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

If a participant is unable or unwilling to wear the VR headset, the participant will be deemed as "ineligible after randomization."

When a participant discontinues from the text message program but not from the study, remaining study procedures will be completed as indicated by the study protocol.

Reasons the subject may be discontinued from the study intervention include

- Participant does not have time to participate in text messaging.

The data to be collected at the time of study intervention discontinuation will include the following:

- The reason(s) for discontinuing the participant from the intervention, and methods for determining the need to discontinue. This will be recorded on an eCRF.
- If the participant is due to complete assessments within 2 weeks of being discontinued from the study intervention, those assessments will be administered at the time of discontinuation; if the next scheduled assessments are more than 2 weeks from the discontinuation date, the discontinued participant will wait for the next scheduled assessment. Thereafter, the participant will be included in all future scheduled assessments, even though not participating in the intervention.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue a participant from the study for the following reasons:

- Participant becomes dangerous to self or others.
- Lost-to-follow up; unable to contact subject (see Section 7.3, Lost to Follow-Up)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the attrition Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are discontinued from the study, will not be replaced. If the subject becomes ineligible, then we will replace the subject but only if the study is within the specified recruitment period.

We will attempt to obtain a final questionnaire assessment and saliva sample (if necessary per protocol) from all subjects who withdraw from the study for any reason. We will make a minimum of 5 attempts to contact the subject in cases of withdrawal and those who relocate.

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator and NIDCR. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination of futility.

7.3 LOST TO FOLLOW-UP

At each assessment point, we will continue to contact participants even if they have not answered one or all of the prior assessments. At each assessment point, we will attempt to contact participants a minimum of 5 times through phone, text, email, and letters. We will use paid services and the EDR to get up to date phone numbers for those that are no longer in service.

The following actions must be taken if a study subject fails to complete a required follow-up assessment:

- The study team will attempt to contact the participant, and counsel the participant on the importance of maintaining the assigned assessment schedule.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant as stated above. These contact attempts will be documented in the participant's study file. Participants who are lost to follow-up will be attempted again at the next follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Participants must be screened for eligibility criteria before they are enrolled in the study. The timeline is as follows:

Time 0: Pre-enrollment

- Boston University GSDM patients and TU School of Dental Medicine patients will be identified and screened within approximately 4-weeks of their scheduled dental appointment at the respective dental clinics. The majority of the screening questions can be answered with 'Yes', 'No', or 'Prefer not to answer'. Participants who select 'Prefer not to answer' will be ineligible for study participation. Screening will be discontinued if participants answer, 'No' or 'Prefer not to answer' to 'Have you smoked any cigarettes (do not include e-cigarettes or vaping in your answer) in the past 7-days?".
- If participants meet all eligibility criteria, they will continue to mobile number verification. If the number is verified, the participant meets all criteria for study participation and can continue to informed consent.
- Informed consent will be obtained either verbally or electronically. Contact information will be collected after informed consent.

Time 1: Dental clinic appointment

- At the dental clinic appointment, all participants will be rescreened to confirm smoking status. Those who self-report no smoking in the past 7 days will be terminated.
- Consented participants who do not complete the baseline questionnaire before the start of their dental appointment will also be terminated if a new dental appointment is not scheduled within 45 days of the date they completed screening.

Endpoints and outcome measures:

- Evidence-based treatments (EBTs) for smoking cessation (assessed at Time 4 – 6). The EBTs for smoking cessation that will be assessed are: 1) the state quitline (operated by National Jewish Health; objective utilization of phone counseling services which also include the number of counseling calls completed, and eligibility for, and provision of, nicotine replacement therapy); 2) the NCI SmokefreeTXT (objective utilization of SmokefreeTXT, the NCI text-message program for smoking cessation, which also includes length of program utilization, and program engagement); 3) clinic-based cessation services (self-report utilization of smoking cessation

counseling, either individual or group sessions, offered by community health centers, hospitals or clinics, which also includes the number of sessions attended, and the provision and use of pharmacologic treatments); 4) pharmacologic treatment (utilization of nicotine replacement therapy products such as the nicotine patch, gum or lozenge, and the nicotine spray or inhaler, and non-nicotine medications such as Zyban, Wellbutrin or Bupropion, Chantix or Varenicline, obtained through physician prescription or, in the case of nicotine replacement products, through the quitline or purchased by participants). Depending on the method of pharmacologic treatment acquisition, pharmacologic treatment utilization may be objective or self-report. Acquisition of nicotine replacement therapy will be verified if participants receive them from the state quitline.

