Preventing Caries in Preschoolers: Testing a Unique Ser
Delivery Model in American Indian Head Start Programs

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Principal Investigator: Patricia Braun, M.D., M.P.H.

NIDCR Program Official: Ruth Nowjack-Raymer, MPH, PhD

NIDCR Medical Monitor: Holli Hamilton, MD, MPH

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STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practices (GCP) as required by the following

1) United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)

2) ICH E6; 62 Federal Register 25691 (1997)

3) NIH Clinical Terms of Award

All key personnel have completed Human Subjects Protection Training.

SIGNATURE PAGE

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

Site Investigator: Patricia Braun, M.D., M.P.H

Signed: Date:

Name: Patricia Braun, M.D., M.P.H
Title: Associate Professor, Department of Pediatrics
Biology, School of Medicine
University of Colorado Anschutz Medical Campus

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LIST OF ABBREVIATIONS

ACASI	Audio Computer Assisted Survey Interview
AE	Adverse Event
AI	American Indian
AI/AN	American Indian/Alaska Native
BRFQ	Basic Research Factors Questionnaire (referred as ACASI survey)
CHRs	Community Health Representatives
CNOHR	Center for Native Oral Health Research
COHS	Community Oral Health Specialist
COMIRB	Colorado Multiple Institutional Review Board
CTCAE	Common Terminology Criteria for Adverse Events
dmfs	Decayed, missing and filled tooth surfaces index (primary)
DSMB	Data and Safety Monitoring Board
ECC	Early Childhood Caries
FV	Fluoride Varnish
HIPAA	Health Information Portability and Accountability Act
HRSA	Health Resources and Services Administration
HS	Head Start
HSCs	Head Start Centers
IHS	Indian Health Service
MAR	Missing at Random
MCAR	Missing Completely at Random
MNAR	Missing Not at Random
MOP	Manual of Procedures
NHANES	National Health and Nutrition Examination Survey
NIDCR	National Institute of Dental and Craniofacial Research
NN	Navajo Nation
NNHRRB	Navajo Nation Human Research Review Board
OHP	Oral Health Promotion
PI	Principal Investigator
RDHs	Registered Dental Hygienists
SA	Specific Aim
SAE	Serious Adverse Event
SODM	School of Dental Medicine
UCD	University of Colorado Anschutz Medical Campus
UP	Unanticipated Problems

PROTOCOL SUMMARY

Title:	Preventing Caries in Preschoolers: Testing a Unique Service Delivery Model in American Indian Head Start Programs
Phase:	IV
Population:	Children ages 3-6 years in Head Start (HS) Programs in the Navajo Nation (NN)
Number of Sites:	3 (Navajo Nation, University of Colorado Anschutz Medical Campus, University of California San Francisco)
Study Duration:	The study duration will be 6 years. This includes 1 year for planning, 6 months for each intervention year (1 & 2) for recruitment, 3 years for implementation of the interventions: baseline and follow-up evaluations, and 1 year for close-out and analysis.
Subject Participation Duration:	Each participant will be in the study for up to 3 years; 2 years of intervention and a third year for follow up measures.
Description of Agent or Intervention:	Intervention will include application of fluoride varnish (FV~~)~~ ~~offered~~) offered 4x a year and oral health promotion (OHP) and education for 2 years.
Objectives:	Primary: 1) To develop, with input from tribal/community members, a manualized intervention protocol for an early childhood caries (ECC) prevention program to be delivered by specially trained community paraprofessionals, called Community Oral Health Specialists (COHS) 2) To implement and evaluate the delivery of FV and OHP programs in American Indian (AI) Head Start Centers (HSCs) under the following conditions: Group #1—FV offered 4x a year and OHP for 2 years provided by COHS Group #2— Usual oral health care made available by the IHS Dental providers (or other usual providers) 3) To assess efficacy by comparing decayed, missing, and filled

primary tooth surfaces (dmfs) over time between the 2 groups.

Secondary:

1) To assess specific caries patterns
2) To investigate moderators/mediators of the intervention conditions as ascertained via questionnaires on oral health knowledge, attitudes, and behaviors
3) To investigate participant utilization of medical and dental services for oral health problems and intervention costs, intervention savings, net intervention costs, costs/net costs per participant, costs/net costs per unit decrease in caries associated with each intervention condition

