

Oral Health 4 Life: Promoting Oral Health among Tobacco Quitline Callers

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial 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.

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*Note: At the time this research was conducted, The Kaiser Permanente Research Institute (KPWHRI) was known as the Group Health Research Institute (GHRI). References to Group Health or GHRI in this protocol are synonymous with KPWHRI.

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LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GHRI	Group Health Research Institute
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
NIDCR	National Institute of Dental and Craniofacial Research, NIH, DHHS
NIH	National Institutes of Health
PPA	Point Prevalence Abstinence
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event/Serious Adverse Experience
UC	Usual Care
UP	Unanticipated Problem
US	United States

PROTOCOL SUMMARY

Title:

Oral Health 4 Life: Promoting Oral Health among Tobacco Quitline Callers

Précis:

Promoting better oral health is a public health priority. Tobacco users, in particular, are at high risk for oral disease compared to non-smokers both as a result of their smoking and the fact that many fail to meet recommendations for basic oral health care, including daily oral hygiene and regular professional dental care.

The current study will test the effectiveness of a multi-modal behavioral intervention (the Oral Health 4 Life program) targeted to smokers who are ready to quit smoking and seeking services through tobacco quitlines. Quitline callers have made a commitment to improving their health and our research suggests most are receptive to learning how to improve their oral health, as well. Moreover, there is reason to believe that promoting basic strategies such as brushing, flossing, or rinsing with fluoride mouthwash in response to cigarette cravings or having a professional dental cleaning to remove tobacco stains could promote better oral health and bolster attempts to quit smoking. Thus, an integrated oral health promotion-tobacco cessation program could have dual benefits.

We will partner with Alere Wellbeing, the nation's largest provider of tobacco quitline services. Leveraging Alere's infrastructure for this intervention increases the likelihood the intervention could be disseminated, if effective.

Smokers (n ~ 742; minimum of 10 and up to ~30 pilot participants and ~712 main trial participants) will be recruited when they call to enroll in services. Eligible smokers who have not received recent dental care will be randomized to either usual care quitline intervention plus control text messaging or an enhanced program which integrates standard tobacco cessation counseling with a multi-modal, behavioral oral health promotion program. The enhanced program includes behavioral counseling, mailed written materials, access to online materials and resources, support/ outreach via text messaging, and referral information for affordable local dental care. Follow-up assessments will be conducted by phone at 2 and 6 months

post-enrollment. Primary outcomes are: receipt of professional dental care following enrollment [yes/no] and self-reported 7 day point prevalent smoking abstinence at 6 months [yes/no]. We hypothesize that persons who receive the enhanced program will be more likely to see a dentist and to quit smoking.

Secondary outcomes and process measures of interest include: whether a participant either receives professional dental care or has scheduled a future dental appointment at 6 months, smoking abstinence at 2 months, and changes in oral health knowledge and relevant attitudes (self-efficacy, motivation, perceived oral disease severity, and outcome expectations/perceived benefits of oral hygiene) at 2 and 6 months. The incremental cost of delivering the Oral Health 4 Life program will also be examined.

Objectives: Primary Objective: To assess the effects of the proposed behavioral intervention on tobacco abstinence and utilization of professional dental services (primary outcomes).

Secondary Objectives:

- Assess the impacts of the enhanced intervention on key secondary behavioral outcomes and select intermediate outcomes/process measures that could mediate treatment effects.
- Determine the effectiveness of the proposed enhanced intervention, whether it warrants dissemination to smokers through tobacco quitline programs nationally in the current form, or whether further refinement and evaluation are warranted.
- Calculate the incremental cost of adding the Oral Health 4 Life program to usual quitline care and create a decision support tool that quitline sponsors (i.e., potential purchasers of the program) can use to inform decisions about whether to offer the program.

Primary Outcome: a) Receipt of professional dental care following enrollment [yes/no]; and b) self-reported 7 day point

prevalent smoking abstinence at 6 months [yes/no; missing cases imputed as smokers].

Secondary Outcomes: a) Whether a person has seen a dental care provider since enrollment or scheduled a future dental appointment at 6 months; b) 7 day point prevalent abstinence at 2 months (with missing cases imputed) and smoking abstinence at the 2 month and 6 month follow-up among respondents only (no missing imputation); c) changes in oral health knowledge; d) and relevant attitudes (self-efficacy, motivation, perceived oral disease severity, and outcome expectations/perceived benefits of oral hygiene) at 2 and 6 months. The incremental cost of delivering the Oral Health 4 Life program will also be examined.

Population:	Male and female adult smokers (n ~ 742) aged 18 or older will be recruited from participating US tobacco quitlines in Oregon, Louisiana, and Nebraska. Those who have not used dental care services in the past 6 months and meet other study criteria (sections 5.1& 5.2) will be eligible to enroll.
Phase:	III
Number of Sites:	Study activities will be conducted at two research sites: Group Health Research Institute (GHRI) and Alere Wellbeing, each located in downtown Seattle. However, participants will be recruited from multiple state tobacco quitline programs managed by Alere.
Description of Intervention:	Participants will receive a multi-modal, behavioral intervention offered in conjunction with standard care tobacco quitline intervention. Oral health promotion intervention will be delivered via behavioral phone counseling, mailed materials (educational self-help information and oral health aids [e.g., toothbrush, floss, etc.]), educational content delivered via a log-in secured study website (OralHealth4Life.com), and additional education and supportive encouragement offered via a series of text messages. Participants will also receive referral information for low cost dental care in their geographic area.
Study Duration:	We estimate it will take about 30 months to complete the proposed RCT. Recruitment will begin at approximately month 7 of the grant phase, depending on the required timeline for finalizing the study materials in collaboration with NIDCR staff. ~742 participants will be enrolled. The first ~10 participants will constitute a vanguard wave. Program refinements will be made,

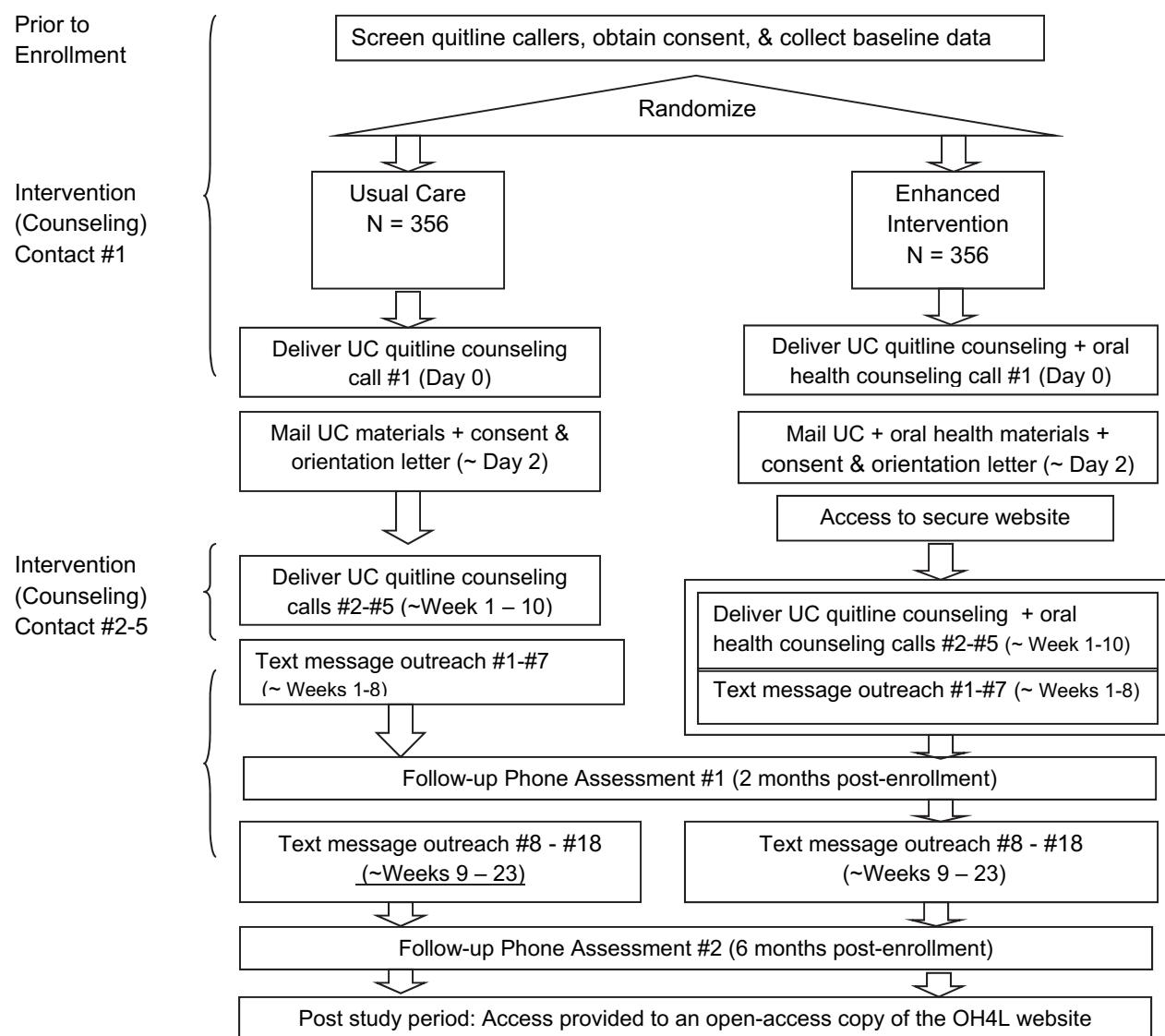
as needed, based on our experience with these participants. Consequently, we have planned a priori to exclude these individuals from the final analytic sample, resulting in a final intent to treat sample of ~712. Recruitment, intervention delivery, and follow-up assessments will continue through approximately month 36. The remainder of the grant period (months 37-48) will be devoted to data management, analyses, interpretation, and dissemination of findings.