    - EBTs for smoking cessation will be operationalized as: 1) utilization of any EBT over the 7-month study period; 2) total number of EBTs utilization during the 7-month study period (ranging 0 to 4); 3) EBT utilization index score (UIS; obtained by first computing a proportion of utilization score for each of the EBTs for each participant, and then adding up the individual proportion scores; see section 9.4.1 for details); 4) combination of at least one form of non-pharmacologic EBT and at least one form of pharmacologic EBT over the 7-month study period.

- Quit smoking attempts (assessed at Time 4 – 6). The number of quitting smoking attempts participants have made, since last contact, that have lasted 24 hours or more and that were not due to hospitalization or illness.
- Motivation to quit smoking (assessed at Time 4 – 6). Participants' motivation to quit smoking within 30 days (yes vs no).
- Smoking abstinence (assessed at Time 4 – 6). Seven-day point-prevalence abstinence (7-day ppa) assessed by self-report of no smoking, not even a puff, in the past 7 days and salivary cotinine level < 15 ng/mL.
- Mediators of treatment effects (assessed at Time 2 – 6). Theoretically driven constructs hypothesized to mediate any observed intervention effect (EBT utilization, quit smoking attempts, motivation to quit, or smoking abstinence) include the social cognitive theory constructs of motivation, self-efficacy, and outcome expectancies.
- Moderators or treatment effects (assessed at baseline). Moderating factors include sex, race or ethnicity, perceived stress and readiness to quit smoking.

8.2 SAFETY ASSESSMENTS

N/A

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, ***whether or not considered intervention-related.***

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The following scale will be used to grade adverse events:

1. Mild: no intervention required; no impact on activities of daily living (ADL)
2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADL
3. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADL

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

To assess relationship of an event to study intervention, the following guidelines will be used:

1. Related (Possible, Probable, Definite)
   a. The event is known to occur with the study intervention.
   b. There is a temporal relationship between the intervention and event onset.
   c. The event abates when the intervention is discontinued.
   d. The event reappears upon a re-challenge with the intervention.

2. Not Related (Unlikely, Not Related)
   a. There is no temporal relationship between the intervention and event onset.
   b. An alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

The study PI will be responsible for determining whether an AE is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

AEs, UPs and SAEs will be recorded in the data collection system throughout the study. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Adverse events that are related to the study (possibly, probably, or definitely related) will be recorded and reported throughout the entire study. The principal investigator will report, in summary form, all AEs to the IRB at the time of continuing review.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

For any AE meeting the specified Serious Adverse Event criteria, the PI or designee will submit an SAE form to NIDCR's centralized safety system via Rho Product Safety. This report may be sent by fax or email. Once submitted, Rho Product Safety will send a confirmation email to the investigator within 1 business day. The investigator should contact Rho Product Safety if this confirmation is not received. This process applies to both initial and follow-up SAE reports.

SAE Reporting Contact Information:

- Product Safety Fax Line (US): 1-888-746-3293
- Product Safety Fax Line (International): 919-287-3998
- Product Safety Email: rho_productsafety@rhoworld.com

General questions about SAE reporting can be directed to the Rho Product Safety Help Line (available 8:00AM – 5:00PM Eastern Time):

- US: 1-888-746-7231
- International: 919-595-6486

The study clinician will complete a Serious Adverse Event Form and submit via fax or email within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the Serious Adverse Event Form and submitted to Product Safety within 24 hours of site awareness.
- Serious adverse events other than death and immediately life-threatening events, regardless of relationship, will be reported by fax within 72 hours of site awareness.

All SAEs will be followed until resolution or stabilization.

The principal investigator will report, in summary form, all SAEs to the IRB at the time of continuing review.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

N/A

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.]

