Free Samples for Health (FreSH) Study 3

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Principal Investigator: Sandra Japuntich, Ph.D.

NIDCR Program Official: Dena Fischer, DDS, MSD, MS

NIDCR Project Scientist: Melissa Riddle, PhD

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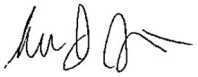
STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice (GCP) (ICH E6) and the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46). National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

SIGNATURE PAGE

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

Signed:  Date: 1JAN2023

Name: Sandra J. Japuntich, PhD

Title: Principal Investigator UG3 and UH3 phases

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
AAR	Ask-Advise-Refer
CO	Carbon Monoxide
CRF	Case Report Form
ET	Electric Toothbrush
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
N	Number (typically refers to participants)
NIDCR	National Institute of Dental and Craniofacial Research, NIH, DHHS
NIH	National Institutes of Health
NOP	Network Operating Procedure
NRTS	Nicotine Replacement Therapy Sampling
OHRP	Office for Human Research Protections
PBRN	Practice-Based Research Network
PI	Principal Investigator
QC	Quality Control
QM	Quality Management
SAE	Serious Adverse Event/Serious Adverse Experience
US	United States

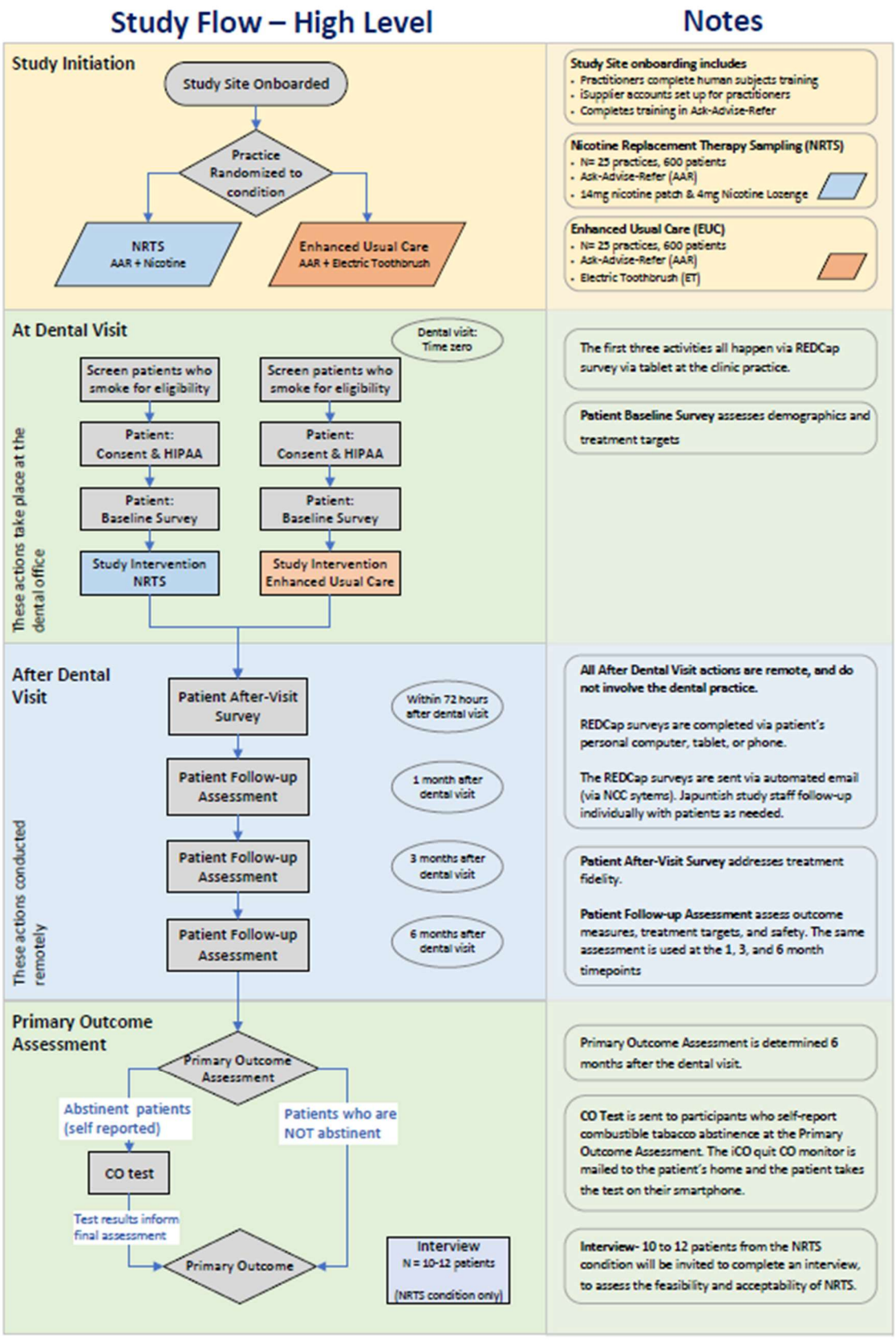
PROTOCOL SUMMARY

Title:	Free Samples for Health (FreSH) Study 3
Précis:	The FreSH study is a phase II, cluster randomized, effectiveness trial. Ask Advise Refer (AAR) + Nicotine Replacement Therapy Sampling (NRTS) will be compared to enhanced usual care (AAR + electric toothbrush; ET) in approximately 1200 patients who smoke combustible cigarettes recruited from approximately 50 practices in the Northeast and Midwest regional nodes of the National Dental Practice-Based Research Network. Study interventions will be delivered within the practices by trained practitioners. Our central hypothesis is that NRTS will produce greater abstinence than ET. Our primary outcome will be carbon monoxide (CO) verified, 7-day point prevalence abstinence at 6-months post-intervention. We also predict that compared to ET, NRTS will increase quit attempts, reduce smoking heaviness, and increase NRT utilization. After the intervention is complete, we will conduct a multi-stakeholder process evaluation of the feasibility and acceptability of the NRTS intervention and a cost-effectiveness analysis to aid future implementation efforts.
Objectives:	Primary objective: 1. Assess the effectiveness of AAR + NRTS compared to enhanced usual care (AAR + electric toothbrush; ET) on 6-month biologically verified 7-day point prevalence abstinence from combusted tobacco. Primary outcome: 1. CO confirmed 7-day point prevalence abstinence from combusted tobacco at 6 months post enrollment Secondary objectives: 2. Assess the effectiveness of AAR + NRT sampling (NRTS) compared to enhanced usual care (AAR + electric toothbrush; ET) on: 1) 24-hour intentional quit attempts, 2) smoking heaviness (cigarettes/day) Secondary outcomes: 1. 24-hour intentional quit attempts in the 6 months

	post enrollment 2. Cigarettes per day in the 6 months post enrollment 3. Assess whether nicotine replacement therapy utilization, attitudes toward NRT, intention to use NRT, and intention to quit smoking mediate the effect of the intervention on abstinence Mediators: 1. Use of Nicotine patch or nicotine lozenge 2. Attitudes towards NRT (safety and efficacy) 3. Intention to use NRT 4. Intention to quit smoking 4. Assess intervention feasibility and acceptability. Conduct a multi-stakeholder process evaluation of the NRTS intervention to aid future implementation through a multi-stakeholder process evaluation. Outcomes: 1. Acceptability of NRTS 2. Feasibility of NRTS 5. Assess the cost effectiveness of the NRTS intervention. Outcomes: 1. Cost per quit 2. Cost per quality adjusted life year
Population:	Target of 50 National Dental PBRN practices and 1200 patients who smoke combustible cigarettes in PBRN practices Gender: Males, Females, non-binary Age range: 18-No limit (except in Nebraska where consent is age ≥ 19 years) Demographic group: National Dental PBRN practitioners and their patients who smoke cigarettes daily, own a smart phone with reliable Internet Access, are willing to receive study emails

	and texts, are free of contraindications to NRT and who have not used tobacco cessation medications in the past week.
Phase or Stage:	phase 2
Number of Sites:	Approximately 50 practices across the Midwest and Northeast National Dental PBRN regional nodes.
Description of Intervention:	2-week supply of 14mg transdermal nicotine patches and a 2-week supply of 4mg nicotine lozenges
Study Duration:	Approximately 3 years, includes ramp-up period (6 months), full-scale trial (2 years), interviews following trial participation, data synthesis and manuscript preparation.
Subject Participation Duration:	Patient participant duration: 6 months Practitioner expected duration to recruit approximately 24 patients: 1 year
Estimated Time to Complete Enrollment:	18 months

1 SCHEMATIC OF STUDY DESIGN


Study Flow – High Level
Notes
Study Initiation
Study Site Onboarded
Practice Randomized to condition
NRTS
AAR + Nicotine
Enhanced Usual Care
AAR + Electric Toothbrush
Study Site onboarding includes
Practitioners complete human subjects training
iSupplier accounts set up for practitioners
Completes training in Ask-Advise-Refer
Nicotine Replacement Therapy Sampling (NRTS)
N= 25 practices, 600 patients
Ask-Advise-Refer (AAR)
14mg nicotine patch & 4mg Nicotine Lozenge
Enhanced Usual Care (EUC)
N= 25 practices, 600 patients
Ask-Advise-Refer (AAR)
Electric Toothbrush (ET)
At Dental Visit
These actions take place at the dental office
Dental visit: Time zero
Screen patients who smoke for eligibility
Patient: Consent & HIPAA
Patient: Baseline Survey
Study Intervention NRTS
Screen patients who smoke for eligibility
Patient: Consent & HIPAA
Patient: Baseline Survey
Study Intervention Enhanced Usual Care
The first three activities all happen via REDCap survey via tablet at the clinic practice.
Patient Baseline Survey assesses demographics and treatment targets
After Dental Visit
These actions conducted remotely
Patient After-Visit Survey
Within 72 hours after dental visit
Patient Follow-up Assessment
1 month after dental visit
Patient Follow-up Assessment
3 months after dental visit
Patient Follow-up Assessment
6 months after dental visit
All After Dental Visit actions are remote, and do not involve the dental practice.
REDCap surveys are completed via patient's personal computer, tablet, or phone.
The REDCap surveys are sent via automated email (via NCC sytems). Japuntish study staff follow-up individually with patients as needed.
Patient After-Visit Survey addresses treatment fidelity.
Patient Follow-up Assessment assess outcome measures, treatment targets, and safety. The same assessment is used at the 1, 3, and 6 month timepoints
Primary Outcome Assessment
Primary Outcome Assessment
Abstinent patients (self reported)
CO test
Test results inform final assessment
Patients who are NOT abstinent
Primary Outcome
Interview
N = 10-12 patients
(NRTS condition only)
Primary Outcome Assessment is determined 6 months after the dental visit.
CO Test is sent to participants who self-report combustible tabacco abstinence at the Primary Outcome Assessment. The iCO quit CO monitor is mailed to the patient's home and the patient takes the test on their smartphone.
Interview- 10 to 12 patients from the NRTS condition will be invited to complete an interview, to assess the feasibility and acceptability of NRTS.