Subject Participation Duration:	Each participant will be enrolled for a period of 6 months.
Estimated Time to Complete Enrollment:	We estimate it will take one month to recruit the vanguard participants and up to, but not more than, twenty-three additional months to recruit the remaining participants. Recruitment pace will depend on the call volume at the participating quitlines. If needed, this will be titrated to ensure that the timing and volume of the counseling and follow-up surveys do not outpace staff capacity to complete these on schedule.

Schematic of Study Design (NOTE: Reflects final analytic sample, n ~ 712):

Cohort	Arm 1	n~ 356	Usual Care (UC)
	Arm 2	N~ 356	Enhanced Intervention

Diagram 1: Study Flow for RCT



NOTES: Intervention call timing is tailored for each person, based on their chosen Quit Date. As a result, calls may or may not be complete prior to the 2 month follow-up for all participants. The chosen target Quit Date will also affect the timing of the text messaging. For more detail on the timing of the intervention events, see Appendix A Schedule of Events.

Table 1. Overview of Study Activities by Site

	GHRI	Alere Wellbeing
Recruit, screen, & enroll participants		X
Collect baseline data		X
Provide phone counseling & usual care tobacco cessation services		X
Mail usual care tobacco cessation materials		X
Mail consents, study welcome letters & oral health promotion materials	X	
Manage text messaging	X	
Maintain study website(s)	X	
Conduct follow-up assessments	X	
Mail participant incentives	X	
Conduct fidelity monitoring	X	X
Provide regular data feeds to GHRI		X
Monitor automated data integrity	X	
Provide final cost data	X	X
Management of final analytic datasets	X	
Data analyses	X	
Interpretation of study findings	X	X
Primary responsibility for publication & dissemination of results	X	

1 KEY ROLES AND CONTACT INFORMATION

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Oral disease is a significant public health threat.

Oral disease affects millions of people in the US. It includes common oral diseases such as periodontitis and dental caries, and less common oral and pharyngeal cancers. Together these diseases exact a large human toll. Oral disease not only results in unnecessary pain, potential physical disfigurement, and emotional suffering, it puts individuals at greater risk for subsequent morbidity and mortality¹. Treating acute oral disease and preventing the onset of future oral disease are important public health goals.

Smokers are a priority population for oral health promotion.

Tobacco use accounts for an estimated 90% of oral and pharyngeal cancers, and smoking is the second leading modifiable risk factor for periodontitis.⁶ According to the National Health and Nutrition Examination Survey (NHANES)⁷, current smokers have a higher prevalence of untreated tooth decay (35.0%) than those who never smoked (18.6%) or former smokers (17.7%). Tooth loss is also strongly associated with smoking and more common in current than former or never smokers.⁸ Two-thirds of current US smokers have at least one unmet dental need compared to 55% of non-smokers.⁹ Two-thirds do not have an annual dental visit and, in general, fewer smokers see the dentist than non-smokers.^{10, 11} In addition, many smokers fail to seek routine health care^{12, 13}, have high rates of alcohol use¹⁴⁻¹⁷, poor diets¹⁸, and low levels of important micronutrients due to oxidative stress from smoking and dietary choices¹⁹—all contributing factors in oral disease. Among smokers treated through tobacco quitlines, we have observed similarly high levels of self-reported oral disease (based on current symptoms) and sub-optimal use of dental care and routine oral hygiene behaviors.^{20, 21} In short, smokers represent an important target group for oral health promotion.

2.2 Rationale

Combined oral health promotion and smoking intervention could have synergistic effects.

Promoting better oral health care in conjunction with quitting smoking could enhance efforts to stop smoking and vice versa. Best practice smoking cessation counseling is grounded in cognitive behavioral therapy (CBT).^{22, 23} Standard CBT for nicotine dependence in part teaches smokers to use distraction techniques as a means for managing cravings and resisting the urge to smoke. This technique can be tailored to also promote better oral health by directing smokers to chew sugar-free gum, brush their teeth with fluoride toothpaste, gargle with a fluoride mouth rinse, or floss in response to cravings to smoke. We've found these distraction techniques to be effective

for many people because they offer a distraction to thinking about smoking, introduce taste sensations which are incompatible with smoking, and engage the smoker in behaviors which are physically incompatible with the act of smoking (e.g., one cannot smoke and brush their teeth concurrently). These are important behavioral therapeutic goals. Importantly, each behavior also serves a dual benefit of reducing plaque and promoting better tooth and gum health.^{1, 24-26} Practicing these behaviors during the quit process could lead to their greater integration in one's normal daily hygiene routine by creating mastery experiences, building individual's confidence (self-efficacy) in their ability to engage in these behaviors, and creating positive outcome expectations (e.g., brushing my teeth makes my mouth feel clean and lessens my desire to smoke). These are all important mediators of behavior change.

Moreover, research shows a positive association between smokers' concerns about tooth discoloration caused by tobacco use and their interest in quitting smoking.²⁷ Thus, smokers ready to quit may be particularly receptive to advice to have their teeth cleaned around their quit date, to remove tobacco stains and start their new life looking like the non-smoker they will soon be. Smokers who might not otherwise seek professional dental care may be willing to do so at this time, particularly if the enhanced intervention includes referral to affordable local dental care (as the Oral Health 4 Life program does). And having one's teeth cleaned could provide continued motivation to remain quit. In other words, we believe that a dual focus on better oral health and tobacco cessation could have potentially powerful synergistic effects to improve cessation rates, promote professional dental care utilization, and alter routine oral hygiene care.

Partnering with state-funded tobacco quitlines to promote oral health.

The Office of the Surgeon General⁶ and Centers for Disease Control and Prevention¹ have each called for greater partnerships between the public and private sector and inclusion of health care organizations, health insurers, and health professionals in efforts to promote oral health. With regard to smokers and tobacco users, the emphasis has been placed on empowering dentists and dental hygienists to intervene with their patients to promote tobacco abstinence. However, oral health care professionals often have limited time and resources to provide behavioral intervention and these efforts fail to reach individuals who do not visit a dentist (which may be more than half of smokers calling state-funded tobacco quitlines).²¹ Moreover, many dental professionals are not formally trained in behavioral counseling and simply providing oral health education alone does not result in lasting behavior change.²⁸⁻³³

A complementary strategy for intervening with smokers, particularly those not routinely seeking dental care, is to integrate oral health promotion efforts into tobacco quitline programs. Tobacco quitlines provide behavioral counseling for tobacco cessation, primarily through proactive counseling calls (i.e., calls initiated by the quitline based on a pre-determined call schedule) with supplemental outreach via online materials, mail,

and/or text messaging. Quitlines have been shown to be an effective public health intervention for smoking cessation.³⁴⁻³⁷

All 50 US states offer free tobacco quitline programs funded through state revenues and/or the CDC. All callers are eligible for at least a single counseling call, with uninsured callers and other special populations (e.g., pregnant smokers) eligible for multi-call programs. According to data from the North American Quitline Consortium, nearly 440,000 people received services from state-sponsored quitlines in 2010.³⁸ Across the various state quitline contracts serviced by Alere Wellbeing, more than 279,000 people received services in 2012, nearly 352,000 people received services through all of their service contracts combined in 2012, and more than 2,235,000 people have received services from this company to date. While the largest in the US, Alere is only one of several US tobacco quitline vendors. Thus, tobacco quitlines represent an efficient way to reach a large number of smokers who are also in need of oral health promotion. Furthermore, our research demonstrates quitline callers are interested in improving their oral health (see section 2.3 below).^{20, 21} And because quitline callers are actively seeking treatment, these individuals may be more amenable to an oral health promotion program delivered in conjunction with their tobacco counseling. That is, reaching tobacco users when they enroll in quitline services may represent a 'teachable moment' for change.