8.4.2 UNANTICIPATED PROBLEMS REPORTING

Unanticipated problems involving risk to human subjects will be recorded and reported throughout the entire study. The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form by the Co-PIs. The report will include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- a detailed description of the adverse event, incident, experience, or outcome;
- an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;

- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB and to NIDCR within 24 hours if death or a life-threatening event or within 72 hours for all other serious adverse events.
- Any other unanticipated problem will be reported to the IRB and to NIDCR within 7 days of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures). The IRB will then report to the supporting agency head (or designee), and OHRP. As per Boston University policy: "the HRPP director will report within 21 days of IRB determination of an Unanticipated Problem, serious or continuing noncompliance, or suspension or termination to, as applicable.

All unanticipated problems will be reported to NIDCR's centralized reporting system via Rho Product Safety:

- Product Safety Fax Line (US): 1-888-746-3293
- Product Safety Fax Line (International): 919-287-3998
- Product Safety Email: *rho_productsafety@rhoworld.com*

General questions about SAE reporting can be directed to the Rho Product Safety Help Line (available 8:00AM – 5:00PM Eastern Time):

- US: 1-888-746-7231
- International: 919-595-6486

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

This study is a phase 3 randomized controlled trial to test the efficacy of a video-based smoking cessation induction intervention delivered via VR headset during a dental cleaning (Intervention) vs. a relaxation video control (Control). Both groups will also receive print brochures about EBTs and a 4-week text message program. The Intervention text message program will focus on motivating smoker to

make contact with EBTs while the control text message program will be limited to mediators assessment-only text messages.

Primary Endpoints:

Aim 1 Hypothesis 1.1. We hypothesize that, compared to smokers who are randomized to the Control group, smokers who are randomized to the Intervention will be more likely to utilize any EBT (Quitline, clinic-based programs, NCI's text message program, nicotine replacement therapy, other evidence-based medication) during the 7-month post-appointment study period. Alternatively, our null hypothesis is that there will be no difference between the two study groups in EBT contact and utilization during the study period.

Aim 1 Hypothesis 1.2. We hypothesize that, compared to smokers who are randomized to the Control group, smokers who receive the Intervention will have greater tobacco treatment utilization (e.g., more EBTs contacted, more days in the NCI text message program, more days using smoking cessation medication, and more phone/clinic counseling sessions) during the 7-month post-appointment study period. Alternatively, our null hypothesis is that there will be no difference between the two study groups in treatment utilization during the study period.

Secondary Endpoints:

We hypothesize that, compared to smokers who receive the Control intervention, smokers who receive the Intervention will:

a) have more quit attempts during the 7-month study period (Aim 2 Hypothesis 2.1)
b) have higher motivation to quit at 1-month post-appointment and 3- and 6-months follow-up (Aim 2 Hypothesis 2.2)
c) have greater biochemically verified abstinence rates at 1-month post-appointment and 3 and 6 months follow-up (Aim 3 Hypothesis 3.1)

Alternatively, our null hypotheses are that there will be no difference between the two study groups on these secondary endpoints.
Exploratory Aims:

Aim 4. We will assess mechanisms through which the intervention effects are expected to impact any EBT engagement (self-efficacy, motivation, outcome expectations) and identify subpopulations for whom intervention effects differ (moderators including perceived stress, readiness to quit, gender, and race/ethnicity).

9.2 SAMPLE SIZE DETERMINATION

Power calculations focus on the comparison of those randomized to the Intervention vs. Control on our primary outcome of any EBT engagement through a chi-square test at the two-sided alpha =0.05 level. We will not adjust p-values for multiple comparisons.

Using the odds ratio as our effect size, we estimate the effect of the Intervention will be OR=2.05 (corresponding to percent with any EBT utilization of 22.7% in the Control vs. 37.6% in the Intervention). Only two published studies tested the efficacy of an intervention on EBT utilization rate, both at 12-months follow-up. Brooks et al [92] reported an EBT utilization rate (i.e., Quitline or clinic-based program) of 29.8% in the intervention group vs. 14.7% in controls (OR=2.4). Fu et al [93] reported an EBT utilization rate (counseling or medications) of 44.2% in the intervention and 30.6% in controls (OR=1.8). Therefore, we use the average EBT utilization rate in the control groups from these studies (22.7%) as our 'any EBT utilization' rate under the null hypothesis in the power analysis. Because neither of the above studies used video or were conducted in a dental setting, we also considered previous studies testing the effectiveness of videos on cessation, which report ORs of 1.9 [72] and 3.0,[76] and previous studies on cessation in dental settings (meta-analysis OR=2.38).[10] Based on all the above, we conservatively chose an anticipated effect size of OR=2.05 (corresponding to rates of 22.7% vs. 37.6%). With alpha=0.05 (two-sided), we need a total sample of n=300 subjects to achieve 0.80 power of detecting this anticipated effect. However, because of potential differences between clinic sites, and assuming an attrition rate of 20% (lost to follow-up or ineligible post-randomization), in consultation with the NIDCR in April 2024 we received authorization to increase the sample size to n=455 subjects (n= 227 for intervention and n=228 for control group). Therefore, with alpha=0.05, the anticipated effect size of OR=2.05, and 364 subjects (455 minus 20% lost to follow-up or ineligible post-randomization), we will have 0.87 power to detect the anticipated effect.