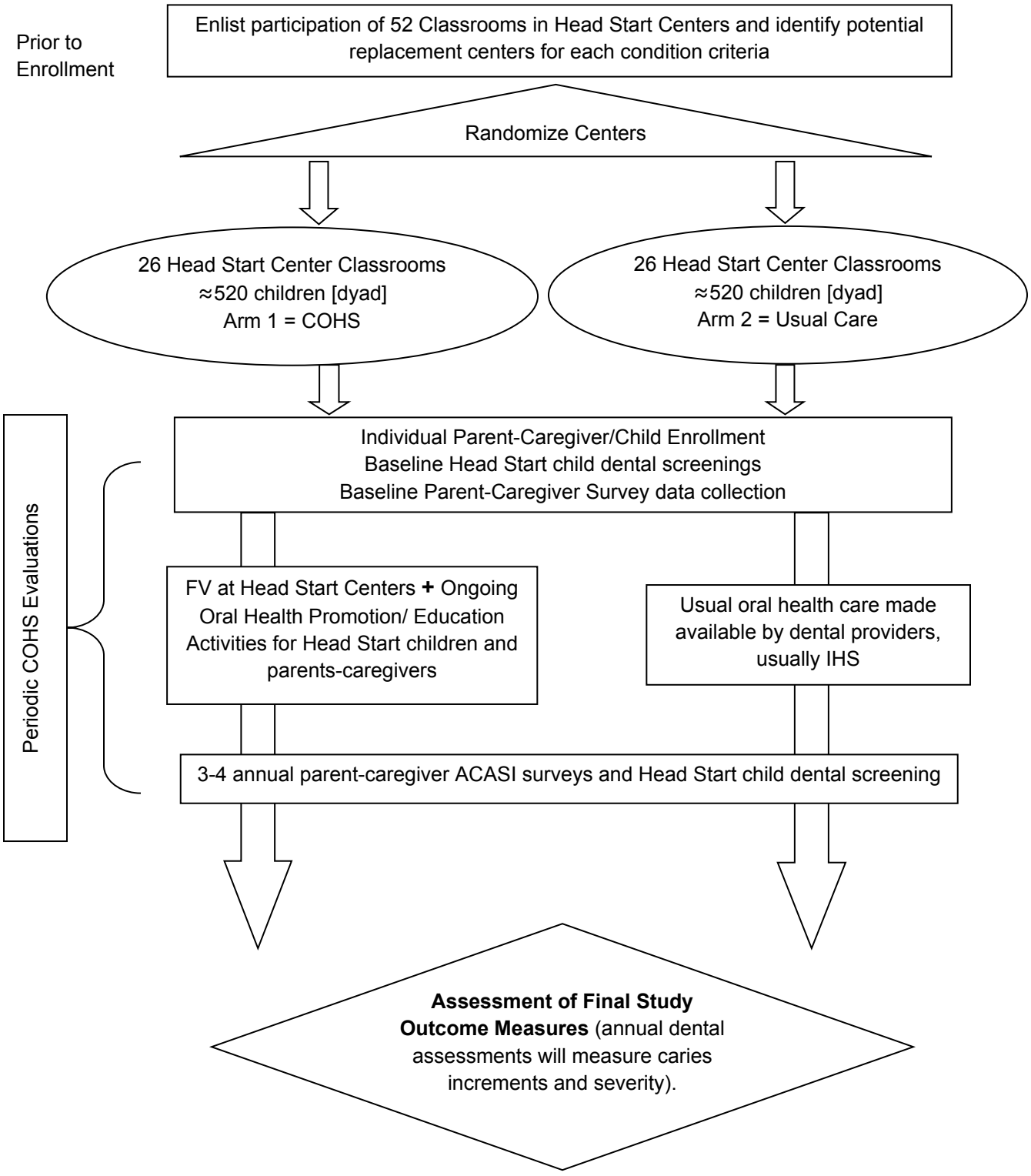
Description of Study Design:

The study design will be a cluster randomized design. HSCs within the Navajo Nation (NN) will be stratified by population size and randomized within strata to the two groups. All children within the HSC classrooms and a parent/primary caregiver of each child will be invited to participate in the intervention condition to which the HSC is randomized. Children will participate after informed consent by the parents and after informed consent by the participating parent/primary caregiver for her/himself. To be consistent with NIDCR, we will count the child and participating parent/primary caregiver dyad as one enrolled participant (unit). Baseline and annual measures of dmfs and of dental knowledge, attitudes, and behavior will be collected. Changes in these outcome measures will be compared between the two groups.