2 KEY ROLES AND CONTACT INFORMATION

Principal Investigator:	Sandra Japuntich, PhD Clinician Investigator Hennepin Healthcare Associate Professor of Medicine University of Minnesota Medical School 701 Park Ave. S.9.303 Minneapolis, MN, 55415 (612) 873-6856 sandra.japuntich@hcmed.org
NIDCR Program Official:	Dena Fischer, DDS, MSD, MS Director, Center for Clinical Research Program Director, Clinical Trials and Practice-Based Research National Institute of Dental and Craniofacial Research 6701 Democracy Boulevard, MSC 4878 Bethesda, MD 20892-4878 Phone: 301 594 4876 Email address: dena.fischer@nih.gov
NIDCR Project Scientist	Melissa Riddle, PhD Chief, Behavioral and Social Sciences Research Branch Division of Extramural Research National Institute of Dental and Craniofacial Research National Institutes of Health Democracy One, Room 646 6701 Democracy Blvd MSC 4878 Bethesda, MD 20892-4878 (301) 451-3888 riddleme@nidcr.nih.gov
The National Dental Practice-Based Research Network Admin & Resource Center (ARC) Network Director	Gregg Gilbert, DDS, MBA, FAAHD, FACD, FICD Distinguished Professor and Chair, Department of Clinical & Community Sciences School of Dentistry, University of Alabama at Birmingham 1720 Second Avenue South Birmingham, AL 35294

	Phone: 205-934-5123 Email address: ghg@uab.edu
Principal Node Director:	D. Brad Rindal, DDS HealthPartners Institute for Education and Research 8170 33rd Avenue South P.O. Box 1524, MS 23301A Minneapolis MN 55440-1524 Phone: 952-967-5026 Email address: Donald.B.Rindal@HealthPartners.Com
Northeast Node Director:	Cyril Meyerowitz, D.D.S., M.S. Eastman Institute for Oral Health 265 Crittenden Blvd. Saunders Research Building, Box 686 Rochester, NY 14642 Cyril_Meyerowitz@urmc.rochester.edu
Network Coordinating Center Director:	Mary Ann McBurnie, PhD Senior Investigator Kaiser Permanente Center for Health Research 3800 N Interstate Ave Portland, OR 97227 Phone: (503) 528-3952 Email address: MaryAnn.McBurnie@kpchr.org
NCC Study Manager	Tamara Lischka, BA Kaiser Permanente Center for Health Research 3800 N Interstate Ave Portland, OR 97227 Phone: 971-212-9656 Email: Tamara.R.Lischka@kpchr.org
NCC Data Manager	Arthur Truong, MS Kaiser Permanente Center for Health Research 3800 N Interstate Ave Portland, OR 97227

	Phone: 503-528-3943 Email: Arthur.J.Truong@kpchr.org
Statistician	Michael Leo, PhD Kaiser Permanente Center for Health Research 3800 N Interstate Ave Portland, OR 97227 Phone: 503-528-3909 Email: Michael.C.Leo@kpchr.org
Institutions:	The National Dental Practice-Based Research Network (the Network), which is a consortium of participating dental practitioners who conduct practice-based oral health research in their practices and dental organizations. It encompasses six regional Nodes, each with an administrator, or Node Director. The National Administrative and Resource Center is located at the University of Alabama at Birmingham, and the National Coordinating Center is located at the Kaiser Permanente Center for Health Research in Portland, OR. The National Dental Practice-Based Research Network Admin & Resource Center Gregg H. Gilbert, DDS, MBA, FAAHD, FACD, FICD Distinguished Professor and Chair, Department of Clinical & Community Sciences School of Dentistry, University of Alabama at Birmingham 1720 Second Avenue South Birmingham, AL 35294 Phone: 205-934-5123 E-mail address: ghg@uab.edu The National Dental Practice-Based Research Network National Coordinating Center Mary Ann McBurnie, PhD Senior Investigator 3800 Interstate Ave Portland, OR 97227 Kaiser Permanente

	Center for Health Research 3800 N Interstate Ave Portland, OR 97227 Phone: 503.528.3952 Email address: maryann.mcburnie@kpchr.org
Principal Node Coordinator 1. Midwest Node Coordinator	Sarah Basile, MPH HealthPartners Institute for Education and Research 8170 33rd Avenue South P.O. Box 1524, MS 23301A Minneapolis MN 55440-1524 Phone: 952-967-5277 Email: Sarah.M.Basile@HealthPartners.Com

3 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

3.1 Background Information

A brief description of the health problem that the study will address

Cigarette smoking has significant negative effects on oral health including: oral cancer, periodontal disease, tooth loss, and bone loss.[1–3] Current smokers are twice as likely as former smokers and four times as likely as never smokers to have poor oral health.[4] Smoking decreases the effectiveness of oral health treatments.[3] Tobacco cessation treatments are effective but underutilized.[5] During quit attempts, less than 30 percent of smokers use medication and less than ten percent receive counseling.[6] Novel approaches to encourage use of evidence-based tobacco treatment are needed.

The oral health effects of tobacco develop earlier and are more perceptible to smokers than diseases that affect internal organs.[7] Oral health problems increase motivation to stop smoking and are opportunities for intervention.[8] About half of adult smokers visit a dentist annually[9] and the majority of patients who smoke would be motivated to make a quit attempt if encouraged by a dental practitioner.[10] Therefore, dental practice may be an ideal setting for tobacco intervention. A meta-analysis of 20 tobacco intervention studies conducted in oral healthcare settings indicated that interventions which included brief advice and nicotine replacement therapy increased abstinence by 2.7 times compared to usual care.[11]

Discussion of important research relevant to the study that provides background and scientific justification for the study

The US Public Health Service Clinical Practice Guideline for Treating tobacco use and Dependence recommends that every patient in every healthcare setting receive tobacco intervention.[12] Receipt of cessation advice from more than one type of health practitioner improves outcomes.[12] The American Dental Hygienists Association recommends that oral health professionals: Ask about tobacco use, Advise tobacco users to quit, and Refer smokers to quitlines (AAR).[13] While AAR connects patients to counseling, it does not directly connect patients to pharmacotherapy, as the guideline recommends. Only 31% of smokers who visited the dentist in the past year reported that they were advised to quit, only 4% were advised to use tobacco cessation medication.[9] Strategies are needed to connect smokers to tobacco cessation medication in dental settings.

Among the 7 FDA-approved tobacco cessation medications, nicotine replacement therapies (NRT) are the most widely used. Three of the five types of NRT (nicotine patch, gum and lozenge) are available over-the-counter with few contraindications. Over the counter NRT is best suited for distribution within dental practices where providers have limited time and need not be well-versed in prescription-only medications. NRT reduces withdrawal and craving[14] and meta-analytic evidence from 100+ trials shows a doubling of long-term abstinence.

Nicotine replacement therapy sampling (NRTS) is an innovative method of delivering NRT by providing short, starter packs of NRT, which can be added to existing AAR protocols. NRTS is distinct from a full course of NRT: the intent is to engage smokers in the process of quitting, without a requirement or expectation to quit immediately and abruptly. It is designed to reduce barriers to obtaining and heighten the acceptance of NRT and enhance motivation and self-efficacy. It is rooted in marketing research, which shows that free samples of products increase positive opinion and use.[15] NRTS can induce quit attempts even in those unmotivated to quit.[16]

The goal of NRTS is to increase NRT use behavior and thereby increase abstinence from tobacco. NRTS is guided by the Theory of Planned Behavior, which posits that health behavior intentions are guided by attitudes, subjective norms, and perceived behavioral control.[17] Smokers hold misperceptions about NRT safety (e.g., addiction potential, adverse events) and efficacy.[18] Having NRT recommended by a health professional could improve a smoker's perception of subjective norms about NRT (e.g., "it must be ok if my dentist recommends it."). Finally, as smokers gain confidence in controlling smoking through NRT use, they may start to believe abstinence is possible. By encouraging favorable attitudes and subjective norms towards NRT and perceived behavioral control over quitting and NRT use, NRTS may heighten quitting intentions and intentions to use NRT. Whereas abrupt quitting is daunting, gradual exposure to cessation, facilitated by NRT, might remove perceived barriers to quitting (e.g., "This isn't bad. I can do this.").

Quitlines are an example of how providing free NRT can reduce barriers to use. Quitlines that offer free medication have higher cessation rates than those who don't.[19,20] Some research suggests that a 2-week supply of NRT is as cost-effective as an extended supply.[21] Thus, NRT give away programs need not be intensive.

NRTS may be an ideal strategy for dental settings. Providing free samples of products that promote oral hygiene (e.g., toothbrush and floss) is a routine part of preventive dental care. Tobacco cessation is consistent with the goals of routine oral healthcare, including oral cancer screening and prevention. Patients expect dentists to counsel them about smoking.[10] Dentists report that tobacco dependence treatment is part of their role and that their patients' perception of them would improve if they provided it.[22]

Oral health providers currently do little to address smoking and are particularly unlikely to prescribe or distribute tobacco cessation medication.[9] The current study is a replication of a study conducted in primary care patients where all patients who smoke, regardless of heaviness of smoking or motivation to quit were provided a universal dose of a 2-week supply of the 14mg nicotine patch and the 4mg nicotine lozenge during a routine primary care visit. That study found that this universal sample dose produced a 50% increase in point prevalence abstinence 6 months post distribution of the sample.[23] The 14mg patch was selected because it can be used for all tobacco users safely (package instructions recommend use of the 14mg patch for those smoking ≤10 cigarettes per day). The high-dose 4mg lozenge (recommended for those who smoke within 30 min of waking) was selected to allow for titration of nicotine level by the

patient. The universal dosing used in this study simplifies the intervention for oral health practitioners who are already overwhelmed by recommending smoking cessation medication. We do not exclude people who smoke >10 cigarettes per day in the study because we believe they will be able to titrate to an appropriate dose with the combination of nicotine patch and lozenge. In addition, as heavier smoking is associated with greater negative health outcomes, we do not believe it is ethical to exclude those patients who stand to benefit the most from smoking cessation.

3.2 Rationale

Cigarette smoking is detrimental to oral health. While most people who smoke cigarettes want to quit, and about half make quit attempts each year, few use medication to help them quit. Oral health practitioners are well-suited to address tobacco use, and many assess tobacco use and advise those who use tobacco to quit, but few provide assistance in quitting. The current study tests the effectiveness of nicotine replacement therapy sampling (giving free samples of nicotine replacement therapy to patients in dental practices as part of routine dental care) at promoting medication use, quit attempts, and smoking cessation. The primary study hypothesis is that providing a 2-week supply of nicotine replacement therapy samples (nicotine patch and nicotine lozenge) will result in higher biochemically confirmed abstinence 6 months later than a cost-matched oral health related sample (electric toothbrushes).

NRTS, when added to the American Dental Hygienist's Association AAR model during routine dental care could leverage a novel point of intervention with smokers. NRTS: 1) takes less than 5 minutes to implement, 2) requires no further follow-up, and 3) is a concrete behavioral exercise that smokers and practitioners can "hang their hat on." Sampling is inexpensive and its translational potential is strong.

3.3 Potential Risks and Benefits

3.3.1 Potential Risks

Negative emotional reaction to study procedures

Risk. It is possible that study procedures involving discussion and/or reporting on tobacco use and cessation (telephone interviews, online surveys) and/or interventions could be upsetting to oral health professionals and/or patients.

Minimization. All members of the research team who conduct telephone interviews and supervise administration of follow-up surveys, and all practice staff who are responsible for screening, consenting, administering the baseline assessment, and delivering intervention to patients will be skilled in talking about sensitive information such as tobacco use. Any participant (patient or professional) may decide to end their

participation at any time. Should any participant have a negative reaction to any study procedure, a licensed clinician (Dr. Japuntich or covering provider), will be available at all times to help manage these clinical issues. We will assess the nature of the negative reaction, including whether it is likely to damage the patient-practitioner relationship, and form a plan to ameliorate the negative reaction, including the practitioner if indicated.

Breach of confidentiality or loss of privacy

Risk. Confidentiality could be breached, or participants could suffer a loss of privacy during data collection.