Significance & Impact Summary

There is good reason to expect promoting positive oral health care in conjunction with smoking cessation will improve abstinence rates and it is known that quitting smoking improves oral health outcomes.¹ Additionally, increasing utilization of professional dental care can reduce risk of disease and allow existing pathology to be treated, possibly preventing more serious and costly future disease. Thus, it is reasonable to promote better oral health in tandem with nicotine dependence treatment. Working through the tobacco quitlines is an innovative strategy to test this approach. More importantly, this partnership enhances the public health significance of the research because our intervention has been carefully designed in collaboration with the largest US tobacco quitline provider so it can be disseminated on a national level, if effective. As such, this work holds the potential to improve oral health care, cessation rates, and oral health outcomes among hundreds of thousands of smokers nationwide. Finally, this study will provide important information about the added cost of the Oral Health 4 Life program to inform quitline purchasers' (payers) future decisions about offering this program.

Innovation

Good oral health is good public health. Promoting better oral health among smokers should not be shouldered by professional dental care professionals alone. This study represents the first time tobacco quitlines, or any nicotine dependence treatment program to our knowledge, have been leveraged to promote better oral health care and

smoking cessation. This study will provide critical information about the effectiveness and additional cost of this public health intervention strategy for promoting abstinence and use of dental health services. It also offers an important complement to ongoing efforts in many dental care settings to promote smoking cessation and refer patients to the tobacco quitlines.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Potential risks include breach of confidentiality and discomfort associated with answering research questions.

Persons who stop smoking may experience symptoms of nicotine withdrawal (e.g., irritability and mood changes, headaches, trouble sleeping, constipation, cravings to smoke). These are typically transient and resolve within a few weeks after cessation. Nicotine withdrawal symptoms may be reduced in smokers who use nicotine replacement therapy (NRT) as an adjunct to the quitline counseling; however, they may experience side-effects associated with NRT patch including headaches, nausea, trouble sleeping, and rash/irritation at the local patch site. These symptoms are typically temporary and resolve either within a few days or upon discontinuation of NRT. Participants in this study may be eligible to receive NRT as per the standard of care provided by each participating quitline.

Participants who visit a dentist or increase their routine brushing and flossing may experience mild and temporary discomfort or gum bleeding (e.g., from tooth cleaning or flossing). This will resolve with continued regular oral hygiene.

2.3.2 Potential Benefits

Participants may quit smoking. As a result, they may reduce their risk of chronic disease onset or exacerbation, save money, and benefit from the good feeling of knowing that they are tobacco free.

Participants who see a dentist or change their routine oral health care can reduce their risk for future oral disease, may experience improved cosmetic appearance and self-esteem, and may experience reduced halitosis or tooth stains.

All participants in the experimental arm may benefit from increased awareness of proper oral hygiene behaviors and receipt of provided oral hygiene tools (e.g., toothbrush, floss, etc.). Those who also change other relevant behaviors such as limiting or reducing sugary beverages and alcohol use or increasing fruit and vegetable intake could experience additional positive health effects. The positive health effects include better oral health, reduced weight, and/or reduced risk of chronic disease onset or exacerbation.

All participants, regardless of intervention arm, may benefit from the sense of well-being associated with contributing to research.

3 OBJECTIVES

3.1 Study Objectives

The primary objective of this study is to assess the effects of the proposed behavioral intervention on tobacco abstinence and utilization of professional dental services.

The secondary objectives of this study include:

- Assess the impacts of the enhanced intervention on key secondary behavioral outcomes and select intermediate outcomes/process measures that could mediate treatment effects.
- Determine the effectiveness of the proposed enhanced intervention, whether it warrants dissemination to smokers through tobacco quitline programs nationally in the current form, or whether further refinement and evaluation are warranted.
- Calculate the incremental cost of adding the Oral Health 4 Life program to usual quitline care and create a decision support tool that quitline sponsors (i.e., potential purchasers of the program) can use to inform decisions about whether to offer the program.

The results of this project will inform whether the proposed intervention warrants further evaluation or dissemination through tobacco quitlines based on its effectiveness and help purchasers make informed decisions about providing the program.

The intervention will be offered to people seeking treatment for smoking cessation through one of the participating state-funded tobacco quitlines and will reach a high-need, lower-income population who are eligible for these free services.

Additional detail on the proposed enhanced intervention is included in sections 6 and 7.

3.2 Study Outcome Measures

Study outcome measures are discussed below. Copies of the baseline and follow-up assessment measures are included in Appendices B and C.

3.2.1 Primary

Smoking abstinence. Per convention, this will be assessed by a self-report of no smoking, even a puff, in the past 7 days assessed at 6 month follow-up (i.e., 7 day point prevalent abstinence). Missing data will be imputed using a worst case scenario in which individuals with missing outcomes will be assumed to be smoking for the main outcome analyses.

Professional dental care in the past 6 months. This will be assessed by a self-report of professional dental care in the past 6 months at the 2 or 6 month follow-up using the a standardized National Health Interview Survey (NHIS) item. Missing data will be imputed using a worst case scenario in which individuals with missing outcomes will be assumed to have not seen the dentist for the main outcome analyses.

We will use a ‘bogus pipeline’ strategy to encourage valid self-reported dental care utilization. Per this standard social psychology methodology, participants are told in advance their answers may be verified (e.g., we may contact their provider), thereby promoting more truthful reporting. We will also inform participants we are collecting the names and contact information for their dental care providers, again to discourage false reporting of service utilization (see scripting in follow-up surveys, Appendix C).

3.2.2 Secondary

Secondary behavioral outcomes and process variables of interest are:

- **Smoking abstinence** assessed at 2 month follow-up (7 day point prevalent abstinence [PPA] with missing cases imputed). Additionally, we will assess abstinence at 2 and 6 months using a complete case (respondent only) analysis where missing data values are not imputed, to determine if imputation has a meaningful effect on the study results.
- We will assess whether groups differ in terms of the proportion of participants who either seek professional dental care following enrollment or have a future appointment scheduled at 6 months.
- Change in **oral health knowledge** from baseline to 2 and 6 month follow-up will be assessed using a scale adapted from Brennan et al⁴⁵ to address oral health behaviors (as opposed to tooth decay); include smoking, alcohol use, sugar free gum, and fruits and vegetables intake; and modify scripting for better phone delivery.
- Change in self-reported **self-efficacy** and **motivation** from baseline to 2 and 6 month follow-up. Self-efficacy and motivation will be assessed using a 5 point Likert-type scale.

3.2.2.1 Customer Satisfaction and Qualitative Feedback

Feedback will be collected at the end of the 6 month assessment. All participants will be asked to rate how helpful and how satisfied they were with each component of the

UC intervention (e.g., calls with a quit coach, Quit for Life stop smoking website, mailed stop smoking materials, nicotine replacement, etc.). Helpfulness and satisfaction will be rated on a 5-point Likert scale from “not at all” to “helpful”. Participants receiving the enhanced intervention will also rate each component of the Oral Health 4 Life program (e.g., oral health counseling, mailed materials, log-in secured website, oral health aids, referral information for low cost dental care, etc.). Finally, enhanced intervention participants will be asked a series of open-ended questions about which enhanced intervention components they used, what they liked best, and what they liked least. Responses will be transcribed verbatim for future content analysis.

3.2.2.2 Cost Analysis Measures and Outcomes

Because the goal of the current study is to assess the degree to which the Oral Health 4 Life program increases the likelihood of both quitting smoking and visiting a dentist and each of these outcomes may be of interest to different purchasers, we will provide a detailed assessment of the costs for each outcome. The analysis will examine the incremental cost of adding the Oral Health 4 Life program to the standard quitline program from the purchaser/payer perspective.

We will assess the estimated additional **cost per counseling call** for which the Oral Health 4 Life program is included and the **cost per successful cessation event**, based on six month outcomes. These calculate these costs we will estimate all resources required to develop and maintain the intervention materials (print and web-based), the increased personnel time to provide oral health counseling, and other outreach services related to Oral Health 4 Life (e.g., text messaging). All associated effort, labor costs, and material costs associated with delivering of the intervention will be tracked at GHRI and Alere.

We will also calculate the **cost per dental visit** attributable to the Oral Health 4 Life program and the **cost per both a successful cessation event and dental visit**, each assessed based on primary 6 month outcomes. The **cost per dental visit** will be assessed as the amount reimbursed by providers for routine preventive office visits. This is appropriate because our analysis takes the payer/provider perspective and while the amount reimbursed per visit is not the cost incurred by the practice it does capture the payer's financial responsibility. We will not include patient incurred costs, whether due to lost productive time or out of pocket expenses, because these costs are not the payer's responsibility. Because we will not have claims data containing details about specific reimbursable services provided at each visit attributable to the Oral Health 4 Life program, we will assign the mean dollar amount dental practices are reimbursed for

preventive visits based on relative resource intensity weights using the American Dental Association's Current Dental Terminology (CDT) coding scheme.