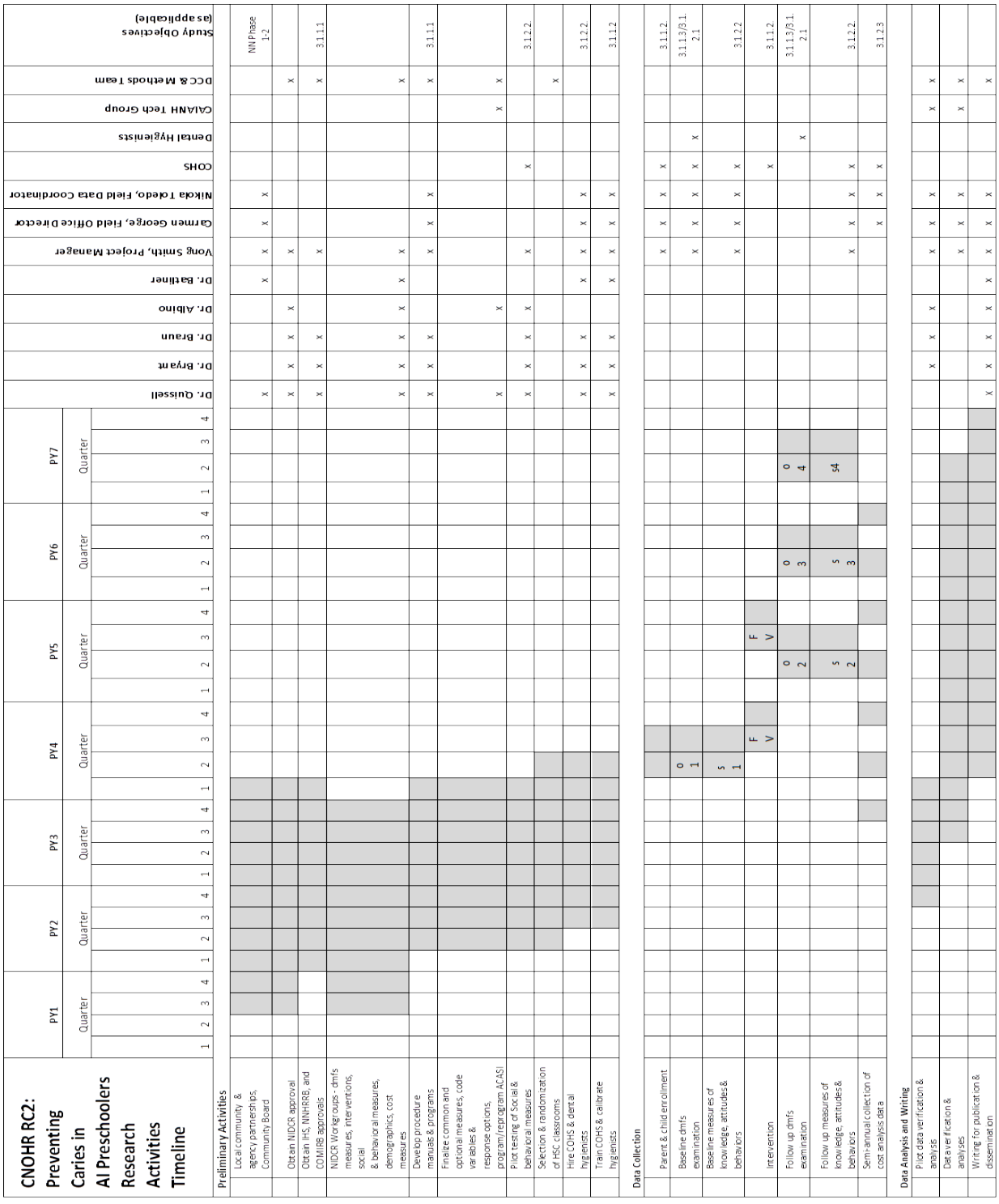
Estimated Time to Complete Enrollment:

6 months for each intervention year (year 1 and year 2)

Schematic of Study Design:



Study Timeline:



1 KEY ROLES

Individuals:

Program Official: Ruth Nowjack-Raymer, MPH, PhD
Title: Program Official
National Institute of Dental and Craniofacial Research
Address: 6701 Democracy Blvd.
Room 640 Mail Stop 4878
Bethesda, Maryland 20892-4878
Phone: (301)594-5394 Fax:
e-mail: Ruth.Nowjack-Raymer@nih.gov

Principal Investigator: Patricia Braun, M.D., M.P.H
Title: Associate Professor, Department of Pediatrics, School of Medicine
Address: University of Colorado Anschutz Medical Campus Denver Healtth and Hospital,
Eastside Family Health Center
501 28th St. Denver, CO 80205 Phone: 303-436-4694Fax: 303-436-4665
e-mail: patricia.braun@ucdenver.edu

Medical Monitor: Holli Hamilton, MD, MPH
Title: Senior Medical Officer
National Institute of Dental and Craniofacial Research
Address: 6701 Democracy Blvd.
Room 638 Mail Stop 4878
Bethesda, Maryland 20892-4878
Phone: (301)451-3852 Fax: 301-480-8322
Email: hamiltonho@nidcr.nih.gov

Institutions:

University of Colorado Anschutz Medical Campus
American Indian and Alaska Native Programs
Center for Native Oral Health Research PI: Judith Albino, PhD
Address: Nighthorse Campbell Native Health Building - Mail Stop F800
13055 E. 17th Avenue, 3rd Floor
Aurora, CO 80045
Phone: 303-724-0151 Fax: 303-724-1474
e-mail: Judith.albino@ucdenver.edu

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Early childhood caries (ECC) is defined as dental caries in the primary teeth of children of the ages of 0-6 years.[1] Although ECC is largely preventable and the general prevalence of this common childhood infection is in decline, marked disparities exist.[2-4] The disease levels seen in American Indian/Alaska Native (AI/AN) children reflect the most extreme disparities, suggesting the need for effective, culturally accepted interventions.[5-7] Approaches that combine simple clinical procedures such as Fluoride Varnish (FV) with Oral Health Promotion (OHP) activities for children and parents/caregivers in a community-based setting appear to offer effective and efficient interventions in the prevention of ECC,[8-13] yet professional personnel for delivery of these services are not always available. Consequently, alternative provider concepts, such as the use of dental therapists as extenders of the current dental care delivery system, are increasingly being explored, especially for use in geographically isolated communities.[14-16] Although the effectiveness of some of these new strategies has not yet been fully demonstrated, there is evidence that health outcomes can be enhanced through interventions provided by trained paraprofessionals in community settings.[17-22] This study will test innovative prevention services delivery programs and measure their effects on caries incidence in an AI preschool population.