Minimization. All research team members and practice staff who will screen for eligibility, obtain informed consent, conduct interviews, administer assessments, and/or deliver interventions will be fully trained in relevant ethical principles and procedures, particularly around confidentiality. Appropriate precautions will be taken and procedures will be followed to maintain confidentiality. These include use of unique study codes for participants, encryption of electronic data for transmission to the coordinating center, and password-protected computers for data storage. Compliance with all IRB regulations concerning data collection, data analysis, data storage, and data destruction will be strictly observed. Only authorized individuals will have access to participant names and contact information and the ability to match this information to participant ID numbers (i.e., only those who need this information to carry out study procedures). Participant identifying information will not be included in any published reports or public use datasets.

Risks of using Nicotine Replacement Therapy (NRT) samples

Risk Summary. Patients in practices assigned to NRTS will receive a two-week supply of both nicotine patches and nicotine lozenges. These two products are both available over-the-counter (OTC) and have received extensive research support for their efficacy and safety.[24–30] One review in particular[17] provides significant rationale by which combined NRT (i.e., using two NRT products concomitantly) should not incur significant risks, since NRTs provide lower doses per unit or per hour than are typically obtained by cigarette smoking, and the rate of nicotine administration for all NRT products is substantially slower than that from an inhaled cigarette. In April 2013, the U.S. Food and Drug Administration (FDA) published a report in the *Federal Register* that stated “Upon reviewing the published reports of these and other studies, we have determined that the concomitant use of OTC NRT products with cigarettes or with other nicotine-containing products does not raise significant safety concerns. The published literature contains few reports of adverse events arising from the use of NRT products while smoking or using another NRT product. The Agency also notes that few adverse events have been reported in studies of concomitant use conducted under the investigational new drug (IND) process, which involves mandatory reporting of adverse

events."[31] In this report, the FDA recommended two changes to NRT product labeling to reflect this determination of safety: 1) removing warnings that instruct NRT users not to use an NRT product concurrently with other nicotine-containing products, and 2) replacing instructions to completely abstain from smoking while using the NRT product with an instruction to "begin using the NRT product on your quit day". Furthermore, a comprehensive meta-analysis of 129 studies involving 177,390 individuals concluded that there was no significant difference between NRT and placebo in prevalence of severe adverse events (SAEs) including suicidal ideation, heart attack, and mortality.[32] Therefore, we expect that risks of using NRT samples will be minimal and mild.

Specific risks of using nicotine lozenge. The most common adverse effects of using nicotine lozenge are nausea/GI upset, mouth/throat irritation, and hiccups. In previous studies of lozenge, drop-out due to AEs were very low (<10%) and SAEs have been reported in <2% of the sample (with no deaths or irreversible injuries attributed to lozenge use) and have not differed between lozenge and placebo.[33–35]

Specific Risks of using nicotine patch. The most common adverse effects of using nicotine patch include local skin irritation at the site of the patch, disturbed sleep and vivid dreams, headache, and nausea. Less common are allergic skin reactions to the patch. In a recent trial,[33] 7% of participants discontinued patch use due to adverse events.

Specific risks of using nicotine patch and nicotine lozenge concurrently. Our sampling intervention allows smokers to briefly try both nicotine patch and nicotine lozenge, either singularly or concurrently. We will not explicitly encourage dual use, but we will not discourage it either. Combination treatments are often suggested for more dependent smokers and/or smokers with chronic medical conditions.[36–38] In a recent trial of placebo vs. single vs. multiple medications for smoking cessation,[33] the four most common adverse events within the combined patch/lozenge group (n = 262) were: 1) disturbed sleep: 9.0%, compared to 5.6% in placebo group, and 2) skin irritation: 8.9%, compared to 2.7% in placebo group, 3) nausea: 7.9%, compared to 4.4% in placebo group, and 4) mouth/throat irritation: 5.7%, compared to 3.3% in placebo group. All other adverse events occurred <5%.

Risks of medication being used by a person other that the participant. Nicotine replacement therapy is available over the counter and as such, risks of use by someone other than the participant are similarly low as those of the participant. Nicotine replacement therapy products should not be used by children.

Minimization of risks of using NRT. The primary protection against risks of using nicotine patch and nicotine lozenge (both OTC products) is the short duration for which they will be provided– only a 2-week supply. The packet of print materials that participants will receive includes FDA package instructions and a supplemental handout

with instructions on how to minimize side effects including moving the site of nicotine patch placement each day and not repeating site of use for at least one week to minimize the risk of skin irritation. Also, participants will be instructed to remove the patch before bed if it significantly interferes with sleep. Finally, these materials will discuss anticipated negative consequences of dual use (nausea, headache) and advise participants to discontinue one or both products should they arise. To reduce the risks of medications being given to those other than study participants, we will instruct participants upon distribution of samples not to give medication to others. Medication packages will also have a sticker that says "for FreSH participant use only- do not distribute." Medication comes in childproof packaging.

Our Data and Safety Monitoring Plan includes monitoring of Adverse Events (AEs). We will exclude patients based on standard FDA contraindications for NRT use (pregnancy, recent cardiovascular trauma). We will clearly advise against use of NRT during pregnancy and breastfeeding and will exclude patients who report that they are pregnant or breastfeeding. As part of routine dental visits, patients are asked about their pregnancy status, as some dental procedures and medications are contraindicated for pregnant women. A physician will be available throughout the study for consultation about AEs, etc. Participants will be instructed to discontinue use of the patch and/or lozenge entirely if a severe reaction develops. They will be encouraged to contact the research team (not their dentist) as soon as possible if they experience a SAE or if they have a reaction for which OTC labeling suggests seeing a provider. In the AAR training, dentists will get training on how to manage adverse events of NRT. However, for this study, participants and dentists will be advised that the study team, not the dentist, is responsible for managing study-related AEs. We will advise patients who have a study-related SAE to discontinue use of the study treatment (NRT or ET). Following any AEs or SAEs, if the study physician, the participant's personal physician or the participant wishes it, the participant will be withdrawn from the study.

Risks of using NRT concurrently with cigarettes and/or other tobacco products

Risks. Our study allows smokers to sample individual or combined NRT products, but without a specific instruction to make a formal quit attempt. Thus, smokers may use NRT products concurrently (same day) as smoking. This could result in symptoms such as nausea, dizziness, headache, stomachache, etc.[39] A review of prior smoking reduction studies found most participants did not have higher than normal cotinine levels with concurrent use of cigarettes and NRT, and there were few AEs reported.[40]

Minimization. The primary protection against risks of using NRT concurrently with cigarettes and/or other tobacco products is the short duration for which NRT will be provided– only a 2-week supply.

Risk of electric toothbrush use

Risk. There are minimal risks related to the use of the electric (powered) toothbrushes, including electrical safety, tuft retention, mechanical strength and chemical resistance.

Minimization. To minimize the above risks, we will provide electric toothbrushes that earned the Seal of Approval from ADA (American Dental Association). The Seal program requires the electric toothbrushes to be tested for safety and effectiveness in a clinical trial. They need to meet the ANSI/ADA Standards for testing (No. 120 for Powered Toothbrushes ADA120-2009). Additionally, the practitioners will demonstrate the proper use of the electric toothbrush to their patients.

3.3.2 Potential Benefits

There is the potential for patient participants to receive direct benefit from study participation. Patients may stop smoking as a result of either study intervention condition. Quitting smoking has clear benefits for oral and physical health. Those participants assigned to the comparison condition (ET) will still receive active treatment in the form of brief intervention (AAR) from an oral health professional and the print materials that include information about smoking cessation medications and a referral to their local quitline. Participants in the ET condition may also improve their oral health as a result of receiving an ET. Additionally, patients will be assessed on various factors related to their cigarette smoking, thereby potentially increasing their knowledge of their cigarette smoking and related issues.

4 OBJECTIVES AND OUTCOME MEASURES

4.1 Primary

Objective	Brief Description/Justification of Outcome Measure	Outcome Measured By	Time Frame
Assess the effectiveness of NRTS compared to ET on 6-month biologically verified 7-day point prevalence abstinence from combusted tobacco	Seven day point prevalence abstinence (no combustible tobacco use in the past 7 days) is the recommended outcome for cessation induction trials as it measures a clinically-significant change in the long term, but reflects that participants may quit at any time following the intervention.[41] Biochemical verification with breath carbon monoxide adds additional rigor to the primary outcome.[42] Carbon monoxide will detect combustible tobacco use and not nicotine replacement therapy use.	Self-report survey using timeline follow-back and iCO quit personal CO monitor. Following the CO test and result, we will compute a binary variable: abstinent vs. non-abstinent. Those who report abstinence on all 7 days prior to the 6-month follow-up and have a CO test result of <6ppm will be considered abstinent. Those who report smoking in the past 7 days, or have a CO result >6ppm, or who do not respond to the survey will be classified as non-abstinent.	6 months following baseline

4.2 Secondary

Objective	Brief Description/ Justification of Outcome Measure	Outcome Measured By	Time Frame
Assess the effectiveness of NRTs compared to ET on 1-month self-report 7-day point prevalence abstinence from combusted tobacco	The Society for Nicotine and Tobacco Research recommends measuring outcomes of clinical trials at multiple timepoints to determine at what point interventions may be having an effect.[41]	Self-report survey using timeline follow-back. From the timeline follow-back we will compute a binary variable with those who report no smoking on all 7 days prior to the assessment classified as abstinent, those who report smoking on any of the past 7 days classified as non-abstinent. Those missing smoking status data will be classified as non-abstinent.	1-month following baseline
Assess the effectiveness of NRTs compared to ET on 3-month self-report 7-day point prevalence abstinence from combusted tobacco	The Society for Nicotine and Tobacco Research recommends measuring outcomes of clinical trials at multiple timepoints to determine at what point interventions may be having an effect.[41]	Self-report survey using timeline follow-back. From the timeline follow-back we will compute a binary variable with those who report no smoking on all 7 days prior to the assessment classified as abstinent, those who report smoking on any of the past 7 days classified as non-abstinent. Those missing smoking status data will be classified as non-abstinent.	3-months following baseline

Objective	Brief Description/ Justification of Outcome Measure	Outcome Measured By	Time Frame
Assess the effectiveness of NRTS compared to ET on 24 hour quit attempts.	24-hour intentional quit attempts reflect periods of abstinence due to an attempt to quit (not abstinence due to other reasons such as hospitalization etc.). FreSH is a cessation induction study. Thus, we measure the effect of NRTS to induce cessation behavior including quit attempts.	Self-report survey item from the Phenx toolkit. We will measure this item on the 1-, 3- and 6-month follow-up survey. We will then create a dichotomous variable indicating whether there has been a quit attempt at any time in the past 6 months by classifying any participant reporting a quit attempt on any follow-up survey as having had a quit attempt. Those who did not report a quit attempt on any survey will be classified as not having a quit attempt.	6 months following baseline

Objective	Brief Description/ Justification of Outcome Measure	Outcome Measured By	Time Frame
Assess the effectiveness of NRTS compared to ET on smoking heaviness	In addition to assessing the effectiveness of NRTS on abstinence, we want to assess the effect of NRTS on cessation-related behavior including reducing heaviness of smoking.	Smoking heaviness indicates cigarettes per day. Timeline follow-back measure of cigarettes per day on each of the past 7 days at 6-months post quit. We will measure cigarettes per day at baseline. We will then compute cigarettes per day at each follow-up timepoint by summing the number of cigarettes each person reports on each day of their follow-up survey and dividing by 7.	6 months following baseline.
Assess whether cessation medication utilization mediates the effectiveness of NRTS on 6-month abstinence.	Treatment utilization is one mechanism by which NRTS is hypothesized to have its effect.	Self-report survey items of use of the nicotine patch and nicotine lozenge at 1-, 3-, and 6- months post baseline. These items will be dichotomized as used NRT vs. hasn't used NRT in the 6 months post intervention. In addition, days of NRT use will be computed.	6-months following baseline.