These data will then inform the creation of a 'willing to pay' decision support tool for future quitline sponsors that will allow purchasers (e.g., state departments of health) to calculate the cost per quit and cost per dental visit using data from the study.

4 STUDY DESIGN

We will conduct a randomized, two arm trial including a small vanguard wave (n up to ~30) followed by a larger intent to treat sample wave (n ~ 712). The design and methods used in each sample wave will be the same, except the vanguard will launch approximately 2 months prior to the main sample wave in order to pilot all methods and procedures and allow time to make adjustments, as necessary. Participants in the vanguard wave will not be included in the final analytic sample.

Participants will be smokers who call to enroll in services in one of the participating quitlines [Louisiana, Oregon, and Nebraska], meet eligibility criteria (see sections 5.1 and 5.2), and volunteer to participate in this study. Each person will be followed for 6 months and will complete phone surveys at baseline, 2 months post-enrollment, and 6 months post-enrollment.

While not a formal pragmatic trial, the study has been designed to be delivered under the conditions of real-world care provided by the tobacco quitlines. As a result, study assessments, consent processes, and other activities which are not part of the standard of care have been purposefully designed to be brief in order to minimize the impact on the standard flow of care, while still allowing us to assess the most important primary and secondary outcomes of interest.

Additionally, due to the nature of the trial, neither participants nor counselors (quit coaches) in the enhanced intervention (experimental arm) will be blinded to participants' treatment assignment. Quit coaches delivering usual care will be aware that participants' are enrolled in a non-standard contract (e.g., a research study), but they will not be trained in or exposed to the enhanced intervention to prevent contamination. Group Health research staff who conduct follow-up assessments will be blinded to treatment assignment.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Subject Inclusion Criteria

In order to be eligible to participate in this study, a participant must meet all of the following criteria (see also Eligibility Screen in Appendix D):

- Male or female, aged 18 or older
- Eligible for multi-call services through a participating tobacco quitline [in Louisiana, Nebraska, or Oregon] managed by Alere Wellbeing
- Can read and speak in English
- Able to comfortably read small print (i.e., no significant visual impairments that limit ability to read the intervention materials)
- Current daily smoker and smokes at least 5 cigarettes a day
- Interested in quitting smoking in next 30 days
- Have some or all natural teeth
- Have not visited a dentist for a checkup or teeth cleaning in the past 6 months and do not have an appointment scheduled in the next 6 months
- Has a cell phone capable of receiving text messages and provides cell phone number
- Has internet access for personal use
- Willing to talk about ways to improve their oral health
- Provides verbal consent to participate

5.2 Subject Exclusion Criteria

Individuals will be excluded if they:

- Self-report a diagnosis of bipolar disorder, mania, schizophrenia, dementia (e.g., has significant cognitive impairment)
- Plans to move in the next 6 months
- Are currently enrolled in an in-patient substance abuse treatment facility or are incarcerated

- Has a household member already enrolled in the study, based on self-report and/or mailing address on file

5.3 Strategies for Recruitment and Retention

Recruitment: Following completion of the normal tobacco quitline registration process, persons calling each of the eligible quitlines and who have not been deemed ineligible based on screening criteria which are collected as part of the normal intake will be informed of the study and invited to complete the eligibility screening process. If eligible and interested, potential participants will then be transferred to staff in the Research Implementation Unit (RIU). RIU staff will collect and document verbal consent. Responses will be recorded. Participants who provide consent will complete a baseline assessment and then be randomized to treatment using an automated algorithm, prior to the treatment initiation.

If participants do not complete the study enrollment call due to dropping off/hanging up the RIU coach will make five attempts on five separate days to be attempting to get them back to complete enrollment. Call attempts will begin the same day or the following day that the call is lost. One voicemail will be left for participants that consented to receiving voicemails during Registration. Staff will stop trying to enroll the participant after five call attempts go unanswered.

Retention: We will use standard procedures to ensure study retention, including offering an incentive for completion of each survey (\$30), sending reminder letters one week prior to each scheduled assessment and marked for return service requested, and using phone and internet records to track participants who move and do not have a change of address on file with the Post Office or Alere Wellbeing. Difficult to reach subjects will be texted an offer of an extra \$15 incentive if they call in to complete the survey by phone.

Phone counseling calls will be proactively scheduled and initiated by Alere quit coaches on the standard call schedule (see section 7.3). Consistent with standard practice as dictated by each quitline contract, at least 3 attempts will be made to complete each of the 5 counseling calls with all participants. Text messages are offered to all study participants. The text messages will be proactively delivered on a pre-determined schedule with automated delivery (see section 7.3).

Participants who request to drop out of the intervention will be asked if they are willing to remain in the study and be contacted for follow-up assessment. If not, they will be dropped from further contact.

5.4 Treatment Assignment Procedures

5.4.1 Randomization Procedures

Eligible participants who provide consent will be block randomized using an automated algorithm built into the Alere systems software. Randomization will be stratified based on whether participants have dental insurance coverage [yes/no] and which tobacco quitline they are enrolled in [Louisiana, Nebraska or Oregon], to ensure balance across each treatment arm. Participants will then be randomly assigned to either the usual care quitline program or an enhanced quitline program (usual care tobacco quitline program + multi-modal oral health promotion intervention).

Randomization assignments will be monitored by the study biostatistician to confirm balanced assignment between groups. Unless anomalies are noted in the group assignments, such as due to a programming error, no changes will be made to the randomization code.

5.4.2 Masking Procedures

Intervention: Due to the nature of the trial, neither participants nor counselors (quit coaches) in the enhanced intervention (experimental arm) will be blinded to participants' treatment assignment. Quit coaches delivering usual care will be aware that participants' are enrolled in a non-standard contract (e.g., a research study), but they will not be trained in or exposed to the enhanced intervention to prevent contamination.

Assessment: GHRI staff conducting follow-up assessments will be blinded to treatment assignment.

5.5 Subject Withdrawal

Subjects may withdraw voluntarily from the study or the investigator may terminate a subject's participation.

5.5.1 Reasons for Withdrawal

Subjects are free to withdraw from participation in the study at any time upon request.

An investigator may terminate a study subject's participation in the study if:

- Any adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation. For example, the participant is found to be ineligible after enrollment (e.g., prior household member enrolled).

5.5.2 *Handling of Subject Withdrawals or Subject Discontinuation of Study Intervention*

Participants who request to drop out will be given the option to withdraw from participation in the intervention only, but to still participate in the follow-up evaluations. Participants who refuse this offer and request to completely withdraw from the study will no longer be contacted. However, previously obtained data will be retained with subject consent.

We will not recruit replacement participants for drop-outs. Persons who withdraw as a result of an adverse event will be referred for appropriate care.

5.6 Premature Termination or Suspension of Study

This study may be prematurely terminated if, in the opinion of the investigator, the sponsor or the IRB there is sufficient reasonable cause. Written notification, documenting the reason for study termination, will be provided to the investigator and/or sponsor by the terminating party. 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.
- Failure to obtain sufficient follow-up data to evaluate the effectiveness of the intervention.

If the study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

6 STUDY INTERVENTION

6.1 Study Behavioral or Social Intervention(s) Description

Participants will be randomized to receive usual care treatment through their tobacco quitline or the enhanced intervention combining usual care with a multi-modal behavioral oral health promotion program.

Usual care: Usual care participants will receive standard quitline counseling as described below (section 7.3):

- Written usual care resources offered by mail and Internet, as consistent with the standard quitline intervention program
- Access to a standard course of nicotine replacement therapy, if medically appropriate.

All materials are focused on tobacco cessation and do not include oral health promotion materials. Average call duration in the participating quitlines ranges from 13.76 minutes (Oregon) to 14.36 minutes (Nebraska). To control for the effects of the texting intervention, we will augment usual care with an attention-matched texting outreach focused on health behaviors other than smoking cessation or oral health promotion. Additional detail on the texting program is included appendix G.

The intervention protocol for the usual care counseling is proprietary and is not described in this protocol. Standard program components for each state's program is detailed in the table below. Additional information regarding call timing can be found in section 7.3.

	Phone Counseling	Web-based Intervention	Text Messaging	Nicotine Replacement
Oregon	4 proactive calls	Yes	Not currently	2 week supply patch/gum to uninsured
Nebraska	5 proactive calls	Yes	Not currently	None
Louisiana	5 proactive calls	Yes	Not currently	2 week supply patch or gum

Enhanced (Experimental) Intervention: Experimental participants will receive the following care:

- usual care tobacco quitline counseling
- additional counseling content focused on oral health promotion
- mailed oral health promotion materials
- access to the OralHealth4Life.com log-in secured website and
- a series of proactively delivered oral health promotion text messages.

Materials also include referral information for local, low cost professional dental care services, a toothbrush, floss, and other oral health hygiene materials. Additional detail on the intervention and timing of the contacts is summarized below in section 7 and outlined in Appendix A (Schedule of Events).