For the outcome of the amount of EBT utilization, to our knowledge there are no trials on which to base power. To be conservative, our power analysis was based on an ANCOVA model. Assuming a two-sided alpha=0.05, a medium effect size (Cohen's f=0.25), and controlling for confounders, with a total of n=364 participants, we will have 0.92 power to detect group differences.

9.3 POPULATIONS FOR ANALYSES

We will conduct intention-to-treat (ITT) analyses where we include all patients based on their randomized groups, regardless of their subsequent withdrawal from treatment or deviation from the protocol. Primary analyses will be based on participants who are evaluated at 6-month follow-up. In the case of missing data, we will collect reasons for dropout to inform our assumption about missing mechanism. Secondary analyses using multiple imputation or inverse probability weighting to account for missing data will be explored. Sensitivity analyses will be performed to explore the effects of departures from assumptions made in these missing-data analyses.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

For descriptive statistics, categorical data will be presented through percentages and continuous variables will be presented through means and standard deviations. For statistical tests, a two-tailed p-value less than 0.05 or a 95% confidence interval not including the null value will be used for statistical significance.

EBT utilization will be analyzed by computing a utilization index score (UIS). The UIS will be created by first computing a proportion of utilization score for each of the EBTs for each participant. For example, a participant who completed 4 of 5 quitline calls has a proportion score of 80. For NRT, the recommended length of treatment is 8 weeks and the proportion completed by each participant will be computed. For the NCI smoke-free text message program, the recommended length of participation is 56 days, and we will compute the proportion of days completed, as well as the proportion of text messages responded to (of those that required a response). For clinic-based programs, the proportion will be calculated as the number of sessions attended divided by maximum number of sessions offered at the corresponding clinic. Because participants may use one or more EBT programs, the overall "utilization index score" will be the sum of the above individual proportion scores of each EBT for each person. These individual scores will be summed to obtain the UIS (continuous variable). The distribution of our UIS will be examined for approximate normality, and transformations to improve normality or categorization of the index score will be considered if appropriate. For primary analyses, we will control for age, gender, and race/ethnicity, along with variables identified through preliminary analyses as significantly differing between study groups.

This study will be registered with Clinical Trials.gov prior to the start of participant enrollment.

A formal Statistical Analysis Plan (SAP) will be completed prior to the completion of the study and the unblinding of the study data.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Aim 1 Hypothesis 1.1. Between group differences in any EBT utilization. The outcome is any EBT utilization over the 7-month study period, including use of the Quitline, clinic-based programs, NCI's text message program, nicotine replacement therapy, other evidence-based medication (e.g., Bupropion, Varenicline). Quitline use will be based on objective usage data provided by National Jewish Health (the operator of the state's quitline contracted by the Massachusetts Tobacco Cessation and Prevention Program) (e.g., whether contact was made, number of counseling calls, whether patients set a quit date, whether nicotine replacement was requested and delivered to patients), and engagement with NCI's text message program use (e.g., whether patients opted into the program, response rates, length of time in the program) will be obtained objectively from the program. Data on other EBT utilization (clinic-based counseling; receipt of smoking cessation meds outside of the quitline) will be based on self-report. This binary outcome will be analyzed through a logistic regression model, with the intervention effect described through an odds ratio and 95% confidence interval. We will control for age, gender, race/ethnicity, and variables identified through preliminary analyses as significantly differing between study groups.