Objective	Brief Description/ Justification of Outcome Measure	Outcome Measured By	Time Frame
Assess whether attitudes towards NRT (safety and efficacy) mediate the effectiveness of NRTS on 6-month abstinence.	We hypothesize that one mechanism of action of NRTS is to cause more favorable attitudes towards NRT.	Self-report survey items at baseline, 1-month, 3-month and 6-month surveys of perceptions of nicotine replacement therapy safety and efficacy. We will assess perceptions of NRT efficacy on a 5-point Likert-scale where higher scores indicate greater efficacy. We will assess safety with a single item measure on a 5-point Likert scale where higher scores indicate greater perceptions of NRT safety.	6-months following baseline.

Objective	Brief Description/ Justification of Outcome Measure	Outcome Measured By	Time Frame
Assess whether intention to use NRT mediates the effectiveness of NRTS on 6-month abstinence.	We hypothesize that one mechanism of action of NRTS is increase intentions to use NRT.	Intention to use NRT is measured at baseline and at 1-, 3-, and 6- month follow-up. Self-report survey item of intention to use nicotine patch and nicotine lozenge in the next 6 months. Intention to use the nicotine patch and nicotine lozenge will be assessed using 2 items regarding intentions to use nicotine patch and nicotine lozenge in one of 5 categories (currently using, plan to use in the next 30 days, plan to use in the next 6 months, may use some day, will never use).	6-months following baseline.

Objective	Brief Description/ Justification of Outcome Measure	Outcome Measured By	Time Frame
Assess whether intention to quit smoking mediates the effectiveness of NRTS on 6-month abstinence. .	We hypothesize that one mechanism of action of NRTS is to increase intention to quit smoking.	We will assess intention to quit smoking at baseline, 1-month, 3-months and 6-months using a self-report survey item from the PHENX toolkit on intention to quit smoking in the next 6 months. The item asks if the patient is planning to quit in the next 6 months with 4 answer choices: yes in the next 30 days, yes in the next 6 months, no in the next 6 months, already quit.	6-months following baseline.

Assess feasibility and acceptability of the NRTS intervention to practitioners, staff and patients to aid in future implementation through a multi-stakeholder process evaluation.	Clinical trials are often conducted without regard to implementation concerns. Collecting implementation data along with effectiveness data can speed the time in which it takes effective interventions to be implemented in real-world practice.	Feasibility and acceptability will be measured 3 ways: (1) Surveys: Patients: to assess acceptability, patients will complete the client satisfaction questionnaire regarding the FreSH study interventions given during the after-visit survey. Practitioners and staff will be measured using the Organizational Readiness to Implement Change measure (completed by the main interventionist at the site) prior to and following site data collection. In addition, practitioners and staff involved in the study will complete the Acceptability of Intervention Measure and the Appropriateness of Intervention measure and Feasibility of Intervention measure prior to and following site data collection. Additionally, the amount of time it takes practitioners to administer the intervention will be timed via REDCap.	For practitioners and staff, surveys will be given at the beginning and end of site data collection. For patients, surveys will be given approximately one day following their visit. Interviews will be done at the end of study participation for patients and practitioners. Administrative data will be collected for the duration of study recruitment.

Objective	Brief Description/ Justification of Outcome Measure	Outcome Measured By	Time Frame
		(2) Interviews: 10-12 patients, 10-12 dentists and 10-12 other staff in study sites assigned to the NRTS condition will participate in interviews at the end of site data collection regarding the feasibility and acceptability of the NRTS intervention. (3) Administrative data: we will assess feasibility of the intervention by assessing the number of patients qualifying for the intervention (NRTS), the number qualifying who are offered the intervention. We will assess acceptability by the number of patients offered the intervention who accept it.	

Objective	Brief Description/ Justification of Outcome Measure	Outcome Measured By	Time Frame
Assess the cost effectiveness of the NRTS intervention.	To aid in future implementation, we will determine how much the intervention costs relative to how effective the intervention is at increasing abstinence from smoking.	We will assess cost per quit and cost per quality adjusted life year. Costs of the intervention will be determined by the value of time for practitioners to take the AAR training, provide AAR to patients, and counsel on NRT use, the costs for the ADA brochures, NRT (based on national average purchase price), and any additional smoking cessation services used by participants (based on national average purchase price). Quality adjusted life years will be estimated based on differences in future healthcare costs based on existing literature.	N/A

5 STUDY DESIGN

Study design. This is a 2-arm, phase 2, cluster randomized effectiveness clinical trial that will be conducted in the National Dental PBRN, which is a network of participating dental practitioners who conduct practice-based oral health research. This study will utilize the resources of the ARC and NCC. The node coordinators will utilize ARC's established communication methods to inform prospective dental practitioners about the study opportunity. Enrolled practitioners will recruit and enroll patients during routine dental care appointments.

Study Population: The practitioner study population will include National Dental PBRN practitioners, dental therapists and hygienists. We will enroll approximately 50 practices across the Midwest and Northeast Regions of the PBRN. Each practice will recruit approximately 24 patients for a patient population of 1200.

Means of Data Collection: Data collection will be centralized. Survey data will be collected using the REDCap platform administered by the NCC. CO data will be collected via the iCO quit personal CO monitor. The iCO quit devices will be mailed to participants who will take the test using an app downloaded to their smartphone. Interviews will be completed by phone and audiorecorded.

Interview. Following a practitioner's participation in the trial, we will conduct stakeholder interviews with 10-12 dentists, 10-12 other staff, and 10-12 patients. Topics include patient and practitioner experiences with the intervention, provider perceptions of barriers and facilitators to adoption and tools/supports/structures needed for implementation.

Collection Timeframe: Following screening and consent, patient data will be collected at 5 timepoints, baseline, immediately following the baseline visit, and target of 1 month, 3 months, and 6 months following the visit. For practitioners, data collection will occur prior to initiation of site data collection and following completion of site data collection.

6 STUDY POPULATION

6.1 Participant Inclusion Criteria

In order to be eligible to participate in this study, a practitioner must be a National Dental PBRN practitioner who meet the following criteria:

- Willing to consent patients to the study following regionally approved procedures
- Is expected to remain in the practice for the 1-year study duration and agrees to collect participant research data
- Verbally affirms that the practice can devote sufficient time in patient scheduling to allow focused recording of all data required for the study. Study activities take approximately 20-25 mins per participant.
- Does not anticipate retiring, selling the practice or moving during the study
- Is affiliated with the National Dental PBRN or is willing to affiliate with the National Dental PBRN in order to participate in the study.

In order to be eligible to participate in this study, a patient must meet all of the following criteria:

- Provide a signed and dated informed consent form
- Willing to comply with all study procedures and be available for the duration of the study
- Age ≥ 18 (except in Nebraska where age of consent is ≥19 years)
- Smokes at least 1 combustible cigarette per day 25 days/month
- Willing to receive texts and emails from the study

6.2 Participant Exclusion Criteria

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

- Does not own a smart phone with internet access
- Unwilling or unable to provide informed consent
- Myocardial infarction or stroke in the past 3 months
- Pregnant or breastfeeding
- Use of tobacco cessation medication in the past week
- Previously enrolled in the study

6.3 Strategies for Recruitment and Retention

Practice recruitment. Network dentists of all specialties, hygienists, and dental therapists in the Midwest and Northeast regional nodes will be approached for interest in study participation by node coordinators. The National Coordinating Center (NCC) will maintain the practitioner database to facilitate recruitment and track Network practitioner training. The node coordinators will use several methods to recruit practices including network webinars, network newsletters, announcements at network meetings, email blasts, and directly targeting practitioners with existing relationships with node coordinators. Interested practitioners will be made "research ready" by being oriented to the Network and completing any institutionally required human subjects research protection training.

Patient participants will be recruited directly by practitioners within each practice during a routine dental visit. Practices will aim to recruit at least 2 patients per month. Practitioners or practice staff will approach consecutive adult patients with a chart documented smoking history and invite them to participate. To increase interest in the FreSH study, practitioners will be given posters and flyers for their offices. Interested patients will begin a self-screening process. The screening process will take place on a tablet computer. Patients will read a study description and indicate whether they are interested in the study. If they are interested, they will complete an eligibility screen on the tablet.

Retention of Practices and Providers within Practices. Several steps will be taken to retain practices. (1) Procedures for recruitment and retention have been tailored to dental practices through an iterative development process involving the piloting of study procedures and feedback from practices. Practitioners will be given a "quick guide" detailing all recruitment procedures. (2) The NCs will leverage their existing relationships with PBRN practitioners to keep them engaged. They will be in regular contact with the practices, providing feedback and support. (3) Incentives will be provided to each practice including "lunch and learns" and study monogramed trinkets designed to increase commitment to the study. (4) Practitioners will be remunerated $100 per patient participant who receives the study intervention and a tablet computer to obtain electronic informed consent (when not using a paper consent form) and administer baseline surveys that they may keep at the end of the study if allowable by their affiliated institution.

Retention of Patients. As part of the enrollment process, patient participants will provide contact information, including mobile/home/work phone numbers, email address, mailing address, and contact information for up to five alternative contacts. They will be asked to provide only phone numbers/addresses at which they give permission for the study team to contact them and leave messages (phone call/voicemails, text messages, and email). Participants will be asked to rank their preferred methods of communication

and Hennepin Healthcare study staff will try their preferred method first. Follow-up assessments will be conducted via online survey (using REDCap). Patient participants will be emailed and/or texted a direct link to the follow-up survey on the first date of their follow-up window. Participants will be able to complete their follow-up surveys on a web browser on any Internet-connected device including a smartphone or tablet. Those who do not respond within 24 hours will be sent the survey link every 24 hours for up to 5 days. If the participant does not complete the follow-up survey by the 5th day, Hennepin Healthcare study staff will begin contacting the participant by telephone and offer the option of doing the follow-up survey via telephone interview. Study staff will attempt to reach participants for up to two weeks. If we do not reach them by phone, email or text, Hennepin Healthcare study staff will call their alternate contacts for updated contact information and send a final letter to their mailing address stating that we have been unable to reach them including a contact information sheet, and a postage paid envelope. We may also send a paper version of the survey. Participants may choose to complete the survey out of the two-week timeframe without prompting from study staff. In addition, their dental practitioner will be contacted by the node coordinator and asked for any updated contact information and to reach out to the participant to ask them to contact the study. Study staff will maintain numbers screened, eligible, consented, randomized, and completed assessments. Whenever possible, we will attempt to collect reasons for dropping out of the study.

Patient participants will receive a custom printed bag with the study name and logo. The bag will contain study materials, information on smoking and oral health, a flyer for the state quitline and some small tokens of appreciation such as stylus pens that have the study name, phone number, and email address printed on them so that they also serve as reminders of study participation (total value of study promotional items will be < $10). Throughout their participation, participants will be treated with respect and study staff will aim to maintain excellent rapport. Study staff will frequently express appreciation to participants and emphasize that by participating they are making a valuable contribution to science. Finally, patient participants will be remunerated for their time and efforts to encourage retention during the follow-up period. Patient participants will receive $20 for the after-visit survey and $20 for completing each of 3 follow-up surveys. Patients in the NRTS arm who report abstinence will be sent a Bedfont iCOquit expired breath CO monitor intended for single patient use and will receive an additional $50 for using the iCOquit to take an exhaled breath CO test. Participants will keep the CO monitor (a $68 value) as it is for single user only. Finally, 10-12 patient participants will be paid $50 for completion of an end of study interview.

6.4 Treatment Assignment Procedures

This is a group randomized trial. All patients within a practice are assigned to the same condition. Practices will be instructed not to tell their patients to which condition the practice has been assigned until after the baseline survey is completed to prevent selection bias.