The most recent Indian Health Service (IHS) report cites caries experience rates of 79% for AI/AN preschool children, with 68% having untreated dental decay, a prevalence more than 3 times greater than their non-Native counterparts[5, 22] In Navajo Area, dental decay among preschool children is severe; with the mean number of decayed, missing and filled tooth surfaces (dmfs) for 2-5 year olds reaching 19.0 surfaces,[23] the highest in Indian Country. These data suggest that rates of dental decay experienced by AI/AN children today are the highest in the U.S., and perhaps the highest in the world.

While substantial evidence exists to document the poor oral health status of these children, there have been very few reports of intervention. Only Bruerd[20] has successfully demonstrated a community-based intervention to prevent ECC with AI/AN children. The project was funded from 1985-1990 to determine whether community-based health education could reduce the prevalence of decay among AI/AN children[21]. Twelve pilot Head Start (HS) sites received varying levels of OHP training and planned multidisciplinary educational interventions for individuals and communities. For the 12 sites, the average prevalence of decay in the post-program cohort was 25% less after 4 years; for the 5 sites that continued to implement the

program for 4 additional years, the difference was 38%.[20] The project did not deliver any direct clinical preventive services, and it did not have a controlled design.

Among the clinical interventions to prevent caries in children, the use of fluoride demonstrates the strongest evidence base and most predictable success.[17] Professional and public health measures, including the use of fluoride mouth rinses, gels, dentifrices, and dietary supplements, are common means of preventing dental caries.[1] These measures are limited in scope, however, and benefit primarily those individuals who have financial means and access to regular professional oral health care services. FV is a professionally available topical agent that has been employed in the prevention of caries since 1964. It has been used extensively in European countries, and was approved by the FDA in 1991 as a cavity liner and desensitizing agent. Evidence from systematic studies of FV, while far more robust than for other professionally applied modalities, remains limited.[18] Systematic reviews and meta analyses establish mean caries prevention at approximately 33% for primary teeth with the use of FV at 6-month intervals.[9, 19, 23] These recent reviews, paired with the unique and favorable clinical characteristics of FV, have prompted the publication of clinical practice recommendations from the American Dental Association that support use of FV as the preferred technique for caries prevention therapy in children under the age of 6.[18]

Education programs attempt to increase knowledge, positive attitudes toward oral health care, and ensuing behaviors on the part of parents/caregivers about ECC and contributing factors. Parent education efforts may be aimed at influencing behaviors such as promoting dental visits, feeding, and/or oral hygiene practices. While parental educational attainment has an inverse relationship with ECC, knowledge alone appears to be insufficient to produce behavior change in children or adults. Systematic review of dental health education literature yields very few well-designed intervention studies and insufficient evidence for long term behavior change or significant reductions in caries incidence.[24]

On the basis of treaties, the U.S. government has a trust responsibility to provide health care to members of federally recognized tribes—a duty filled by the IHS since 1955. IHS, however, provides care to only about 1.5 million out of 4.1 million who identify themselves as AI/AN, and is tremendously underfunded. This underfunding leads to very limited funding for dental health care within the IHS. Long waits for routine dental visits are common and specialty dental services are not provided.[25]

Community-based health services have sometimes been delivered by specially trained paraprofessionals drawn from the community being served, with the implicit logic that members of a community are able to better communicate with patients and understand the barriers to care. In AI/AN communities, trained paraprofessionals known as Community Health Representatives (CHRs) have extended health care services for many years. While these paraprofessionals have worked successfully to educate clients in such areas as diabetes

control, smoking cessation, cardiovascular disease prevention, and medication compliance, their usefulness in promoting oral health has not been tested.

Head Start (HS) is a comprehensive child development program serving children ages 3-6 and their families. This community-based, child-focused program has an overarching goal of increasing the social competence of young children in low-income families. The HS Performance Standards mandate the program of services that grantee and delegate agencies must maintain; among these are standards supporting the provision of health, including oral health, education and services to children and families.[26]

A pilot study of specially-trained Community Oral Health Specialists (COHS) administering FV and OHP in AI children on a Northern Plains reservation was developed and implemented in 2001-2005 by the initial Principal Investigator of this study, Dr. David Quissell, to reduce ECC in AI children. The program was funded by a grant from HRSA Office of Rural Health Policy (HRSA 4 DIARH0003). The COHS completed a 160-hour training program that included orientation to health and oral health, science and prevention of dental caries, clinical procedures, and clinical activities related to screening, varnish application, and referrals. The program was based on home visits. The COHS completed 2,379 visits to 1,263 children. Among the children enrolled, about 83% received at least 1 COHS service and more than half received 2 or more standard doses of FV. An evaluation of the program was done using dental exams at baseline and follow-up, but the evaluation did not have sufficient statistical power to demonstrate efficacy of the intervention.