Aim 1 Hypothesis 1.2. Dose of EBT utilization. The outcome is our UIS (described in 9.4.1) which summarizes participation in one or more EBTs (the quitline, nicotine replacement or other medications, the NCI SmokefreeTXT program, and clinic based programs). Multiple linear regression will be used to compare the Intervention vs. Control, controlling for age, gender, race/ethnicity, and variables identified through preliminary analyses as significantly differing between study groups. The intervention effect will be described through the slope, representing the difference in mean UIS for those in the Intervention vs. Control group.

We will conduct intention-to-treat (ITT) analyses where we include all patients based on their randomized groups, regardless of their subsequent withdrawal from treatment or deviation from the protocol. Primary analyses will be based on participants who are evaluated at 6-month follow-up. In the case of missing data, we will collect reasons for dropout to inform our assumption about missing mechanism. Secondary analyses using multiple imputation or inverse probability weighting to account for missing data will be explored. Sensitivity analyses will be performed to explore the effects of departures from assumptions made in these missing-data analyses.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Aim 1 Hypothesis 1.2. Dose of EBT utilization. As a secondary outcome, we will examine the total number of EBTs contacted over the 7-month study period (ranging from 0 to 4, for the quitline, any clinic-based program, NCI's text message program, and nicotine replacement or other medication). Participation in the Quitline or NCI's text message program will be based on usage data from the programs. Participation in clinic-based programs or use of smoking cessation medication outside of the quitline will be based on self-report. The number of EBTs utilized will be analyzed through Poisson regression for count data, with the intervention effect described through a rate ratio and 95% confidence interval describing the increased probability of engaging in an additional EBT for those in the Intervention vs. Control. We will control for age, gender, race/ethnicity, and variables identified through preliminary analyses as significantly differing between study groups.

Aim 1 Hypothesis 1.2. Dose of EBT utilization. As a secondary outcome, we will also create a binary indicator of use of a combination of counseling (including quitline, clinic-based programs, and the NCI's text message program) and medications over the 7-month study period. The Intervention will be compared to Control on this outcome through logistic regression, with the intervention effect summarized through an odds ratio and 95% confidence interval. We will control for age, gender, race/ethnicity, and variables identified through preliminary analyses as significantly differing between study groups.

Aim 2. Quit attempts and motivation to quit, and Aim 3. Biochemically verified abstinence. Dichotomous data on quit attempts, motivation to quit, and biochemically verified abstinence will be collected at one-month post-appointment (the end of the text message program), and at 3 and 6 months follow-up. Data on quit attempts will be based on the question "Since last contact, how many times have you stopped smoking for at least 24 hours because you were trying to quit smoking (not due to illness/hospitalization)?" Our main analyses for this outcome will examine the dichotomized outcome of 'any quit attempt', although we will collect data on the number of attempts and duration. Motivation to quit will be based on the question "Are you seriously thinking of quitting smoking in the next 30 days (yes or no)?" To determine point-prevalence abstinence, participants will be asked "In the last 7 days, have you smoked any cigarettes at all, even a puff?" [106] For those responding 'no', biochemical verification will be implemented with salivary cotinine, with abstinence defined as cotinine values < 15 ng/mL. [98] If participants indicate use of Nicotine Replacement Therapy or electronic nicotine delivery system use, these data will be recorded and reported separately from cotinine-validated abstinence. For these outcomes, the Intervention will be compared to the Control on data from 1-month post-appointment and at 3 and 6 month follow-up through mixed effect logistic regression models with random intercepts for longitudinal dichotomous data. These models will include indicator variables for intervention group, time, and interaction between intervention group and time (which will model and test whether changes in motivation to quit follows different patterns over time in the

Intervention vs. Control group). Intervention effects will be described through odds ratios and 95% confidence intervals. In the case of significant intervention by time interaction, separate odds ratios will be given for intervention effects at each time point. We will control for age, gender, race/ethnicity, and variables identified through preliminary analyses as significantly differing between study groups.

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline demographic and smoking-related characteristics will be compared for those randomized to the Intervention vs. Control groups. Because of randomization, we do not anticipate baseline differences between groups, but if significant differences are found, those variables will be considered as potential confounders in later analyses. Categorical characteristics will be described through percentages and compared across groups through chi-square tests, and continuous measures will be described through means and standard deviations and be compared through t-tests.

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

Differences in the effect of the Intervention vs. Control on any EBT utilization over the 7-month study period will be examined through logistic regression models including interaction terms between the intervention and demographic and baseline characteristics. We will examine perceived stress, readiness to quit smoking at baseline, gender, and race/ethnicity as possible effect modifiers.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will not be presented.