6.4.1 Randomization Procedures

The NCC Data Manager, who will have no contact with participants or practices, will conduct randomization. Practices will be randomized to NRT or ET (approximately 25 practitioners per condition). Condition assignment will be stratified by practice level patient demographic data (highest percentage minority race/ethnicity vs. lowest) and practice payer mix (highest vs. lowest public insurance/free care). We will use block randomization with permutated block size of 2 and 4. Randomization will occur once the practice has completed all activities required for onboarding.

6.5 Participant Withdrawal or Discontinuation from Study Procedures/Intervention

6.5.1 Reasons for Participant Withdrawal or Discontinuation from Study Procedures/Intervention

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

Participants may choose to discontinue the intervention or study procedure but continue to be followed.

Study sites could be closed by the PI if there are persistent problems with recruitment, or if study recruitment goals are met prior to the site completing recruitment.

6.5.2 Handling of Participant Withdrawals from Study or Participant Discontinuation of Study Intervention

Reasons for participant withdrawal will be documented on a dedicated Case Report Form.

Patient participants will be instructed by study staff to discontinue use of the patch and/or lozenge entirely if a severe reaction develops. They will be instructed to contact the study team (not their dentist) as soon as possible if they experience a SAE or if they have a reaction for which OTC labeling suggests seeing a provider. Practitioners will receive training on how to manage adverse events of NRT. However, for this study,

patient participants and practitioners will be advised that the study staff, not the practitioner, is responsible for managing study-related AEs. Patients who have a study-related SAE (as determined by the study PI and the IRB) will be advised to discontinue use of the study treatment (NRT or ET). All study related SAEs will be followed to resolution using a Case Report Form.

Power calculations and sample size estimates for this study account for 11% lost to follow-up/withdrawal. Thus, we will not replace subjects who withdraw unless attrition and withdrawal exceeds 11% of our planned study sample.

6.6 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the principal investigator. The principal investigator will also promptly inform the IRB and NIDCR and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

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

7 STUDY INTERVENTION

7.1 Study Product Description

Nicotine replacement therapy samples will include a 14-day supply of 14mg transdermal nicotine patches and a 14-day supply of 4mg nicotine lozenges.

Electric toothbrushes will be Sonicare brand. The toothbrushes will have the Seal of Approval from the American Dental Association.

7.1.1 Acquisition

Nicotine replacement therapy will be purchased directly from GlaxoSmithKline. If the NRT is out of stock at GlaxoSmithKline, then GlaxoSmithKline branded NRT will be purchased from an authorized retailer.

Electric toothbrushes will be purchased from a commercial vendor.

7.1.2 Formulation, Packaging, and Labeling

Transdermal nicotine patches, intended for 24-hour use, will be commercially packaged including FDA product insert. Packages include 14, 14mg patches.

Nicotine mini lozenges are intended for PRN use. The nicotine lozenges will contain 81 lozenges (a 2-week supply). Nicotine mini lozenges include the active ingredient of Nicotine polacrilex (equal to 4mg nicotine) and inactive Ingredients: Acesulfame potassiumcalcium polycarbophilflavorsmagnesium stearatemannitolpotassium bicarbonatesodium alginatesodium carbonatexanthan gum. The product is packaged for commercial sale and contains the FDA package insert.

Electric toothbrushes: N/A

7.1.3 Product Storage and Stability

Nicotine patches and lozenges are to be stored at room temperature away from excessive humidity.

Electric toothbrush: N/A

7.2 Dosage, Preparation and Administration of Study Product

Nicotine patches and lozenges do not require preparation. Nicotine patches are the 14mg strength, nicotine lozenges are the 4mg strength.

Electric toothbrushes: N/A

7.3 Accountability Procedures for the Study Product

Nicotine patches, lozenges and toothbrushes will arrive at Hennepin Healthcare. When they arrive, we will log their arrival and expiration date. We will document when they are mailed to the practice, the tracking number, and when they are received. Distribution will be measured via the patient after visit survey.

7.4 Study Behavioral Intervention Description

Practices will be randomly assigned to study condition (NRTS or ET). Practices will be instructed not to disclose the intervention condition to the patient participant until after the baseline survey has been completed.

AAR (both conditions): Practitioners (NRTS and ET) will be encouraged to deliver AAR to all patients regardless of trial participation.

Patient participants will receive:

- monogramed study bag
- study trinkets such as pens and post-it notes
- a brochure published by the ADA describing the effects of tobacco use on oral and general health
- contact information for their state tobacco quitline
- information about tobacco cessation medications
- study contact information
- the follow-up schedule
- condition specific information about NRT/ET
- consent form
- HIPAA form

NRT sampling (NRTS): Practices assigned to NRTS will dispense NRT samples in addition to AAR.

Patient participants will receive: a “starter pack” consisting of a 2-week supply of both nicotine patches (14 mg) and lozenges (4 mg; combination NRT [C-NRT]). Practitioners will spend 1-3 minutes on instruction prior to dispensing samples. Instructions for NRT use are provided on each medication package. We will also include FAQs and information dispelling misconceptions. Practitioners will neither explicitly advise nor discourage combined use or concomitant use with cigarettes. Patients will receive oral and written instructions including how to obtain more nicotine replacement therapy if interested (e.g., from their primary care provider, or purchased over the counter). Practitioners will instruct patients that the samples are an opportunity for smokers to learn about two NRT products that can be used individually or together (participant choice, including none at all). Some suggested uses could be:

- to get experience with the products and determine if they like them
- to reduce smoking or restrict where they smoke

- to make a practice quit attempt
- to get started on quitting

Electric Toothbrush: ET practices will provide participants with an ET in addition to AAR. We selected ET to incentivize participation in usual care practices. ETs are more effective than manual toothbrushes at removing plaque and reducing gingivitis and gum bleeding. We will select an ET with the ADA seal of acceptance with a value similar to the NRT samples to equalize incentives and practitioner time across groups. Patients will receive instructions from the practitioner about how to use the ET.

7.5 Administration of Intervention

The intervention will take place in person during dental visits. Providers will ask all patients if they smoke, advise those who smoke to quit, and refer patients to the state quit line. Participants will then be given a sample (either nicotine replacement therapy or an electric toothbrush) and given brief use instructions. REDCap will automatically record the time it takes to give participants the intervention by timing the amount of time spent on each screen which displays the intervention script. Practitioners can opt out of having this information used for data analysis.

7.6 Procedures for Training Interventionists and Monitoring Intervention Fidelity

Training. Practitioners will complete an online training of Ask-Advise-Refer prior to beginning the study intervention. Practitioners will then complete a live training regarding site-specific study procedures. Practitioners will be given quick guides which provide scripts for the intervention and a list of study procedures.

Fidelity. Fidelity will be monitored via the patient after-visit survey which will ask about practitioner intervention behavior as well as whether medication was provided during the patient's visit to the dentist.

8 STUDY SCHEDULE

8.1 Practitioner enrollment

Practitioners enrolled in the National Dental PBRN in the Midwest and Northeast Nodes who express interest in the study and meet eligibility criteria will be invited to participate. Study information and instructions will be provided to interested practitioners by node personnel. After eligibility is determined and practitioners are enrolled, practice training materials will be provided to describe the participant selection procedures, methods for approaching patients and obtaining informed consent, methods for intervention delivery and data collection, and other study procedures for the practitioners and office staff who will help to execute the study. A summary flow chart will provide an overview of all study visits and study procedures/data collection for each visit. The principal node coordinator will conduct training with the NCs. NCs will conduct in-person or remote protocol and electronic data management system training with practitioners and office staff prior to initiating the study. The training ensures that the practitioner and staff understand the study procedures and receive instruction on the consent process, and the electronic data capture system. The NCs will maintain close contact with the practitioners prior to and throughout the study implementation period.

The study schedule will proceed in the following stages on a rolling basis:

- Each Node will enroll practitioners into the study to obtain a total of approximately 25 practitioners;
- Practitioners will complete activities to be deemed research-ready;
- Prior to beginning data collection, practice staff in the NRTS condition will complete assessments about the feasibility and acceptability of the intervention.
- NCs will train research-ready practitioners and their office staff in the appropriate study procedures.
- Practices will screen and enroll eligible patients into the study.
- At the end of site enrollment, practitioners and practice staff will complete feasibility and acceptability assessments again.
- In addition, at the end of site enrollment 10-12 dentists and 10-12 staff involved in the study will complete an interview about acceptability of NRTS and attitudes towards future implementation of NRTS.

An overview of patient study procedures to be completed at each study visit can be found in Appendix A, and the Schedule of Events has been provided in the Appendix at the end of this document.

8.2 Screening/Enrollment/Baseline/study intervention

Visit 1, Day 0

- Practitioner Reviews dental record to determine eligibility criteria
- Practitioner verifies inclusion/exclusion criteria via an electronic screening questionnaire taken by the participant
- Practitioner obtains and documents consent from participant with electronic consent or paper consent. Participants will digitally sign the consent form if offered electronically, and will sign paper consent forms if a paper version is used.
- Participant completes contact information form
- Participant completes baseline survey
- Practitioner provides study intervention

8.3 Follow up Visits[1]

Data collection timepoint 2, Day 0 (allowable range 0-14)

- Following visit, administer after visit survey via email, text, or phone.

Data collection timepoint 3, Day 30 (allowable range 28-44)

- Administer 1-month follow-up survey via email, text or phone.
    - Assess adverse events via survey.

Data collection timepoint 4, Day 90 (allowable range 83-104)

- Administer 3-month follow-up survey via email, text or phone.
    - Assess adverse events via survey.

Data collection timepoint 6, Day 180 (allowable range 173-210)

- Administer 6-month follow-up survey via email, text or phone.
    - Assess adverse events via survey.

Data collection timepoint 7, Day 180 (allowable range 174-234)

- Participants who are abstinent will take a CO test

Data collection timepoint 8, Day 180 (allowable range 173-240)

[1] Note: Participants may choose to complete the survey out of the timeframe without prompting from study staff.

- 10-12 patient participants in NRTS condition complete an interview about acceptability of NRTS and attitudes about future implementation of NRTS

9 STUDY PROCEDURES/EVALUATIONS

9.1 Study Procedures/Evaluations

9.1.1 Screening and enrollment (day 0; in dental practice)

- Participants will be enrolled during a routine dental visit at their general practice dental provider's office. Patients who smoke combustible cigarettes will be offered the study.
- Interested participants will complete a screening assessment via REDCap on tablet or via a link texted or emailed to their phone. The self-report eligibility screen includes age, smoking status, smartphone ownership, medical contraindications to NRT (pregnancy, breastfeeding, recent heart attack or stroke), and smoking cessation medication use in the past week (any use of nicotine replacement therapy [patch, gum, inhaler, lozenge, nasal spray], any use of Chantix/varenicline, use of bupropion/zyban/Wellbutrin for the purpose of quitting smoking).
- Finally, interested and eligible participants will complete an electronic written informed consent via REDCap or will complete a paper consent form. If required a HIPAA form will be completed on paper or electronically (depending on the regional IRB rules).

9.1.2 Baseline survey (day 0; in dental practice)

The baseline survey will be administered prior to the intervention. It includes the following measures:

- Contact information
- Demographics (biological sex, gender, ethnicity, race, age)
- Toothbrushing habits
- Smoking history (cigarettes per day, time to first cigarette in the morning, previous quit attempts, past cessation treatment)
- Interest in quitting
- Confidence to quit
- Attitudes about nicotine replacement therapy

9.1.2 Study intervention (day 0; in dental practice)

Practitioners, using a script, will provide the study intervention (see 7.4). They will:

- Ask about smoking status
- Advise those who report smoking to quit
- Offer a referral to the state quitline

- Provide a sample bag containing either nicotine replacement therapy or an electric toothbrush.