Intervention content is included in Appendix G (Oral Health 4 Life booklet), Appendix F (Counseling Protocol and Training Materials), Appendix G (Text Messages and Delivery Schedule), and at www.OralHealth4Life.com (*website access is restricted during the study period*).

6.2 Administration of Intervention

The timing of each intervention component is detailed below in section 7 (Study Schedule), Diagram 1 (Study Flow for RCT), and Appendix A (Schedule of Events).

All phone counseling will be delivered by quit coaches at Alere Wellbeing. Oral health counseling will be integrated into each tobacco cessation counseling call following a structured intervention protocol. Each participant may receive up to 5 integrated oral health promotion-tobacco cessation counseling calls.

Written oral health materials and other study-provided oral health aids (e.g., toothbrush, floss) will be mailed to participants by staff at GHRI. Materials will be mailed within 1-2 days after participants enroll in the study.

Participants will have secure access to the OralHealth4Life website (OralHealth4Life.com) starting on the day of their enrollment. Directions for accessing the site will be provided during the initial counseling call and included in the written study materials provided by mail. Following the study, open-access copies of the website will be made available to participants randomized to both study arms.

GHRI staff will oversee delivery of the intervention text messages, which will be sent on a standardized schedule (see section 7.3). Participants will receive up to 16 total text messages during the period ranging from the day before their chosen target smoking Quit Date to 22 days following their target Quit Date. Persons who request to stop receiving text messages will be opted out of receiving messages at that time.

6.3 Procedures for Training Interventionists and Monitoring Intervention Fidelity

Usual care counselors will be trained by Alere using their standard protocols and procedures. These counselors will also be informed about the basic study overview in order to field general questions from participants, but will not be trained on or have access to the oral health counseling protocol.

Counselors delivering the enhanced intervention will be trained to deliver usual care smoking intervention and the oral health counseling by Alere staff. Training in the oral health content will be led by Alere staff, under the direction of Drs. McClure and Catz. The additional oral health counseling will be added to the usual care counseling for subjects receiving the enhanced intervention.

Calls (usual care and enhanced) will also be audio taped per Alere's standard protocol and a random sample involving at least 10% of calls will be monitored and coded for fidelity to the study protocol. More calls will be monitored, as needed, based on observation of interventionist drift or as needed to monitor the enhanced intervention, in particular.

6.4 Assessment of Subject Compliance with Study Intervention

Compliance with the counseling will be monitored through automated tracking of participants' quitline calls (e.g., number of calls taken, duration of calls).

Participants will also be surveyed about their utilization of the written content, log-in secured website, and text messages.

7 STUDY SCHEDULE

7.1 Screening (Call 1, Day 0)

Persons who are eligible for services through one of the participating quitlines and preliminarily eligible for the study based on eligibility criteria assessed as part of the standard quitline registration process will be informed of the study and invited participate. They will be screened for eligibility at the time of their initial quitline registration call. The screening will be conducted by phone by Alere staff trained in the study procedures. Respondents will answer each screening eligibility question. If a caller refuses to answer any screening questions or fails to meet the inclusion criteria above, they will be deemed ineligible. The screening assessment will continue until a person is deemed ineligible or the entire survey is completed.

Eligible persons will be invited to learn more about the study and will be read a scripted informed consent. Persons who give verbal consent to join the study will then complete a baseline assessment by phone and be randomized to treatment. Following enrollment, participants will be mailed a written copy of the consent form for their records (Appendix H).

Alere staff will document the consent process for each person including whether they agreed to provide consent to be screened [yes/no] and/or to enroll in the study [yes/no].

Each person will receive a screening disposition of:

- Ineligible (with the reason coded)
- eligible but refused
- or eligible and enrolled

7.2 Enrollment/Baseline (Call 1, Day 0)

Following completion of the consent process, participants will complete a baseline phone interview and be randomized to treatment using the automated algorithm. Persons who are randomized to usual care will then be transferred to a usual care quit coach. The quit coaches will have no training in or exposure to the enhanced intervention protocol in order to prevent contamination. Persons assigned to the experimental arm will receive counseling from a quit coach in Alere's Research Implementation Unit who has been trained in the enhanced intervention protocol. [NOTE: This contact occurs during the same registration call as the screening, consent, and baseline interview.]

7.3 Intermediate Visits

7.3.1 *Control Intervention*

Participants randomized to the control condition will receive standard quitline counseling, plus usual care resources offered by mail, Internet, as consistent with the standard quitline intervention program. All materials are focused on tobacco cessation and do not include oral health promotion content. The intervention protocol for this counseling is proprietary and is not detailed here. All standard intervention materials will be delivered by Alere per standard procedures. Control participants will also receive an attention-matched texting program. Texts will be sent on the same delivery schedule detailed below for enhanced intervention participants.

The call schedule is tailored for each person, based on their availability, planned quit date(s), and continued program engagement, but generally follows the timeline below:

- Call 1: Enrollment call/treatment session 1 (pre-target Quit Date [QD])
- Call 2: QD or QD +1 day (~week 1-2 after Call 1)
- Call 3: QD + 1-2 weeks (~week 2-4 after Call 1)
- Call 4: Call 3 + 3 weeks (~week 4-6 after Call 1)
- Call 5: Call 4 + 3 weeks (~week 6-10 after Call 1)

Following completion of the first counseling call, usual care participants will receive a welcome letter, \$30 thank you, and a written copy of the study consent form for their records (Appendix H). These materials will be mailed by GHRI study staff.

7.3.1.1 Post-Study Access to Website

Following completion of the study, control arm participants will be sent a link via text and mail to an open-access copy of the study intervention website. Anonymous administrative usage statistics will be collected (e.g., number of page hits, time spent per page, etc.) for the control arm copy of the open-access website.

7.3.2 *Enhanced Intervention: (Usual Care + Oral Health Promotion)*

7.3.2.1 Phone Contact 1 & Mailed Materials

Participants assigned to the enhanced intervention will receive standard quitline counseling plus additional counseling focused on oral health promotion. Following completion of this call, participants will be mailed usual care tobacco cessation materials by Alere Wellbeing staff. GHRI staff will mail an oral health promotion packet to the subjects randomized to receive enhanced intervention. The packet will include a study welcome letter, a written oral health booklet (Oral Health 4 Life: A Quick Guide to

Better Oral Health) developed for study participants, access to the OralHealth4Life.com log-in secured study website which includes additional oral health promotion resources and information, oral health promotion supplies (e.g, toothbrush, toothpaste, floss), a copy of the written consent form, and a \$30 thank you.

Additional behavioral intervention will be delivered during future phone counseling sessions as outlined in the interventionist training materials and via text, as described below.

7.3.2.2 Phone Contact 2-5

Participants will be contacted by phone per the standard Quit for Life tobacco cessation program timeline and outreach protocol. This is a 4 or 5 call program, depending on the state contract. Call 1 occurs prior to the quit date. Call 2 occurs within a day of the target quit date (TQD). Calls 3-5 are typically scheduled following the TQD. During each of these counseling calls, participants will receive standard cessation counseling plus additional counseling to promote better oral health outcomes. This includes advising all participants to schedule a dental check-up/cleaning in the near future, advising them to brush and floss daily, providing information about the health benefits of routine oral hygiene and risks of tobacco and alcohol to oral health; and recommending participants engage in strategies designed to both help them stop smoking and promote oral health (e.g., promoting use of sugar free gum, tooth brushing, and flossing as strategies for distracting oneself from smoking and managing cravings). The oral health promotion counseling is designed to be 'front loaded' in calls 1-3, with booster content reviewed in calls 4 and 5. Additional detail is included in the Oral Health 4 Life Counseling Protocol and Training Materials (Appendix F).

7.3.2.3 Text Messaging (Enhanced Intervention Group)

Participants will receive a series of text messages designed to reinforce the pro-oral health messaging delivered by the quitline counselors and promote use of the Oral Health 4 Life log-in secured website. The messages and timing were developed through an iterative process involving focus group feedback and feedback from individual smokers to ensure appropriate content, timing, and frequency of contacts. Messages are intentionally brief and do not exceed the maximum 160 SMS character limit, to prevent wrapping across multiple text messages or truncation. Message content was designed to be responsive to smokers' specific requests for information and encouragement for behavior change. Message timing was also based on feedback provided by smokers, although the messaging will be less frequent than the daily schedule focus group participants requested.

Text messages will be delivered on a standardized schedule based on each person's initial target tobacco quit date (TQD), as follows:

- One day prior to the TQD

- One message per week from TQD + 1 week to TQD + 8 weeks
- One message every 2 weeks from TQD + 14 weeks through TQD + 22 weeks.

The same schedule will be used to send text messages in the control arm (see message content in Appendix G).

To ensure consistent delivery and adherence to the planned schedule, GHRI staff will set up automatic delivery of all messages within 3 days of enrollment. All text messages will be managed through an online text messaging vendor program.