9.4.9 EXPLORATORY ANALYSES

Aim 4. Mediation. Exploratory analyses will examine the role of social cognitive factors as mediators of the intervention effect on any EBT utilization. Our analyses will account for the temporal precedence assumption of mediation. If participants utilize the EBT within one month of their dental appointment, we will compute change from baseline to the time point prior to first initiation of any EBT. If participants contact an EBT after the first month, we will compute change scores between baseline and end of treatment (1-month post-appointment). Our primary approach to establishing mediation effects will be the product of coefficients method, which utilizes a multiple mediation model to simultaneously test the effects of the potential mediators. [107,108] Corresponding standard errors will be calculated using bootstrapping (10,000 bootstrapped sample). Multiple mediation allows for simultaneous testing of the

effect of a set of mediators while controlling for the effects of the others, and a comparison of the effects of the mediators to determine the relative influence of each mediator.

Aim 4. Effect modification. We will explore whether the Intervention has different effects on any EBT utilization over the 7-month study period for different subpopulations by examining interactions between potential moderators and intervention using logistic regression models. We will examine perceived stress, readiness to quit smoking at baseline, gender, and race/ethnicity as potential effect modifiers.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

IRB approved and IRB stamped Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and verbal (or electronically obtained) documentation of informed consent will be completed prior to starting the study intervention. The Informed Consent form submitted to the IRB for approval is submitted with this protocol.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

The Informed consent process is initiated prior to an individual participating in the study and continues throughout study participation. Prior to screening, we will obtain brief verbal consent to be screened. If screening takes place over the phone and the participant is eligible, we will retain their data and their identifiable contact information and the link between the two. Thus, we will also request a waiver of documentation of consent. If the screening takes place over the phone and the participant is ineligible, we will retain their non-identifiable screening information and destroy their contact information and any link between their contact information and screening data. For eligible participants, a full consent form will be sent electronically to the participant for completion or, for GSDM participants only, consent will be conducted in-person at the GSDM clinic. A hard copy of the IRB approved informed consent form will be given to all consented participants at the clinic visit. In all cases, the study RA will review the IRB approved informed consent form with participants and answer any questions that may arise. Participants will be informed that they may withdraw consent at any time throughout the course of the study. The rights and welfare of the participant will be protected by emphasizing that the quality of their dental care will not be adversely affected if they decline to participate in this study at any point. Participants must provide documented informed consent to the RA in order to complete study enrollment procedures. If the participant does not have adequate time to complete the consent process over the phone, they may choose to have the consent form emailed to them to complete in their own time.

The consent process will be conducted in REDCap by RAs and research study staff members conducting enrollment and all potential participants will be given sufficient time to consider their choice to participate or not. The RA or qualified study staff member will verbally review the informed consent in REDCap with the individual to ensure that the potential participant understands the study. Participants indicate that they agree to participate and the date informed consent is given is also obtained electronically in REDCap. Informed consent eCRF will be saved electronically in the participant's research record. Participants will also be given a copy of the informed consent document in person at the clinic.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator and NIDCR. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Insufficient adherence to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility.

10.1.3 CONFIDENTIALITY AND PRIVACY

Subject confidentiality is strictly held in trust by the investigators, study staff, and the funding agency and their agents. The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the funding agency.

Any authorized representatives of the funding agency, including the study monitor, may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at our site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Boston University BEDAC. Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by BEDAC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the BEDAC and at GSDM.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies.
It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms

used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Certificate of Confidentiality.
To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in *45 CFR Part 75.303(a)* and *NIHGPS Chapter 8.3*, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

This study will collect saliva sample(s) from participants for biochemical verification of smoking abstinence. This sample will be used to analyze the chemical cotinine, a by-product of nicotine found in the body that is used by many researchers to differentiate between smokers and non-smokers. No other tests or analyses will be performed on these saliva samples. We will store the saliva in a medical grade ultra-low-temperature freezer located at the Boston University medical campus and later ship to Salimetrics (Salimetrics®LLC; a leading company in saliva biomarker research) for cotinine analysis. The samples will only be identified with the study ID number. No identifiable information will be shared with Salimetrics, and no other test will be performed on the saliva samples either by us or other investigators. Samples will be destroyed according to Salimetrics's protocol after cotinine analysis.