In summary, ECC is a major oral health problem among AI/AN children, and oral health funding for these children through the IHS is very limited. The investigators of this study will design an oral health intervention that has the potential of being cost-effective in the AI/AN community. Several elements will be combined together to create an oral health intervention that might reduce ECC in AI/AN children. These elements will include the use of specially trained COHS to administer FV and OHP in AI/AN children within HS programs. The program will also undergo a rigorous statistical evaluation.

2.2 Rationale

The hypothesis of this study is that an intensive intervention of specially trained COHS administering FV (offered 4x a year) and OHP for 2 years for AI children ages 3-6 in HSCs (Group 1) vs. the delivery of usual oral health care made available by the IHS Dental providers or other usual providers (Group 2) will reduce the dmfs increment in the Group 1 children when compared to the Group 2 children and show improved parent/caregiver dental knowledge, attitudes, and behaviors.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Potential risks include disclosure of confidential information including oral health status, extent of oral disease, oral health knowledge, attitudes, and behaviors, and effect mediators or moderators. There is also the potential of psychological distress associated with the oral health screening and application of the FV with young children. Parents/caregivers and children will have the opportunity to terminate their involvement in the study at any time. Study staff will be trained in techniques to keep study data confidential. Patient identifying information will not be included in the research databases. Once data are collected, a research database will be created in which data are recorded using research ID numbers. All data will be stored on password-protected network drives, and paper copies of any data or consent forms will be kept in locked file cabinets.

Adverse reactions to the FV are extremely rare; particularly since dispensing of the FV and the single unit dosage delivered to each participant will be controlled. Adverse reactions may include temporary change in tooth color[27] or potential risk of contact allergy to the colophonium resin base if the varnish is applied to ulcerated gingival tissues. According to the FV package insert, edematous swelling has been reported only in rare instances, especially following application to extensive surfaces with FV. Though extremely rare, acute exacerbation of asthmatic conditions, or dyspnea, has occurred in asthmatic people. Nausea can occur in patients with known sensitive digestive systems, especially following extensive applications. More information is available from the FV MSDS form *(Appendix A)* attached. Intervention staff will be instructed to monitor children following fluoride application, recognize these adverse reactions and respond with prompt referral to the IHS dental clinic. After attending to urgent or emergent needs of the child, intervention staff will contact the study PI immediately to report the event and complete reporting requirements.

2.3.2 Known Potential Benefits

Families in the intervention arm will be provided with toothbrushes and toothpaste supplied at regular intervals to meet the needs of all family members throughout the study. Families in the usual care arm will also receive toothbrushes and toothpaste after the completion of each annual survey. All participating children will receive a thorough oral health screening, a service not always available. If a child is found to have a dental emergency, e.g., a dental abscess, he/she will be immediately referred to the Head Start teacher, who has procedures in place for managing medical emergencies.

The study will provide knowledge to potentially allow for the development and implementation of an effective oral health program for the prevention of ECC in rural AI populations.

3 OBJECTIVES

3.1 Study Objectives

3.1.1 Primary:

3.1.1.1 To develop, with the input from tribal/community members, a manualized intervention protocol for an ECC prevention program for delivery by specially trained community paraprofessionals, called Community Oral Health Specialists (COHS)

3.1.1.2 To implement and evaluate the delivery of FV and OHP programs in AI Head Start Centers under the following conditions:

Group 1 - FV (offered 4x a year) and OHP for 2 years by specially trained COHS; toothbrushes and toothpaste supplied for entire family

Group 2 - Usual oral health care made available by their usual dental providers, usually IHS; toothbrushes and toothpaste supplied for entire family

3.1.1.3 To assess efficacy by comparing dmfs over time between the two groups

3.1.2 Secondary:

3.1.2.1 To assess specific caries patterns

3.1.2.2 To investigate moderators/mediators of the intervention conditions as ascertained via questionnaires on knowledge, attitudes, and behaviors

3.1.2.3 To investigate participant utilization of medical and dental services for oral health problems and intervention costs, intervention savings, net intervention costs, costs/net costs per participant, costs/net costs per unit decrease in caries associated with each intervention condition

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measure

Decayed, missing, and filled primary tooth surfaces (dmfs) of the children in the study at baseline, and annually for 3 years.