Participants will be informed not to respond to text messages. If they do, they will receive an automated reply which informs them we cannot respond directly to their text and directs them to the Oral Health 4 Life log-in secured website or to a quitline counselor for more information.

Participants can request to discontinue receiving text messages and remain enrolled in the study.

7.3.2.4 Website

Participants in the enhanced intervention will receive access to the OralHealth4Life.com log-in secured website. This site includes similar, but expanded, content to that in the Oral Health 4 Life pamphlet including detailed information on where to find local, low-cost professional dental care in each participating state. Content was developed through an iterative process including feedback from oral health specialists (dentist, periodontist, & oral pathologist), behavioral scientists, and smokers participating in focus groups and individual usability evaluation assessments. Access to the site will require a log-in ID and password, in order to track individual use of the website.

7.3.2.4.1 *Post-Study Access to Website*

Log-in requirements are known to present a barrier to use. Therefore following completion of the study, enhanced intervention participants will be sent a link via text and mail to an open-access copy of the study website. Anonymous administrative usage statistics will be collected (e.g., number of page hits, time spent per page, etc.) for the intervention arm copy of the open-access website..

7.3.2.5 Follow-up Assessments

Follow-up phone surveys will be conducted by the GHRI Survey Research Program at 2 and 6 months post-enrollment. Each participant will receive a reminder letter and text message approximately one week prior to their interview due date. Professional interviewers will then contact each person by phone to complete the standardized interview.

Persons who are reached by phone but who decline to participate in the full interview will be asked to provide information on each of the main outcomes of interest. Each

person who completes an interview (full or abbreviated) will be mailed a thank you letter and \$30 check or gift card as a thank you for their time.

During each follow-up contact, survey staff will confirm that the contact information on file is correct for each participant (mail address, cell phone number, home number, and email address).

Persons who cannot be reached within 2 weeks of their scheduled due date will be mailed a written survey to complete and return by mail. Persons who are not reached by phone and do not return the written survey within 4 weeks post-due date at 2 month follow-up or 6 weeks post-due date at 6 month follow-up will be coded as unable to reach. Other response options include: refused, deceased, and unknown.

7.4 Withdrawal Visit

Participants who ask to withdraw from all future study contacts (intervention and assessment) will be allowed to do so. We will not conduct an early termination visit, but individuals will be asked their reason for drop out and may be asked to provide information on the primary outcome variables if drop out occurs within ~ one month of a scheduled follow-up assessment. These interviews will be conducted by study staff at GHRI.

7.5 Unscheduled Visit

Since phone counseling is delivered proactively by tobacco quitline staff in accordance with a standardized timeline, there will be no unscheduled intervention visits. Per the quitline protocol, participants can call in at any time to receive ad-hoc tobacco cessation counseling. If they occur, these contacts will be separate from the intervention delivered as part of this trial, but their occurrence will be tracked by Alere for study purposes. Oral health counseling will be included in these calls. If the quit coach neglects to deliver the oral health counseling, a call back will be made to attempt to deliver this content.

8 STUDY PROCEDURES /EVALUATIONS

Standard operating procedures for the study will be detailed in the Manual of Procedures (MOP), which will be provided to study staff prior to study start-up. Overviews of the procedures are provided here. Data collected will be directly entered into our electronic data collection system.

Additional detail regarding study procedures are included in sections 3.2.1, 5, 6, and 7 above. Baseline and follow-up surveys can be found in the Appendices.

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

This is a minimal risk behavioral intervention. Nevertheless, adverse events (AEs) will be recorded and reported over the course of the study as outlined below:

9.1.1 *Unanticipated Problems*

The Office for Human Research Protections (OHRP) considers unanticipated problems (UP) 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.

9.1.2 *Adverse Events (AE)/Serious Adverse Events (SAE)*

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

9.1.3 *Expected Adverse Reactions*

Persons who visit a dental professional or change their daily oral hygiene regimen may experience temporary changes in gum bleeding or tooth sensitivity.

Because the study will use phone, mail, and Internet to communicate with participants, it is possible that others may learn of their participation in this study (e.g., breach of confidentiality). Expected AE's in this study are generally considered to be mild (easily tolerated) to moderate (discomfort with some interference in usual activities), but not severe (incapacitating).

Persons who stop smoking may experience symptoms of nicotine withdrawal.

See additional discussion of potential adverse reactions in section 2.3.1(Potential Risks).

9.2 Time Period and Frequency for Event Assessment and Follow-Up

Unanticipated problems will be recorded in the data collection system throughout the study.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, Alere staff will inquire about and record the occurrence of AE/SAEs since the last contact. Events will be followed for outcome information until resolution or stabilization.

9.3 Characteristics of an Adverse Event

9.3.1 Relationship to Study Intervention

AE's deemed possibly related to the study intervention by Alere staff and Dr. Bush will be shared with the PI (Dr. McClure), who will make a final determination whether each AE is due to study involvement. The following guidelines will be used. [NOTE: Some AE's associated with quitting smoking, but which are not clearly associated with study participation will not be passed on to the PI by Dr. Bush or Alere staff. For example, AE's which are deemed to be related to the stop smoking medication use. These will be managed per Alere's standard internal protocols for medical oversight.]

- Associated – The event is temporally related to the study participation and no other etiology explains the event.
- Not Associated – The event is temporally independent of study participation and/or the event appears to be explained by another etiology

9.3.2 Expectedness of SAEs

The NIDCR Medical Monitor and the Study PI will be responsible for determining whether an SAE 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.

9.3.3 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.

9.4 Reporting Procedures

9.4.1 *Unanticipated Problem Reporting to IRB and NIDCR*

Incidents or events that meet the OHRP criteria for unanticipated problems will be reported to the IRB. Unanticipated problem reports will include:

- 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

Reporting of Unanticipated Problems to NIDCR is accomplished by submission of an Unanticipated Problem Report via fax or email to Rho Product Safety. Once submitted, Rho Product Safety will send a confirmation email to the investigator within 1 business day.

UP Reporting Contact Information:

- Product Safety Hot Line: 1-888-746-7231
- Product Safety Fax Line: 1-888-746-3293
- Product Safety Email: rho_productsafety@rheworld.com

9.4.2 *Serious Adverse Event Reporting to NIDCR*

Any AE meeting the specified Serious Adverse Event criteria will be submitted on 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 Hot Line: 1-888-746-7231 (International: 919-595-6486)

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

General questions about SAE reporting can be directed to the Rho Product Safety Help Line (available 8:00AM – 5:00PM Eastern Time) at 1-888-746-7231 or 919-595-6486.

The study PI or Project Manager will complete a Serious Adverse Event Form 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 sent by fax or email 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 or email within 72 hours of site awareness.

Other supporting documentation of the event may be requested by the pharmacovigilance contractor and should be provided as soon as possible.

All SAEs will be followed until satisfactory resolution or until the PI or Sub-investigator deems the event to be chronic or the patient to be stable

9.5 Halting Rules

Study halting may occur as required by the IRB, NIDCR, or DSMB. The study PI may temporarily suspend enrollment pending review by these authorities if warranted based on the presence, type, or frequency of SAE's or other changes in the study protocol which may place participants at greater than anticipated risk.

10 STUDY OVERSIGHT

A Data and Safety Monitoring Board (DSMB) will be convened to periodically review and evaluate the accumulated study data for participant safety, study conduct and progress. Efficacy will not be explicitly monitored as it will not be possible to assess the intervention's efficacy in a meaningful way based on an incomplete sample and the study's low risk level. The DSMB will also make recommendations to NIDCR concerning the continuation, modification, or termination of the study.

The Board will consist of 6 voting members chosen by NIDCR for their expertise in tobacco cessation treatment, quitline counseling, oral health, or biostatistics. The NIDCR Medical Monitor will be a blinded, non-voting member of the Board. The Board will meet at least once a year while the study is actively recruiting or providing intervention to participants, but may meet more frequently as deemed necessary by the Board members. The DSMB will operate under the rules of an NIDCR-approved charter that will be written at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will advise NIDCR of its findings. Reports will also be shared annually with the IRB as required.

Confidentiality will be maintained during all phases of the DSMB review and deliberations. Only voting members will have access to interim analyses of outcome data identified by treatment group, except as noted or required by the DSMB.

All DSMB activities will be in compliance with NIDCR guidelines at note at <http://www.nidcr.nih.gov/Research/ToolsforResearchers/Toolkit/DSMBGuidelines.htm>.

11 CLINICAL SITE MONITORING

Clinical site monitoring will not be done for this study; however, the NIDCR reserves the right to conduct independent audits or clinical monitoring as necessary.