We will store paper files in locked filing cabinets, and electronic files in computer systems with password protection and encryption. We will protect information by identifying all of the data we collect including saliva samples with a unique study ID number, which will only be linked to a name through a document kept securely locked at the study team office. Only study team members will have access to this document. The mastercode will be kept for 7 years after the end of the study to allow for reidentification for auditing purposes and in compliance with Boston University policy #FA-002.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor or Independent Safety Monitor**

Belinda Borrelli, Ph.D., (Director and PI). Professor, Boston University, Henry M. Goldman School of Dental Medicine 560 Harrison Avenue, 3rd floor, Boston, MA 02118. PH: 617-358-3358; FAX: 617-638-6381 *belindab@bu.edu*	Not applicable
Institutions:	**NIDCR Program Official:**
Trustees of Boston University, BUMC Office of Sponsored Programs 85 East Newton Street, M-921 Boston, MA 02118-2340 Diane Baldwin Assistant Vice President, Sponsored Programs PH: 617-638-4600; FAX: 617-638-4686 bumc-era@bu.edu	Jill L. Mattia, Ph.D. Behavioral and Social Sciences Research Branch BG NIHBC 31, Room 2C39 31 Center Dr. Bethesda, MD 20892-4878 United States (301) 451-7770 jill.mattia@nih.gov

The Virtual Reality study Leadership Team is comprised of the Principal Investigator, Belinda Borrelli, PhD. Dr. Borrelli is primarily responsible for the oversight of the conduct of the entire study and development and implementation of all policies, procedures and processes. Dr. Borrelli is the Lead/contact PI and will assume fiscal and administrative management including maintaining communication among key personnel. She will also be responsible for communication with NIDCR, NIH and submission of annual reports, and serve as the primary liaison with industry partner, Agile Health (the text messaging platform company) and National Jewish Health (the operator of the Massachusetts smoker quitline contracted by the Massachusetts Department of Public Health, Massachusetts Tobacco Cessation and Prevention Program).
Dr. Carlos Fernando Mourão (D.D.S., M.S., Ph.D.) is the site PI at Tufts University, School of Dental Medicine (Comprehensive Care Clinic and Periodontal Clinic).

The Project Advisory Team is comprised of the Research Project Manager and Co-investigators who serve to facilitate scheduling of study activities at study sites and are also responsible for the logistical aspects of study implementation.

Compliance officers assist the PI in ensuring that the study is conducted according to applicable regulations. Other study staff including the Research Project Manager and research assistants are responsible for conducting study activities according to protocol and will report their activities to the administrative staff and study leadership.

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of the study team with the PI taking primary responsibility. A quality management plan will be in place.

10.1.7 CLINICAL MONITORING

Clinical site monitoring for this study will be performed by the Primary Investigator or designee, in consultation with the NIDCR Program Officer. Monitoring will be conducted to ensure that study processes and documentation are consistent with NIDCR standards, and with guidelines of the

International Conference on Harmonisation (ICH), E6: Good Clinical Practice (GCP), and will include prompt follow-up of any findings or study deficiencies. At a minimum, study activities will be monitored that relate to protection of the rights of human subjects, the implementation of the study in accordance with the protocol and/or other operating procedures, and quality and integrity of study data and data collection methods.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality Management is the overall process of establishing and ensuring the quality of processes, data, and documentation associated with clinical research activities. It encompasses both quality control (QC), and quality assurance (QA) activities.

Ultimate responsibility for implementation and maintaining quality assurance and quality control systems with written operating procedures to ensure that the trial is conducted and data are generated, documented and reported in compliance with the protocol resides with the principal investigators of the study. The project director, BEDAC and Agile Health will provide regular reports on the fidelity and administration of the intervention to the PI. These processes are outlined in the study's Quality Management Plan.

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed**.**

Source documents and the electronic data --- Data will be initially captured on source documents (see **Section 10.1.9, Data Handling and Record Keeping**) and will ultimately be entered into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.
Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2.1, Interventionist Training and Tracking**.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical trial staff at the site under the supervision of the principal investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by Boston University BEDAC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 7 years after the study has concluded. The mastercode will also be kept for 7 years after the end of the study to allow for reidentification for auditing purposes and to be in compliance with BU policy.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or Good Clinical Practice (GCP) requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed and implemented promptly as determined by the IRB.