9.1.3 After visit survey (Target day 0, in dental practice or remotely)

Following the dental visit, participants will be sent a link via email or text with an after-visit survey. If participants do not respond to the survey within 3 days, they will receive a phone call from Hennepin Healthcare study staff. They will be paid $20 for after visit survey completion.

The after-visit survey will assess the following:

- the elements of ask-advise-refer as a fidelity check (asked about smoking, advised to quit, asked about interest in quitting, discussed medications, advised to use medication, provided with medication, referred to quit line)
- Demographics (educational attainment, urban/suburban/rural community, zip code, number in household, income, health insurance, dental insurance)
- oral health status
- relationship with dentist
- other non-cigarette tobacco product use
- acceptability of the intervention

9.1.4 1-month follow-up survey (target day 30, conducted remotely)

The one-month follow-up survey will be conducted via email or text. Participants who do not respond will be followed up by phone and/or mail. Participants will be paid $20 for survey completion.

The one-month follow-up survey will assess the following:

- smoking behavior (smoking each day for the past 7 days, date of last cigarette)
- use of other tobacco products (electronic cigarettes, hookah, cigars, chewing tobacco, snus, pipes, other)
- quit attempts
- use of nicotine patch and lozenge (including sample patches and patches purchased outside of study; use in past 7 days, ever use)
- reasons for nicotine patch/lozenge use
- perceived patch/lozenge effectiveness
- enjoyment of patch/lozenge
- use/purchase of smoking cessation medications,
- use of smoking cessation counseling
- patch/lozenge side effects (nausea, headache, heartburn, mouth soreness, dizziness, dry mouth, sore jaw, excessive salivation, insomnia, hiccups, burning in throat/mouth, skin irritation, skin redness, skin itchiness)

- belief that side effects were caused by patch/lozenge
- perceived oral health status
- frequency of toothbrushing
- type of toothbrush
- interest in stopping smoking
- readiness to quit
- attitudes about nicotine patch, lozenges.

9.1.5 3-month follow-up survey (Target day 90, conducted remotely)

The 3-month follow-up survey will be conducted via email or text. Participants who do not respond will be followed up by phone and/or mail. Participants will be paid $20 for survey completion.

The 3-month follow-up survey will assess the following:

- smoking behavior (smoking each day for the past 7 days, date of last cigarette)
- use of other tobacco products (electronic cigarettes, hookah, cigars, chewing tobacco, snus, pipes, other)
- quit attempts
- use of nicotine patch and lozenge (including sample patches and patches purchased outside of study; use in past 7 days, ever use)
- reasons for nicotine patch/lozenge use
- perceived patch/lozenge effectiveness
- enjoyment of patch/lozenge
- use/purchase of smoking cessation medications,
- use of smoking cessation counseling
- patch/lozenge side effects (nausea, headache, heartburn, mouth soreness, dizziness, dry mouth, sore jaw, excessive salivation, insomnia, hiccups, burning in throat/mouth, skin irritation, skin redness, skin itchiness)
- belief that side effects were caused by patch/lozenge
- perceived oral health status
- frequency of toothbrushing
- type of toothbrush
- interest in stopping smoking
- readiness to quit
- attitudes about nicotine patch, lozenges.

9.1.5 6-month follow-up survey (Target day 180, conducted remotely)

The 6-month follow-up survey will be conducted via email or text. Participants who do not respond will be followed up by phone and/or mail. Participants will be paid $20 for survey completion.

The 6-month follow-up survey will assess the following:

- smoking behavior (smoking each day for the past 7 days, date of last cigarette)
- use of other tobacco products (electronic cigarettes, hookah, cigars, chewing tobacco, snus, pipes, other)
- quit attempts
- use of nicotine patch and lozenge (including sample patches and patches purchased outside of study; use in past 7 days, ever use)
- reasons for nicotine patch/lozenge use
- perceived patch/lozenge effectiveness
- enjoyment of patch/lozenge
- use/purchase of smoking cessation medications,
- use of smoking cessation counseling
- patch/lozenge side effects (nausea, headache, heartburn, mouth soreness, dizziness, dry mouth, sore jaw, excessive salivation, insomnia, hiccups, burning in throat/mouth, skin irritation, skin redness, skin itchiness)
- belief that side effects were caused by patch/lozenge
- perceived oral health status
- frequency of toothbrushing
- type of toothbrush
- interest in stopping smoking
- readiness to quit
- attitudes about nicotine patch, lozenges.

9.1.6 CO test (target day: within one week of 6-month follow up survey)

Participants who report being abstinent for the past 7 days on the 6-month follow-up survey will be sent, via overnight mail, a portable CO monitor (iCOquit, Bedfont Scientific) with instructions for use. Participants will be instructed to take the CO test within 24 hours of receipt. If they do not take the test within 24 hours, the study will provide email, text, or phone reminders daily for 14 days. Patient participants will download the iCOquit app onto their cellphones. The study will provide a username and password for the app. The participant will then follow the instructions on the app to take a CO test. Hennepin Healthcare study staff will log into the app (with the pre-specified username and password given to the participant) to get the test result. Thus, all the data from the iCOquit is deidentified (a username and passcode provided by the study, and the participant's test result). They will be instructed to delete the app once CO data is received. Participants will be paid $50 for a completed CO test.

9.1.7 Patient interview (target day: within one month of 6-month follow-up survey)

10-12 patients in the NRTS condition will be selected to participate in a 60-minute interview by study staff at Northwestern University about the feasibility and acceptability of NRTS. Participants will be paid $50 to participate in the interview.

9.1.8 Clinic Staff Baseline Surveys (Prior to staff training in study procedures)

Prior to receiving training, all clinic staff at sites assigned to the NRTS condition who will be involved in the conduct of the FreSH trial will complete baseline surveys. Surveys to be administered include:

- Organizational Readiness for Change (to be completed by the person at the clinic who will perform the study intervention)
- Feasibility of intervention measure
- Acceptability of intervention measure
- Appropriateness of intervention measure

9.1.9 Clinic Staff Follow-up Surveys (end of site data collection)

Following the end of recruitment at a site, all staff in practices who were assigned to the NRTS condition and who were involved in the FreSH trial will complete follow-up surveys. Surveys to be administered include:

- Organizational Readiness for Change (to be completed by the person at the clinic who will perform the study intervention)
- Feasibility of intervention measure
- Acceptability of intervention measure
- Appropriateness of intervention measure

9.1.10 Clinic staff interviews (end of site data collection)

10-12 dentists and 10-12 other staff from practices assigned to the NRTS condition will participate in a 60-minute phone interview conducted by Northwestern University Co-Investigators to gain information about future implementation of NRTS in dental practices. The interviews will focus on obtaining feedback about feasibility, acceptability, and implementation of NRTS. Participants will be paid $50 for completing the interviews.

10 ASSESSMENT OF SAFETY

10.1 Specification of Safety Parameters

Safety monitoring for this study will focus on Unanticipated Problems (UPs) involving risks to participants, including unanticipated problems that meet the definition of a serious adverse event. In addition, adverse events (AEs) including SAEs will be recorded, and the PI will monitor these events to grade severity, relationship to the study intervention, and assess whether the nature, severity, or frequency is unexpected. Any time a participant spontaneously reports (calls the study or the practitioner) an AE including SAE or UP, it will be recorded. Practitioners will be trained to direct any participants reporting AEs to Hennepin Healthcare study staff and will alert study staff of any reports of AEs. Adverse events to study medication will be queried at the 1-, 3-, and 6-month follow-up assessments.

Safety events will be recorded and reported into the National Dental PBRN safety event reporting system maintained by the NCC if the events are determined to be both unexpected and related to the study intervention. Study PI Japuntich, will be informed via the safety event system when events are reported.

10.1.1 Unanticipated Problems

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

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

10.1.2 Adverse Events

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.

10.1.3 Serious Adverse Events

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

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

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

The PI will record all 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, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization. We also instruct participants to contact study staff via phone if they have problems with the medication

10.3 Characteristics of an Adverse Event

Each event will be recorded on an appropriate case report form that includes assessment of the characteristics defined below. These characteristics, along with the frequency of an event's occurrence, will be considered in determining if the event is a UP.

10.3.1 Relationship to Study Intervention

To assess relationship of an event to study intervention the following guidelines are used:

1. Related (Possible, Probable, Definite)

a. The event is known to occur with the study intervention, and/or

b. There is a temporal relationship between the intervention and event onset and/or

c. The event abates when the intervention is discontinued, and/or

d. The event reappears upon a re-challenge with the intervention.

2. Not Related (Unlikely, Not Related)

a. There is no temporal relationship between the intervention and event onset, and/or

b. An alternate etiology has been established.

10.3.2 Expectedness

The Study PI and/or study-appointed, clinically/medically responsible individual will determine whether an AE is expected or unexpected. An AE 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.

10.3.3 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

10.4 Reporting Procedures

10.4.1 Unanticipated Problem Reporting

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

- appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- a detailed description of the adverse event, incident, experience, or outcome;

- an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

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

- Unanticipated problems that are serious adverse events will be reported to the IRB within 1 week of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

All unanticipated problems will be reported to NIDCR concurrently with reporting to the IRB. These reports will be made to NIDCR's centralized reporting system via Rho Product Safety:

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

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

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

10.4.2 Serious Adverse Event Reporting

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

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

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

All SAEs will be followed until resolution or stabilization.

11 STUDY OVERSIGHT

The principal investigator will be responsible for study oversight, including monitoring safety, ensuring that the study is conducted according to the protocol and ensuring data integrity. Study progress and safety will be reviewed monthly by the PI, when data will be reviewed for safety concerns and data trends. Reportable events that arise during the conduct of the study will be promptly submitted to the IRB. If necessary, additional steps may be taken to ensure data integrity and protocol compliance.

12 CLINICAL SITE MONITORING

NIDCR will determine whether clinical site monitoring is needed.

Node Coordinators will provide study training to practitioner sites. Remote monitoring activities will be conducted at the NCC and ARC Nodes to evaluate study processes and documentation based on NIDCR standards and principles of good clinical practice.

Remote monitoring activities will primarily involve quality management (QM) procedures to ensure completeness and accuracy of data collection. This study will follow the general guidelines for conducting monitoring for the network's clinical studies documented in Chapter 6 of the National Dental PBRN Network Operating Procedures. The NOP and all study-specific documentation will be stored on the HUB website and accessible to all study team members. The NIDCR reserves the right to conduct independent clinical site monitoring as necessary.

STATISTICAL CONSIDERATIONS

12.1 Study Hypotheses

Hypothesis 1 (primary): Participants receiving the NRTS intervention will have a higher frequency of biochemically confirmed abstinence at 6 months post enrollment compared to ET.

Hypothesis 2a: Participants receiving NRTS will be more likely to have a 24-hour quit attempt than ET.

Hypothesis 2b: Participants receiving NRTS will have greater reductions in smoking heaviness compared to baseline than ET.

Hypothesis 3a: Use of nicotine replacement therapy (patch and lozenge) will mediate the effect of NRTS on biochemically confirmed abstinence at 6 months post enrollment.

Hypothesis 3b: Perceptions of NRT safety and efficacy will mediate the effect of NRTS on biochemically confirmed abstinence at 6 months post enrollment.

Hypothesis 3c: Intention to use NRT will mediate the effect of NRTS on biochemically confirmed abstinence at 6 months post enrollment.

Hypothesis 3d: Intention to quit smoking will mediate the effect of NRTS on biochemically confirmed abstinence at 6 months post enrollment.