12 STATISTICAL CONSIDERATIONS

12.1 Study Hypotheses

All hypotheses tested will be evaluations of superiority of the enhanced intervention (UC cessation counseling + oral health promotion program) compared to UC (UC cessation counseling). Null hypotheses assume that participants in the enhanced intervention group are equal to the participants in the UC group. We hypothesize that, compared to people in the UC arm, participants in the enhanced intervention will:

- a. Be more likely to quit smoking as evidenced by 7 day PPA rates at 6 month follow-up (primary outcome) and at 2 month follow-up (secondary outcome)
- b. Be more likely to see a dental care professional in the past 6 months at 6 month follow-up [primary outcome] or at least be more likely to seek dental care or have scheduled a future appointment [secondary outcome].
- c. Exhibit more positive change in relevant oral health knowledge/beliefs and attitudes (e.g., self-efficacy, motivation) that could influence future behavior change [secondary outcomes].

We hypothesize that positive change in participants' knowledge, attitudes, and beliefs at 2 months will mediate positive change in the primary outcome behaviors at 6 months; and that the Oral Health 4 Life program will be acceptable to quitline callers

12.2 Sample Size Considerations

This is the first study to examine whether an integrated oral health promotion-smoking cessation program delivered through tobacco quitlines will increase abstinence rates, so the potential effect size of the intervention is unknown.

Given this, we have powered the study to detect a 9% increase in abstinence rates between the UC (12%) and enhanced intervention (21%) at 6 months. A difference of

this magnitude (nearly a two-fold increase) would be considered clinically meaningful, but is even more significant when viewed in terms of public health impact (defined as reach x effectiveness)⁴⁶ when the potential reach could be hundreds of thousands of smokers annually. Smaller effects could be statistically significant, but an effect of this size would be an unambiguous indicator that the intervention warrants dissemination. The UC cessation base-rate (12%) is estimated based on the actual end of treatment (~6 months) intent to treat 7-day PPA rates observed in the target quitlines (range =

Table 2. Power Calculations

	Effect Sizes		Sample Size
	Control	Intervention	
Abstinence	12%	20%	880
	12%	21%	712
	12%	22%	590
Dental care	5%	11%	856
	5%	12%	664
	5%	15%	376

All power calculations assume 90% power and use a normal approximation approach with pooled variance.

11% - 12.5%) and is consistent with the estimated abstinence rate of tobacco quitlines based on a meta-analysis of the literature (average cessation rate at 6 months = 12.7% (95% CI, 11.3-14.2)).²³ With a sample of ~712 people, we will have 90% power to detect an 9% difference in rates of smoking abstinence at 6 months assuming a two-sided alpha-level=0.05 Wald Z test statistic for a difference between proportions using a normal approximation with pooled variance⁴⁷ and UC rate of 12%. This sample is also more than sufficient to detect a meaningful difference in the proportion of people who receive dental care (see Table 1). Although no participants will have seen a dentist in the past 6 months at enrollment as a condition of eligibility, it is possible a few will spontaneously seek dental care. Thus, we assume a base rate of 5% for this outcome in the UC group at 6 months. With the proposed sample, we will have >90% power to detect a 10% difference in dental care utilization between groups (e.g., 5% vs. 15%) and greater power to detect larger increases in treatment utilization. Increasing treatment utilization by 10% or more in this high risk population also has public health significance given the potential reach of the program. Each sample size estimate is based on complete case follow-up which will occur by design for all primary outcome analyses since we will be imputing missing values for the primary outcomes (missing cases will be assumed to be smokers and to not have visited the dentist). All analyses assume an intent to treat analysis with all subjects included as randomized. With a sample of n = 718, we also have 80% power to detect a difference of 7.6% in smoking abstinence and 5.6% in dental care utilization.

12.3 Planned Interim Analyses (if applicable)

No interim analyses are planned.

12.4 Final Analysis Plan

Analytic Samples. At the request of our DSMB, main outcomes will be analyzed using two analytic samples. One will include all 737 initially enrolled participants, regardless of study eligibility or study retention. Since no follow-up data is being collected on 19 of these individuals because they were ineligible and mistakenly enrolled, primary outcome data for these individuals will be treated as missing data. The second analytic sample (n = 718) will be limited to those individuals who were eligible to participate and included in the study. Analytic findings based on this second analytic sample will be considered the primary study results, but we will present the results from both analyses if results for the primary outcomes differ between the two samples. However, since missing data will be imputed as smokers and non-utilizers of dental care, and the 19 individuals not included in the primary analytic sample were equitably distributed across groups (9 vs. 10), we do not anticipate their exclusion will alter the primary findings. All analyses will use an ITT methodology such that subjects are analyzed according to their assigned treatment group, regardless of noncompliance, protocol deviation or withdrawal from treatment utilization.

Primary and secondary analyses. To assess the difference between the experimental and control groups for smoking abstinence, the regression model will include data from both follow-up time points in a single model to improve power and adjust for possible correlation within

individuals using generalized estimating equations.¹ To assess differences in dental care utilization, we will compute whether participants saw a dentist post-enrollment using data from each follow-up, then run a single logistic regression model. We will specify an independent working correlation structure and estimate robust standard errors to avoid making model assumptions about the variance. Models will use a logit link function for the binary primary outcomes and odds ratios will be used to quantify differences between groups. To improve precision and power, analyses will be adjusted for the following pre-specified baseline characteristics that are expected, based on prior knowledge, to be important predictors of outcome or missing data: sex, age, pharmacotherapy use (e.g., NRT), baseline cigarettes per day, depression history, self-efficacy, and motivation for quitting. Models will also adjust for variables used to stratify randomization (dental insurance coverage and state quitline).

To estimate the effects of the intervention on secondary outcomes (e.g., completing or scheduling a dental appointment, brushing, self-efficacy, motivation, etc.), we will apply similar regression models as described for the primary outcomes, using appropriate link functions dependent on outcome type, and further adjust for baseline outcome value when appropriate.

To handle missing follow-up data for the primary outcomes we will assume that missing subjects are smokers and are non-users of dental service. In sensitivity analyses, we will use modern imputation methods to impute missing outcome data, based on the observed pattern of missingness.² We also will conduct a respondent only missing data sensitivity analysis that only includes subjects with observed outcome data (i.e., a complete case analysis).

Mediation Analyses. If the enhanced UC is more effective than UC for either primary outcome at 6 months, we will then conduct mediator analyses to assess whether relevant secondary outcomes measured at 2 months (self-efficacy, motivation, knowledge,) mediate at least part of this effect. Mediation will be explored separately for each significant main outcome. These analyses will be conducted using the framework recommended by Baron and Kenny,⁴⁹ but using more recent statistical methods developed to better quantify and decompose different aspects of the mediation effect.⁵⁰ Having demonstrated the association between the intervention and the outcome variable (the “total effect” of the intervention on the outcome), the second step will be to demonstrate the association between the intervention and each mediator. We will construct a regression model for each mediator with the 2 month score of the mediator as the dependent variable and intervention indicator as independent variables. We will conduct this for each potential mediator and only include those mediators that have at least a $P < 0.10$ -level significant relationship with the intervention as potential mediators in the following step. The third step is to demonstrate the reduction of the intervention effect on the outcome after removing the effect of the mediator(s). We will construct a multi-mediator inverse probability weighted (IPW) regression model. This approach allows us to estimate the direct effect of intervention after rebalancing the intervention groups with respect to the mediators. The application of the IPW approach, as compared to the traditional approach of adjusting for multiple mediators, allows us to more appropriately account for confounding between a mediator and the outcome both

by additional mediators and by other measured variables. Further, we are better able to estimate the indirect effects of each mediator in a causal framework through decomposition of the total effect of intervention into indirect effects through each mediator and the direct effect after accounting for all mediators. Specifically, we will first model the probability of the intervention given the mediators (all mediators that were found associated with intervention in step 2) using logistic regression adjusting for potential baseline confounders. From this model we will obtain the estimated probabilities that each person received their observed intervention given their observed mediator value. We will then use an IPW regression to model the primary outcomes on intervention status while adjusting for the baseline level of the outcome and mediator and weighting out the effect of the mediator. Comparing the weighted to the unweighted model will allow us to estimate how much of the direct effect of intervention on the outcome can be explained by each potential mediator. We will further be able to quantify the amount of effect explained by each mediator independent of the other mediators.

Process Analyses. Summary statistics will be used to characterize quantitative acceptability ratings and scores. T-tests will be used to compare groups' on continuous ratings and chi-squares for proportions. Open-ended qualitative responses will be reviewed by investigators and may be transcribed and coded thematically, as needed to provide insight into the participants' satisfaction with the intervention programs and their components.