3.2.2 Secondary Outcome Measures

3.2.2.1 Dental caries patterns (anterior, facial/lingual, molar, fissure caries, demineralization, etc.)

3.2.2.2 Variables that may serve as moderators/mediators of the intervention conditions as ascertained via questionnaires on knowledge, attitudes, and behaviors

3.2.2.3 Participant use of dental and health services for oral health problems, program costs associated with each intervention condition, net program costs, costs per participant, costs of caries and caries averted

4 STUDY DESIGN

This is a multicenter, Phase IV, cluster randomized trial to determine whether an intensive intervention of COHS's administering FV (offered 4x a year) and OHP for 2 years in an AI population of children ages 3-6 years in HSCs on the Navajo Reservation vs. usual oral health care made available by the IHS dental providers will reduce the dmfs measure in the children. A cluster randomized design was chosen to reduce the potential for contamination between the 2 intervention groups.

There are approximately 96 HSC classrooms in the NN (based on 2011-2012 school year). We will stratify HSCs on the basis of population size, and randomly assign the HSC classrooms to the 2 arms of the study within the strata. This will make the number of children in each of the 2 arms of the study approximately equal.

The intensive intervention group will have the specially-trained COHS administer FV to the children 4x a year and provide OHP to the parents/caregivers and to the children in the HS classrooms, for 2 years. The other randomized group will have usual oral health care made available by the IHS Dental providers or other community providers.

Enrollment of HSCs will be done over a period of 6 months (in each year, year 1 and year 2). Upon parental consent of the child and parent/primary caregiver consent for her/himself, the HS children from each HSC classroom will be enrolled in the study. Each consented child will participate in the study for up to 3 years. A baseline assessment of the dmfs measure for each child will be done (objective 3.1.1.3 and 3.1.2.1/ outcome 3.2.1 and 3.2.2.1), and a baseline assessment of the dental knowledge, attitudes, and behaviors of the parents/caregivers (objectives 3.1.2.2 and 3.1.2.3/ outcome 3.2.2.2 and 3.2.2.3). The interventions will be administered for 2 years in the Head Start classrooms. The number of interventions a participating child receives will vary with the length of time that the child attends the Head Start class. Annual assessments of the dmfs measure for the children and the dental knowledge, attitudes, and behaviors of the parents/caregivers will be made for 3 years. The 3rd annual assessment is included to determine changes in the outcome measures for up to 18 months after the FV and OHP have ended, to assess the longer term effects of the intervention.

The primary outcome of the study will be changes from baseline in dmfs (dmfs increment at two and three years) between the 2 groups. Secondary outcomes will include possible changes in caries patterns, and potential moderators/mediators of treatment effect such as parental knowledge, attitudes and behaviors, and the cost of each of the two intervention conditions.

The dmfs measures (objective 3.1.1.3 and 3.1.2.1/ outcome 3.2.1 and 3.2.2.1) will be made by oral screening of the children, to be completed by calibrated dental hygienists who will visit each HSC in both the COHS intervention (Group 1) and the Usual Care (Group 2) arms.

Questionnaires, known as the Basic Research Factors Questionnaire (BRFQ) or Audio Computer Assisted Survey Interview (ACASI) survey, of dental knowledge, attitudes, behaviors and service utilization (objectives 3.1.2.2 and 3.1.2.3/ outcome 3.2.2.2 and 3.2.2.3) will be completed by the parents/caregivers annually, and the data will be entered into laptop computers. We will follow the families whose children age out of Head Start and make arrangements for them to complete the child oral health screening and parent questionnaires at a convenient time and location. All data collected on laptops in the field will be sent first to UCD and then uploaded to the central statistical coordinating center.

NIDCR has appointed a Data Safety and Monitoring Board to provide oversight of the studies and review of interim analyses for all ECC projects in the consortium.

A Manual of Procedures (MOP) has been created to detail the conduct and operations of the study. It transforms the study protocol into a guideline that describes all aspects of the study's organization, operational definitions, recruitment, screening, enrollment, randomization, intervention, follow-up procedures, data collection methods, data tracking and transfer, case report forms (CRFs), and quality control procedures.

The MOP is a dynamic document that will be updated throughout the study to reflect any amendments to the protocol, participant consent forms, CRFs and study procedures. The MOP will be submitted once a year at continuing review unless it requires a change in the protocol. At continuing review, tracked changes and a summary of updates to the MOP made throughout the year will be submitted.

4.1 Substudies

There will be no substudies.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Subject Inclusion Criteria

Once the HSCs on the Navajo reservation are selected for the study, the HSC will be randomized to the two intervention groups. Subject inclusion criteria include:

A) Children ages 3-6 years at the time of enrollment in the Navajo reservation HSCs and having a primary caregiver (preferably parent, or the child's legal guardian as documented by the HSC, but another caregiver such as an aunt or grandmother will not be excluded if he or she is the primary caregiver for the child). A parent or legal guardian must be available to give consent for the child to participate in the study. (Note: multiple children from the same family will not be excluded, provided each child is enrolled in the Navajo Head Start Program.)

B) American Indian, as defined by the tribe, or children of other races/ethnic groups who are in the HS classes on the Navajo reservation (the numbers in this latter group are expected to be very small); and

C) Parent/caregiver able to read, understand, and sign a consent form for his or her own participation, and willing and able to follow study procedures and instructions.