Hypothesis 4a: NRTS will be considered feasible to administer in dental settings.

Hypothesis 4b: NRTS will be acceptable to practitioners and patients.

Hypothesis 5: NRTS will be cost effective.

12.2 Sample Size Considerations

The primary outcome for the UH3 trial is biologically verified (via CO testing) 7-day point prevalence abstinence (PPA) from use of combusted tobacco at 6-months post-intervention, and the power calculations presented here pertain to this outcome only.

Calculations were done using a variety of assumptions for cluster size (the number of patients per cluster, which we assumed was fixed across clusters), the Intraclass Correlation Coefficient (ICC), the PPA in the ET group (P¬ET), and the PPA in the NRTS group (P¬NRTS). Specifically, we used ICCs of.01, .013, and.016; cluster sizes of 20, 22, and 24 (corresponding to total sample sizes 1000, 1100, and 1200); P¬ET values of 4.5%, 5%, and 5.5%; and effect sizes (PNRTS – PET) of 5%-7% in increments of 0.5%. The number of clusters was kept fixed at 50, and all calculations assumed a type 1 error of 5% and a two-sided test.

For the ICC, we observed a value of.013 in preliminary studies and assume that is the most likely ICC we will observe in our study. The P¬ET range was based on the observed value of 4.7% in preliminary studies and further assumes CO will verify only 85% of self-report. We believe the effect size range represents achievable intervention effects, and brackets the effect size of 5.5% seen in a similar study.

The target cluster size of 24 was chosen to provide approximately 80% power to detect effect sizes of 5.0 percentage points or greater assuming an ICC of 0.013 and a rate in the ET arm of 5.5% (Table 11.1). Using the point estimates of 4.7% for ET and the effect size of 5.5% seen in a similar study would result in almost 90% power. With an ET rate of 5.5%, power increases to over 90% for effect sizes of 6 percentage points or more, and over 94% for effect sizes of 6.5 percentage points or larger.

Table 11.1. Power to detect given effect sizes

ICC	# clusters	cluster size	Total N	Power					
				Prob in ET arm	Diff in quit rate between NRTS and ET arms				
					5.0%	5.5%	6.0%	6.5%	7.0%
0.010	50	24	1200	4.5%	86.8%	91.5%	94.7%	96.9%	98.2%
				5.0%	84.6%	89.8%	93.5%	96.0%	97.7%
				5.5%	82.4%	88.1%	92.2%	95.1%	97.1%
0.013	50	24	1200	4.5%	84.9%	90.0%	93.6%	96.1%	97.7%
				5.0%	82.6%	88.2%	92.2%	95.1%	97.0%
				5.5%	80.3%	86.3%	90.8%	94.1%	96.3%
0.016	50	24	1200	4.5%	83.0%	88.5%	92.4%	95.2%	97.1%
				5.0%	80.6%	86.5%	90.9%	94.1%	96.3%
				5.5%	78.3%	84.5%	89.3%	92.9%	95.4%

12.3 Final Analysis Plan

Demographics, baseline smoking history, and smoking behavior will be summarized across the aggregate sample and descriptively compared between clinics and treatment groups. Any large imbalances at the individual level will be considered for inclusion as a covariate. We will include the cluster-level stratification factors as covariates (minority race/ethnicity and payer mix). The distribution of each of the primary and secondary

study outcomes will be assessed using both parametric and graphical methods to determine the most appropriate modeling distribution (e.g., binomial, normal and zero-inflated distributions). Transformations of the outcome (e.g., log transform towards normality) will be considered if a model does not meet its assumptions. We will report point estimates (unstandardized effects size/magnitude) and associated 95% confidence intervals (precision). All hypotheses will be evaluated at a two-tailed alpha level of .05.

Sex and race as biological variables. We will test for effect modification by sex and race for the primary outcome. However, insofar as our proposal does not include hypotheses regarding sex and racial differences in treatment outcomes, we will conduct our hypothesis testing using both sexes and all races combined. This will be accomplished by adding a product term of group and sex or race (each will be evaluated separately) to the model. Given the low power for interaction effects, we will report the simple effects and associated confidence intervals both numerically and graphically to determine the nature of any effect modification.

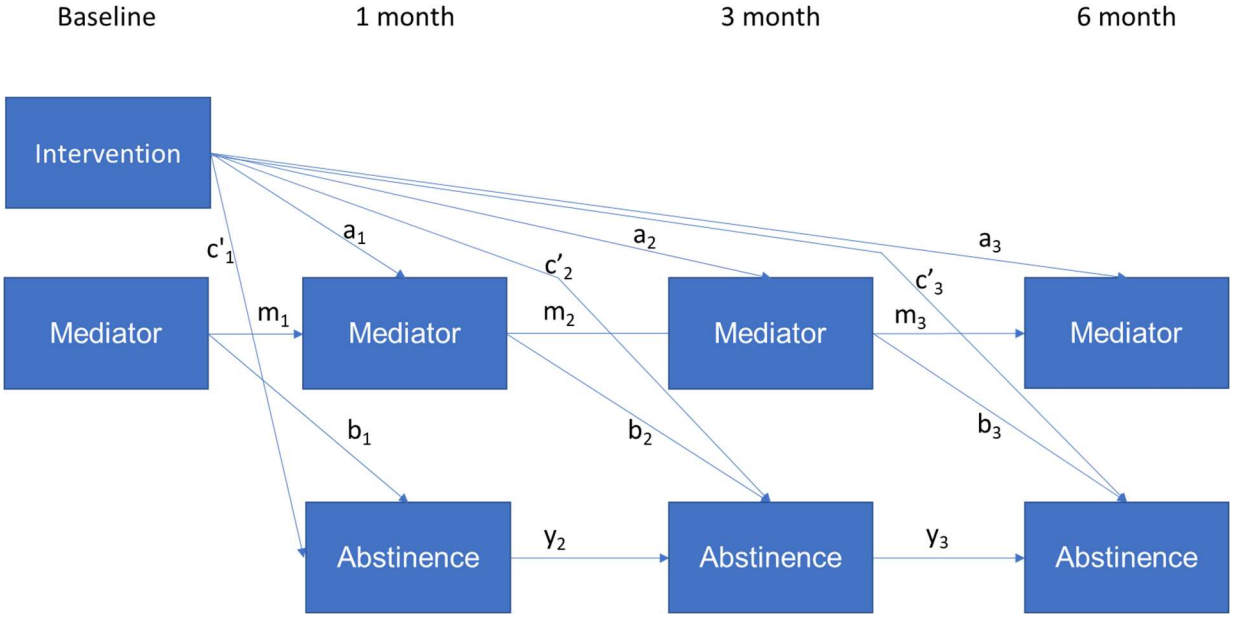
To test hypothesis 1, we will compare treatment groups with respect to the primary outcome (biologically verified 7-day PPA from use of combusted tobacco at six months) using generalized hierarchical linear modeling[43–45] with a binomial distribution and logit link (aka mixed effects logistic regression) that account for the clustering of individual observations within dental practice, while adjusting for various patient and practice related factors.[46,47] The first level of the model (participant) will include any individual level covariates. The second level of the model will include the fixed effects for treatment group (ET=0, NRTS=1) and the cluster level stratification factors and a random effect for the participant level intercept. A significant coefficient for the treatment group indicator with an odds ratio > 1 would provide support for the effectiveness of NRTS on smoking abstinence at 6 months.

This same model framework will be used to examine the secondary outcomes of abstinence at 1 month and abstinence at 3 months and whether there was a quit attempt at 1,3, or 6 months. To determine whether the intervention had an effect on smoking heaviness over time, we will use a three-level hierarchical linear model that will account for the nesting of observations within persons and persons nested within practices. The first level of the model will include a categorical fixed effect for time (baseline [reference group], 1 month, 3 month, 6 month). The second level of the model will include fixed effect for any individual level covariates and random coefficient for the level 1 intercept. The third level will include for treatment group and the cluster level stratification factors and a random effect for the participant level intercept, including the terms for the time vectors representing the cross-level interactions. Significant terms for the cross-level interaction would indicate that the change in smoking heaviness differed

by treatment group, and will be followed up with examination and plots of the estimated marginal means do determine whether those in the NRTS group had greater decreases in smoking heaviness compared to the ET group.

We will test whether NRT utilization, perceptions of NRT effectiveness and safety, intent to use NRT, and intent to quit mediate the relationship between study group (ET vs NRTS) and smoking abstinence using a cross-lagged panel model (CLPM) in a structural equation modeling (SEM) framework.[48,49] In a CLPM, the mediator and outcome at time t is regressed on arm, the mediator at t-1 and the outcome at t-1. Prior to estimating a final model, we will test for stationarity for the structural paths by comparing whether a model in which the paths are invariant fits significantly worse than one in which the paths are free to vary. We will also include the same set of covariates used in the primary analysis as time invariant covariates We will assess model fit using root mean square error of approximation (RMSEA) and the comparative fit index (CFI). Our criteria for good model fit will include an RMSEA of .08 or below[50] and a CFI of .95 or above.[51] A significant indirect effect,[52] based on bootstrapped standard errors,[53] would provide evidence for mediation.[48,54] We will account for the clustering of participants within practices by including a random effect for the intercept terms in each path equation by employing the multilevel form of SEM (2-1-1-1 design).[55,56] We will conduct separate models for each mediator.

Figure X. Cross lagged panel model for testing mediation. Covariates omitted for clarity.



Missing data. For all participants, we will attempt to gather follow-up information and reasons for dropout regardless of protocol completion and censor at the point of drop out. PBRN studies routinely attempt to collect reasons for dropout.[57] We anticipate

having about 11% attrition, as was found in previous work. We will compare baseline data between those with and without missing data and examine whether there are variables that are related to missingness. Analysis will use maximum likelihood (ML) approaches to produce estimates of the model parameters. One advantage of a ML approach when compared to other approaches such as multiple imputation, is that it makes use of all available data without requiring imputation of missing values, it is more efficient, and maintains congeniality between the missing data estimation and the analytical model.[58] ML estimates have been shown to be consistent when missing data is related only to covariates and observed values of the outcome.[59,60]

To evaluate readiness for future implementation, we will conduct qualitative analyses of stakeholder interviews to gain insight into future implementation efforts. Using a structured debriefing form, post-interview notes will be written after each interview and reviewed by all Co-Is. Interviews will be professionally transcribed and deidentified. A qualitative expert will develop analytical codes using an iterative method in which interview notes are reviewed to: 1) consider whether the qualitative research agenda questions are appropriate and complete, 2) whether content saturation has been reached, and 3) develop an initial coding structure. Deductive codes will be drawn from the interview questions; inductive codes will capture concepts that emerge from the interviews. Once the coding scheme is developed, coders will independently code the transcripts and meet to resolve discrepancies. Final codes will be entered into NVivo qualitative data analysis software. A qualitative expert will conduct a framework matrix analysis[61] to identify the most effective ways to organize the content and logistics of conducting the trial to help guide our trial protocol.[61,62]

We will also report on descriptive statistics regarding the patient client satisfaction questionnaire, and the provider implementation measures.

Finally, we will conduct a cost effectiveness analysis (CEA). Our analyses will assess the incremental cost-per-quit and cost-per-quality adjusted life year (QALY) saved from a societal perspective and also a health system (e.g., accountable care organization) perspective in accordance with current practice recommendations.[63] The incremental cost-per-quit of NRTS vs. ET is estimated as: (Total costs at follow-up for NRTS participants - Total costs at follow-up for ET participants)/(Total successful quits at follow-up for NRTS participants - Total successful quits at follow-up for ET participants). The cost per QALY saved is estimated as (Total lifetime costs for NRTS participants - Total lifetime costs for ET participants)/(Total quality-adjusted life expectancy for NRTS participants - Total quality-adjusted life expectancy for ET participants).