Economic Analyses. In addition to addressing the main scientific aims above, we will calculate the incremental cost of adding the Oral Health 4 Life program, from the perspective of a future payer, and produce a decision support tool that will allow quitline sponsors to determine whether, based on their own willingness to pay for quitline services, adding the Oral Health 4 Life program makes economic sense. This deliverable reflects quitline purchasers' concerns about program cost. The decision support tool will be created on a standard Excel spreadsheet and distributed at no cost to any individual or group wishing to assess the financial viability of adding the Oral Health 4 Life program to their quitline calls. The decision tool will have three components. The first is a detailed model of the cost associated with the oral health program. To generate this model component we will use activity accounting methods,⁵¹ which uses micro-costing to assign unit costs to every physical and human resource required to deliver an intervention or program. To micro-cost the additional cost of oral health counseling we will identify each resource required to add this component including development and training time, supplies, the additional time spent per call, etc. The second component of the decision tool is the probability of success for each positive outcome (cessation, dental visit, both) associated with a quitline program incorporating Oral Health 4 Life. This information will be based on trial results and we will incorporate uncertainty by using confidence intervals derived from the analyses of our trial data as described above. The third component will be a user entered factor based on their willingness to pay so that a potential sponsor of Oral Health 4 Life can assess, based on alternative assumptions about cost, programmatic success and

willingness to pay, whether investing in the Oral Health 4 Life program makes financial sense to them. Each user will have the ability to vary each model parameter to determine the circumstances under which they would be willing to invest in purchasing the Oral Health 4 Life program. Thus, each purchaser can decide for themselves what outcomes could be expected based on the amount they are willing to pay. This tool will be shared with quitline purchasers to inform individual decisions about whether the program provides sufficient perceived value to warrant program costs.

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate treatment and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Study staff will permit authorized representatives of NIDCR and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

14 QUALITY CONTROL AND QUALITY ASSURANCE

Alere study staff will be trained on the protocol by Drs. McClure, Catz, and Bush and/or their proxies, as appropriate to staffs' role on the project (e.g., screening, assessment, intervention delivery). Counselor training will involve a combination of didactic learning and experiential role play until each counselor is adept at delivering the counseling and integrating it with usual care.

Electronic records will be routinely reviewed to ensure quality assurance, including:

- Randomization assignments (blinded) will be monitored to ensure equitable distribution of participants in each arm and to ensure the block stratification scheme is maintained.
- Alere will provide routine reports to GHRI summarizing enrollment metrics including: the number of people invited to be screened for eligibility, the number who are screened eligible, reasons for ineligibility, the number invited to consent, the number who provide consent, the number who complete baseline assessments, and metrics on participation in the counseling calls.
- Alere will send weekly feeds of baseline and screening data to GHRI. Surveys will be periodically checked by the biostatistician or GHRI programmer for missing or out of range values, or other evidence of poor data quality. Systematic errors will be addressed, as appropriate.
- The GHRI biostatistician or programmer will conduct regular screening of follow-up assessment data to identify missing or out of range values, or other evidence of poor data quality. Systematic errors will be addressed, as appropriate.

Phone contacts with quitline callers are routinely recorded by Alere. We will randomly audit at least 10% of these calls for study participants to monitor fidelity to the counseling and may audit other study activities (e.g., screening, consent, and baseline interview) as needed. GHRI fidelity monitors will listen to the randomly sampled calls. GHRI staff will be responsible for auditing and coding compliance with study activities, except that Alere staff may be responsible for auditing fidelity to the usual care counseling. Standardized rating forms will be used to document compliance with study activities, including key elements of the counseling protocol. As needed to address protocol drift, Drs. McClure, Catz, and Bush will ensure that study staff receive additional supervision and training.

Compliance with the follow-up phone surveys will be audited by supervisors in the GHRI Survey Research Program following standard protocols for fidelity monitoring

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

15.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

15.3 Informed Consent Process

With IRB approval, participants will provide verbal consent to participate. Consent will be documented by study staff at Alere Wellbeing and all participants will be mailed written copies of the consent form for their records. Informed consent will include permission to participate in the randomized trial, to have all data collected as part of their quitline counseling program shared with GHRI researchers, and for study staff to contact participants by phone, text or email. Participants will be fully informed of the potential risks and benefits of study participation. Those who decline to consent will still be eligible to participate in the usual care tobacco quitline program. Participants will be informed of their right to withdraw their consent to participate at any time. The consent process will conform to all requirements as set forth by the study IRB.

The consent process will be documented in the study database.

15.4 Exclusion of Women, Minorities, and Children (Special Populations)

Individuals of any gender or racial/ethnic group may participate. Children age 18 to 21 may participate but persons under the age of consent (18 y.o.) will be excluded.

15.5 Subject Confidentiality

Appropriate steps will be taken to safeguard participant confidentiality. This includes the following:

- All study data will be maintained on secure, password protected servers at GHRI and Alere. Only study staff who need this information for their work will have access.

- Electronic data that contains PHI will be transmitted between GHRI and Alere using a secure, HIPPA-compliant FTP site.
- Participants will be identified using subject IDs in all study records.
- We will establish a Business User Agreement with the text messaging vendor, to ensure the confidentiality of study participants is maintained.
- The study protocol, documentation, data and all other identifying information will be held in strict confidence. No information about the study will be released without prior written approval of the sponsor. The study monitor or other authorized representatives of the sponsor may inspect records, as needed.

15.6 Future Use of Identifiable Data

Identifiable information will be destroyed within 5 years of the end of the study, consistent with HIPAA and our IRB requirements.

We have no plans to retain identifiable information beyond this period. If this plan changes, we will obtain appropriate IRB approval and participant consent.

See also Study Records Retention, section 16.5.

16 DATA HANDLING AND RECORD KEEPING

16.1 Data Management Responsibilities

Data collected at Alere Wellbeing and by the GHRI Survey Research Program will be captured in electronic records. Any additional data may be collected on paper and added to electronic records (e.g., mailed survey interview if not able to collect by phone).

If needed, all written source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, staff will cross out the original entry with a single line, and initial and date the change. They will NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL SOURCE DOCUMENT.

Final datasets will be saved electronically, clearly labeled and stored in a secure project folder on the GHRI server accessible only to study staff. Data shared between GHRI and Alere Wellbeing will be transferred using a secure FTP site.

No electronic participant data shall be overwritten by study staff. As necessary, variables may be recoded into new variables for analyses, but will be done in a way to preserve the original record. All changes will be documented.

16.2 Data Capture Methods

All data will be captured electronically for this study from either phone surveys (e.g., manual data entry using phone CATI systems), automated intervention records (e.g., Alere system records), or digital audio recordings.

All electronic records will be kept in a 21 CFR Part-11 compliant data capture system, which includes password protection.

16.3 Types of Data

Data for this study will include self-reported survey data (eligibility screening, baseline, and follow-up), electronic data on program utilization (e.g., number of calls completed, duration of behavioral counseling) and program delivery (number of emails and text messages sent), and safety data (e.g., AEs).

16.4 Schedule and Content of Reports

The schedule for data review and reports will be determined by the DSMB during this Board's initial meeting.

16.5 Study Records Retention

All study data will be maintained for at least 5 years after the conclusion of the study. At that time, consistent with HIPAA guidelines, identifying information and linking files will be destroyed unless consent to retain these files is granted by study participants or the IRB.

Following this time, no records will be destroyed without the consent of NIDCR, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained

16.6 Protocol Deviations

All staff will immediately report protocol deviations to the GHRI Project Manager, who will inform the PI. Deviations will be considered any noncompliance with this clinical trial protocol, Good Clinical Practice, or the Manual of Procedures. Deviations will be reported in a timely way to the GH IRB. Deviations will also be reported to the NIDCR Program Official via NIDCR_Reports@rheworld.com once monthly.

17 PUBLICATION/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.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as *ClinicalTrials.gov*, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIDCR grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801 mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials:"

NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

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SUPPLEMENTAL MATERIALS

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

APPENDICES

Appendix A: Schedule of Events

Appendix B: Baseline Survey

Appendix C: Follow-up Surveys

Appendix D: Eligibility Screening and Consent Script

Appendix E: Oral Health 4 Life Intervention Booklet

Appendix F: Counseling and Training Protocol

Appendix G: Text Messages

Appendix H: Written Consent Document

APPENDIX A: SCHEDULE OF EVENTS

		Call #1 (Day 0)	Call 2 (~Week 1-2)	Call 3 (~Week 2-4)	Call 4 (~Week 4-6)	Call 5 (~Week 6-10)	Text messages (~Weeks 1-23)	Follow-up #1 (~Week 8)	Follow-up #2 (~week 24)
Assessment of Eligibility Criteria		x							
Informed Consent		x							
Baseline phone survey		x							
Enhanced Intervention	Counseling	x	x	x	x	x			
	Text Messages ¹						x		
	Access to secure website	x	x	x	x	x	x		
Assessment of Unanticipated Problems			x	x	x	x		x	x
Mail consent, incentive, and written study materials	x (Post-call 1)								
Follow-up phone survey							x	x	
Mail thank you and incentives							x (post-2 month follow-up)	x (post-6 month follow-up)	
Provide open access to copy of study website (invite via text and mail)									(post-study end)

Note: Call timing and text messages are subject to individual variability based on timing of the initial target quit date (TQD) and participant's availability to be reached by phone.

1 Text messages will be sent to both control subjects and those randomized for the enhanced intervention using the time delivery schedule, but content will vary.

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