These practices are consistent with ICH E6:
4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
5.1 Quality Assurance and Quality Control, section 5.1.1
5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the Principal Investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be reported to the BUMC IRB per their guidelines. The CC will provide a facility to log protocol deviations. PIs will be responsible for reporting Reportable PDs (including SDs) and UPs directly to their institutional IRB(s) within the specified IRB timeframe. Per BUMC IRB policy, major deviations are required to be reported in 7 days to the IRB.

All study staff will have weekly reviews with their supervisor to identify compliance to protocol details. Any and all study related meetings will also dedicate time to review the possibility of identifying any protocol deviations. Protocol deviations will be sent to the BUMC IRB per their guidelines. The PI/study staff will be responsible for knowing and adhering to the IRB requirements.
All deviations from the protocol will be addressed in study subject source documents. A completed copy of the NIDCR Protocol Deviation Form will be maintained in the regulatory file, as well as in the subject's source document.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

Data from this study will be shared in accordance with the NIH Data Sharing Policy.
https://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm
The National Institutes of Health (NIH) has issued a policy to promote broad and responsible dissemination of information from NIH-funded clinical trials through ClinicalTrials.gov. The policy establishes the expectation that all investigators conducting clinical trials funded in whole or in part by the NIH will ensure that these trials are registered at ClinicalTrials.gov, and that results information of these trials is submitted to ClinicalTrials.gov. Please see
https://www.federalregister.gov/documents/2016/09/21/2016-22379/nih-policy-on-the-dissemination-of-nih-funded-clinical-trial-information.

10.1.12 CONFLICT OF INTEREST POLICY

To protect against bias or the appearance of bias, investigators on the Boston University Medical Campus (BUMC) (which includes the School of Dental Medicine) must disclose whether they, their spouse, or any of their dependent children have a significant financial interest that could reasonably appear to be affected by the design, conduct, or reporting of covered research. Disclosures are reviewed in accordance with the Boston Medical Campus Policy on Investigators' Conflict of Interest.
Project-Specific Disclosures are required of all Investigators. Each Investigator (defined below) on each research project at BUMC is required to have submitted an up-to-date Project-Specific Disclosure (PSD) form concerning possible financial conflicts of interest as set forth below.

The term "investigator" includes all principal investigators and co-investigators, and other researchers (e.g., graduate students, post-doctoral fellows, and technicians) who are responsible for designing, conducting, or reporting covered research. At any time during the life of the project, a PSD form must be submitted by the Investigator in the event of any material change, specifically:
(1) The investigator is newly added to the project;
(2) There is a material change in the information previously disclosed.

COI forms are maintained at the BUMC Office of Research Administration and copies are kept on file in the regulatory binder and updated as necessary by the Compliance Officer.

10.2 ADDITIONAL CONSIDERATIONS

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
AH	Agile Health
ANCOVA	Analysis of Covariance
BEDAC	Boston University Biostatistics and Epidemiology Data Analytics Center

BUMC	Boston University Medical Campus
BUGSDM	Boston University Goldman School of Dental Medicine
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CRF	Case Report Form
CROMS	Clinical Research Operations and Management Support
DRE	Disease-Related Event
EBT	Evidence-Based Treatment
eCRF	Electronic Case Report Forms
EDR	Electronic Dental Records
GCP	Good Clinical Practice
HHS	Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ICH GCP	International Council on Harmonisation Good Clinical Practice
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
MI	Motivational Interviewing
NCI	National Cancer Institute
NCT	National Clinical Trial
NIDCR	National Institute for Dental and Craniofacial Research
NIH	National Institutes of Health
NRT	Nicotine Replacement Therapy
OCTOM	NIDCR Office of Clinical Trials and Operations Management
OHRP	Office for Human Research Protections
PI	Principal Investigator
PSD	Project-specific Disclosure
QA	Quality Assurance
QC	Quality Control
RA	Research Assistant
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCT	Social Cognitive Theory
SES	Socioeconomic Status
SOA	Schedule of Activities
TU	Tufts University
UIS	Utilization Score Index
UP	Unanticipated Problem
US	United States
VR	Virtual Reality

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

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