The major direct costs for NRTS are described in the table below. Though some costs are incurred in both the NRTS and ET arms, we will measure them explicitly in the event that they do not entirely offset one another.

Cost data		
Cost	Basis for valuation	NRTS and/or ET
RX for Change AAR dental training	Value of time	NRTS & ET
AAR provided to smokers	Value of time	NRTS & ET
ADA Brochures	Purchase/photocopy/printing cost	NRTS & ET
NRT	National average NRT purchase price[162]	NRTS
Counseling on NRT use	Value of time	NRTS
Additional smoking cessation medications and services*	National average purchase price[162]	NRTS & ET

*Applies only to societal-perspective analyses

Personnel time will be valued at the national average wage for the relevant job type. The value of time for clinical personnel who may bill for their services will be based on a prorated fraction of a billing unit specific to the clinician type. We will track all participants' use of smoking cessation services (counseling, medication), whether provided as part of the intervention or not, to determine the net impact of the intervention on treatment use. This will allow us to determine whether the intervention in any way crowds out cessation efforts that would have occurred absent the intervention. We will make the conservative assumption that the provision of an electric toothbrush to participants randomized to ET does not in itself affect cessation and so we will ignore the cost of the toothbrushes. For the cost-per-quit analyses, costs from Table 1 will be assessed for each participant during the full course of follow-up. For the cost per QALY analyses, differences in future health care costs will be estimated based on existing literature.[64–67]

Cessation outcomes for the cost-per-quit analyses will be based on the study's primary outcomes. Quality-adjusted life expectancy will be estimated based on CDC life table data adjusted for smoking status and weighted by health utility (quality adjustment) data from prior studies.[68–71]

We will use Monte Carlo simulation methods which aggregate uncertainty in parameter estimates (e.g., 95% confidence bounds) and develop confidence bounds on our cost-per-quit estimates. Following standard methods of economic evaluation in prior studies, we will also perform parameter-specific sensitivity analyses in which individual parameters are varied singly and in combination, through plausible ranges to assess the relative impact different elements of the program have on overall cost-effectiveness.[72–75]

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate medical and research records for this study, in compliance with regulatory and institutional requirements for the protection of confidentiality of participants. 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.

Summary of Source Data/Documents:

- Screening forms
- Consent forms
- Study questionnaires
- CO test results
- Audio recordings of interviews

14 QUALITY CONTROL AND QUALITY ASSURANCE

Quality Management (QM) is the overall process of establishing and ensuring the quality of processes, data, and documentation associated with clinical research activities. It encompasses both quality control (QC), and quality assurance (QA) activities. Quality management processes involve review of consent procedures and electronic case report forms (CRFs) for completeness, timeliness and accuracy; if irregular trends or other ongoing issues are identified, virtual or in-person monitoring visits may be conducted. The NCC, with input from the study team and ARC, will develop a study-specific Data Quality Management Plan (DQMP) that sets up a continuous quality control process with the goal of reducing the turnaround time between error detection and correction.

Data and safety monitoring will be the joint responsibility of the Hennepin Healthcare study team, ARC and the NCC. The NCC will develop a data management system for study data collection and safety event reporting. Study progress and safety will be reviewed monthly by the PI utilizing reports provided by the NCC. The PI will maintain primary responsibility for reporting of safety events to ensure participant safety and reviewing protocol deviations and considering study modifications if needed to ensure data integrity.

Questionnaire data will be obtained electronically through the NCC-managed study-specific electronic data system. The EDC provides: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation; 3) access to study datasets that can be imported into common statistical packages; and 4) procedures for importing data from external sources.

14.1 Subject Accrual and Compliance

a. Measurement and reporting of subject accrual, adherence to inclusion/exclusion criteria – Review of the rate of patient subject accrual and adherence to inclusion/exclusion criteria will provided by the NCC as part of the study quality management reports. The reports will be made available on a set schedule, throughout the 24-month recruitment period for the study. The study team will review monthly to ensure that participants meet eligibility criteria and diversity goals outlined in the grant proposal. If the enrollment sample shows an imbalance with respect to study sites, or patient characteristics/ demographics, the research team might request modifications to recruitment strategies, such as increasing recruitment at certain offices to offset the imbalance.

b. Measurement and reporting of participant compliance to treatment protocol – Study progress and safety will be reviewed quarterly (and more frequently if needed). Data on adherence to the protocol will be collected monthly by research

staff and reviewed quarterly by the PI with the research team and the study statistician. The study team will review reports as part of their monthly agenda. Compliance will be reviewed with the NIDCR, ARC and NCC at the quarterly meeting and if the study team has concerns about whether compliance has reached a level that might inhibit the ability of the study to test its primary hypotheses, a correction plan will be developed with NCC/ARC/NIDCR and study team input.

c. Measurement and reporting of practitioner compliance to treatment protocol- Practitioner compliance to the treatment protocol will be measured during patient after visit surveys. We will verify that patients report being asked about their smoking status, advised to stop smoking, and offered a referral to treatment. We will also verify that participants received the sample corresponding to their condition. We will monitor this monthly and provide feedback to providers on their performance in the form of an emailed study newsletter.

15.2 Data quality management

The NCC will provide the study team with QC reports that include information on data completeness and accuracy as well as protocol compliance. The QC reports will be updated on a set schedule and accessible through the HUB website. A statement reflecting the results of the review will be sent to the NIDCR in the annual report. Data quality will be assessed using measures such as number of missing forms, percent missing data, and number of missed assessment timepoints. Guidelines for concern regarding these measures are included in the Data and Quality Management Plan.

The NCC will make all reports available on the HUB for review, as needed. The schedule of report posting will be detailed and maintained in the Data and Quality Management Plan

15.3 Plans for data quality assessment

Data quality will be formally assessed on an annual basis. A data quality report will be generated annually that summarizes findings, provides recommendations based on best practices, and suggests follow-up actions.

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, recruitment materials, and all participant materials will be submitted to the sIRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the sIRB before the changes are implemented in the study.

15.3 Informed Consent Process

All consent forms and related documents will be sIRB- approved. For participating patients: an electronic written, informed consent form will be completed via REDCap. HIPAA information as required by state law will be shared with the patient. The practitioner or appropriate trained office staff will explain the research study to the patient and answer any questions that may arise. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study. For participating providers: providers will receive a study consent form and completion of study surveys and/or will be considered consent to participate.

All study participants may withdraw consent at any time throughout the course of the study.

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

For the study, there are no exclusions based on gender, race or ethnicity. Study participation will be limited to adults aged 18 (except in Nebraska where consent age is ≥ 19 years) and over as nicotine replacement therapy is not FDA approved for children.

15.5 Subject Confidentiality

Protection of Subjects - all study data will be kept in strict confidence. No information will be given to anyone without permission from the subject. This statement guarantees confidentiality. Confidentiality is assured by use of identification codes linked to the subject. Health Information Portability and Accountability Act (HIPAA) guidelines of all Network clinical sites will be followed.

Confidentiality during safety event reporting – Safety event reports and annual summaries will not include subject identifiable material. Each will include the identification code only.

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor.

Authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to dental records for the study participants. The clinical study site will permit access to such records.

Certificate of Confidentiality

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

NIH Data Sharing Policies

As described in section 17, it is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). PIs and funding recipient institutions will ensure that all mechanisms used to share data include proper plans and safeguards to protect the rights and privacy of individuals who participate in NIH-sponsored research.

15.6 Future Use of Stored Specimens and Other Identifiable Data

Once interviews are transcribed and transcriptions verified, audio recordings will be destroyed. Deidentified transcripts will be used to analyze interview data. These transcripts and study data will be kept for at least 5 years and until the end of the parent grant.

16 DATA HANDLING AND RECORD KEEPING

The investigators are responsible for ensuring the accuracy, completeness, and timeliness of the data reported. The investigators will maintain adequate case histories of study participants, including accurate case report forms (CRFs), and source documentation (if not collected electronically).

16.1 Data Management Responsibilities

The PI in collaboration with the NCC will review reports of data completeness and accuracy as well as protocol compliance on an ongoing basis throughout the study. A statement reflecting the results of the review will be sent to the NCC/NIDCR in the annual report. Data quality will be assessed using measures such as time from study visit to data entry, time to resolution of data queries, number of missing forms, and proportion of all study variables queried.

16.2 Data Capture Methods

Practitioner and patient CRFs will be captured through the NCC's electronic data capture system, as described in the study-specific data management plan developed and maintained by the NCC. CO tests will be taken through the iCOquit smokerlyzer app. Hennepin Healthcare study staff will enter the CO test results into the electronic data capture system. The electronic data capture system will include participant names and contact information (telephone numbers and mailing addresses). These will be destroyed at the end of data collection.

Interviews will be conducted virtually by secure zoom or by phone. Interviews will be recorded and later transcribed for analysis. The recordings will then be destroyed and there will be no link to any individual identifiers. De-identified transcripts will also be stored in the NCC data management system.

16.3 Types of Data

- Study questionnaires
- CO test results
- Audio recordings of interviews

16.4 Schedule and Content of Reports

16.4.1 Schedule

Ongoing Data Review Meetings	Schedule	Content
Study team meetings	Weekly	Ongoing data review
Study Team PI with NIDCR PO Calls	Monthly	Ongoing data review
Study team biostatistician and analyst meeting with NCC	Monthly	Ongoing data review
Study Team PI and Executive Team	Quarterly	Study update

16.5 Study Records Retention

Study records will be maintained for at least five years from the date that the grant federal financial report (FFR) is submitted to the NIH. Records that were housed by the NCC will be maintained with the NCC; records that were housed by the study team will be maintained by the study team.

16.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol or Good Clinical Practice requirements. The noncompliance may be on the part of the participant, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

These practices are consistent with investigator and sponsor obligations.

All protocol deviations will be entered into the NCC reportable events tracking system and reported to NIDCR and IRB, according to their requirements.

17 PUBLICATION/DATA SHARING

This study will comply with all applicable NIH Data Sharing Policies. See *https://grants.nih.gov/policy/sharing.htm* for policies and resources. 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. As needed we will also refer to the Network's publication policy which is publicly available at https://www.nationaldentalpbrn.org/publications/.

NIH Public Access Policy

The NIH *Public Access Policy* requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to *PubMed Central* immediately upon acceptance for publication. This ensures that the public has access to the published results of NIH funded research.

NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information

The study is a clinical trial and will comply with the NIH policy that establishes the expectation that all investigators conducting clinical trials funded in whole or in part by the NIH will ensure that these trials are registered at ClinicalTrials.gov, and that results of these trials are submitted to ClinicalTrials.gov.

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APPENDICES

APPENDIX A: SCHEDULE OF EVENTS

The following list of documents are officially affiliated with the protocol and will be submitted to the IRB as a part of the protocol. As such, changes to these items will require a protocol amendment.

Appendix A: Patient Schedule of Events

Location	Study Task	Dental visit (Day 0)	After visit (Target date: day 1, allowable window days 0-14)	One-month follow-up (Target date: Day 30, allowable window days 28-44)	Three-month follow-up (Target day 90, allowable window 83-104)	Six-month follow-up (Target day 180, allowable window 173-210)	CO test (Target day 180, allowable range 174-234)	Interview (Target day 180, allowable range 173-240)
Dental visit (Dental clinic)	Assessment of eligibility	X						
	Baseline survey	X						
	Written informed consent	X						
Dental clinic	Study intervention	X						
Research laboratory (remote)	Fidelity monitoring		X					
	Assessment of adverse events			X	X	X		

	Follow-up survey			X	X	X		
	CO test to verify abstinence						X	
	Interview							X