5.2 Subject Exclusion Criteria

A child will be excluded if he/she has any of these conditions:

A) Allergy to any of the components of the FV (for children attending HSCs in Group 1)

B) Ulcerative gingivitis, stomatitis or other conditions resulting in chronically disrupted or irritated oral mucosa (for children attending HSCs in Group 1)

C) Any other conditions or findings that, in the opinion of the investigator, would interfere with or preclude participation in the study in either Group 1 or Group 2.

5.3 Treatment Assignment Procedures

5.3.1 Randomization Procedures

A list of Navajo HSCs and the population sizes will be provided to the University of Colorado Center for Native Oral Health Research (CNOHR) by the Navajo Nation Head Start Program. The HSCs will be stratified by number of HS classes (1 vs. 2-3) and by Navajo

agency (there are 5 agencies), and then the randomization of the HSCs into intervention vs. control will be done within those strata. This will be done to ensure approximately equal sample sizes in the intervention and control groups, and approximately an equal number of intervention and control participants within each Navajo agency. A program will be developed to do the randomization within each stratum. Random numbers will be generated, and if the random number ends with the digit 0-4, the HSC will be assigned to the control arm and if the random number ends with the digit 5-9, the HSC will be assigned to the intervention arm.

5.3.2 Masking Procedures

The interventions will not be masked in this study. Group randomization is being performed in this study in order to minimize cross-contamination of the intervention conditions. Outcome data from the trial will be reviewed centrally by a Data and Safety Monitoring Board for the ECC Consortium. The dental hygienists who screen the children to capture caries outcomes annually will be blinded to the intervention condition, and study investigators will be masked to the final study outcomes, findings, and results until the study is completed.

5.3.3 Reasons for Withdrawal

Children may be withdrawn from the study if they have an adverse reaction to the FV, or any other aspect of the study. They will also be withdrawn if informed consent is withdrawn by the parent/caregiver.

5.3.4 Handling of Withdrawals

If a child withdraws from the study because of an adverse reaction to the FV, it will be requested that the child continue in the evaluation but not the treatment part of the study (i.e., the annual oral health screening, parent education and child classroom sessions, and parent/caregiver questionnaires related to dental knowledge, attitudes, and behavior). This will be done in an attempt to obtain as complete data as possible in follow-up. Of course, if the parent/caregiver wants to withdraw the child from the study entirely, those wishes will be honored.

5.3.5 Termination of Study

The study will be terminated in the field after the intervention and subsequent follow-ups have been completed and the data are completely cleaned and transferred to the investigator's site. The study will be terminated at the investigators' site when all data analyses and study manuscripts have been completed. The central Data and Safety Monitoring Board will be monitoring the safety and efficacy data at intervals specified by them throughout the study, and they have the authority to terminate the study earlier on the basis of these data reviews.

NIDCR, as sponsor, will also be monitoring the study conduct and can recommend termination for cause.

6 STUDY INTERVENTION/ INVESTIGATIONAL PRODUCT

6.1 Study Product Description

6.1.1 Acquisition

The FV will be purchased from 3M (formerly Omnii Oral Pharmaceuticals). The FV will be shipped to the University of Colorado, School of Dental Medicine and forwarded from there to the field office sites.

6.1.2 Formulation, Packaging, and Labeling

The trade-name of the FV is VANISH; it is a 5% Sodium Fluoride white varnish. It is packaged in 0.5ml unit dose packets and applicator brushes. The clearly labeled box contains 1000 sealed unit doses, patient instructions, and dosage stickers to measure quantity dispensed.

6.1.3 Product Storage and Stability

For both intervention conditions, the FV will be labeled and stored in a secure locked office, and out of reach of the children. The FV is a stable agent but is potentially a flammable liquid, so it is recommended that it be stored away from heat, acids, and oxidizing agents. The product MSDS does not provide a recommended storage temperature; we will therefore store it in a climate-controlled, temperature-monitored area between 10°C - 32°C. Handling instructions caution that the product is to be kept away from heat, sparks, open flame, pilot lights and other sources of ignition; avoid breathing vapors, mists, or spray; use general dilution ventilation and/or local exhaust ventilation to control airborne exposures; avoid eye contact; avoid prolonged or repeated skin contact; and recommend the washing of hands after handling and before eating. The product's MSDS is attached to this protocol *(Appendix A)*.

6.2 Dosage, Preparation and Administration of Study Intervention/Investigational Product

Only trained study staff will apply the FV to the teeth of the children whose parents have consented. Aseptic procedures and universal precautions will be maintained at all times. Study records and HS child health records will document the application of the FV. Consistent with CDC Advisory Committee on Immunization Practices and standards of pediatric practice, COHSs will observe the child(ren) for a minimum of 15 minutes following the fluoride varnish

application to observe, resolve, and report any untoward effects. Parents will be provided with post-fluoride instructions each time the FV is administered.

Dosage guidelines include the following:

a. 0.25 mL dosage for children with primary dentition only, or to treat any child requiring limited tooth surface or cavity area coverage

b. 0.40 mL dosage for children with mixed dentition who require extensive tooth surface or cavity area coverage

c. 0.50 mL dosage for children with permanent dentition who require extensive coverage.

Directions for administration are:

1. Treatment areas should minimally be “toothbrush” clean; a prophylaxis is not required.

2. Peel the foil pouch open to expose the VANISH unit-dose package and applicator brush.

3. Tear off the end of the unit-dose package and dispense the entire contents onto the dosing guide.

4. Use the applicator brush to thoroughly mix VANISH, since the components of all sodium fluoride varnishes can separate during storage. While mixing, keep the material evenly distributed inside the inner circle of the dosing guide.

5. Use the dosing guide to determine the amount of VANISH required.

6. For best results, excessive saliva is removed by blotting the tooth surfaces with gauze. Avoid passing applicator brush through pooled saliva to prevent premature setting on bristles.

7. Paint VANISH evenly to the areas being treated.

8. Consistent with CDC Advisory Committee on Immunization Practices and standards of pediatric practice, the COHSs will observe the child(ren) for a minimum of 15 minutes following the fluoride varnish application to observe, resolve, and report any untoward effects.

9. It is best for the patient to keep VANISH in contact with tooth surfaces as long as possible, minimally for 4 hours. During the treatment period, the patient and the parent/caregiver should be instructed to avoid hard foods, brushing teeth, and use of products containing alcohol (beverages, oral rinses). A thorough brushing and flossing will remove excess VANISH from tooth surfaces following the treatment period.

6.3 Modification of Study Intervention/Investigational Product for a Participant

No modifications of the FV will be made.

6.4 Accountability Procedures for the Study Intervention/Investigational Product(s)

Study staff involved in the delivery of the FV will be required to sign out the inventory prior to use. The field office will maintain records of FV units in the inventory and signed out to the study personnel. Lot numbers and expiration dates of the product will also be tracked. Unopened packages and expired fluoride varnish will be returned to the NNFO, where investigators will determine the method of disposal.

6.5 Assessment of Subject Compliance with Study Intervention/Investigational Product

Records of the FV applications and post application observation will be kept for each child in the COHS intervention group as a record of compliance with the intervention. A copy of this information will be placed in the child's Head Start Health Record. Data will be collected on the dental service utilization of each child in the study at the time of the annual ACASI survey measures completed by parents (objectives 3.1.2.2 and 3.1.2.3/ outcome 3.2.2.2 and 3.2.2.3).

6.6 Concomitant Medications/Treatments

Children taking fluoride supplements should discontinue the use of the supplements for 2-3 days following each FV application.

7 STUDY SCHEDULE

7.1 Screening

Children and parents will be screened for entry into the study according to inclusion/ exclusion criteria at the time of enrollment.

7.2 Enrollment

Once the HS programs that will participate in the two treatment arms have been identified, study staff will travel to each participating site and host sessions for teachers, staff and parents to explain the program and begin obtaining informed consent from parents. Upon obtaining informed consent from a parent/legal guardian, the child will be enrolled in the study, along with his/her parent/primary caregiver, who also will provide informed consent. A baseline oral health screening will be completed, along with the ACASI survey completed by the parents/caregivers regarding demographic information about the children, health history, and the parents'/caregivers' dental knowledge, attitudes, and behaviors. Toothbrushes and toothpaste will be given, enough for each family member in the household.

Prior to the varnish dates, under normal and usual conditions, notices will be sent home with children notifying parents of the upcoming varnish date(s) for the COHS intervention group. The notice will state the date(s) that the COHS will be administering FV in the HS classroom.

7.3 Follow-up Visits for FV

The applications of FV for HS children and OHP will be delivered in the HSCs by the COHS (Group 1). FV will be offered 4x a year for 2 years to children in the classroom on the scheduled day; multiple attempts will be made to provide FV to children not in the classroom on the scheduled day. Group 2 participants will receive usual oral health care made available by the IHS Dental providers (or other dental providers outside the reservation).

Annual dmfs measure of the children, and parent ACASI survey to collect dental knowledge, attitudes, and behaviors will take place annually for 3 years. We will follow the families whose children age out of Head Start and make arrangements for them to complete the child oral health screening and parent ACASI survey at a convenient time and location. All annual follow-up assessments will be done as near as possible to the anniversary of the previous year's oral health screening at that HSC, with the goal of completing them within a month either side of that date.

7.4 Follow-up Safety Contact One Week After FV

The COHS will contact the parent/caregiver of each child who received FV 3-10 business days after administration to inquire if the child had any adverse reaction, and/or required any unscheduled (urgent or emergent) health care consultation or visit. If the child had a reaction or required a health care consultation or visit, information regarding the encounter will be documented on the adverse event form and the PI will be notified.

7.5 Final Study Visit

The final study visit will be the third year follow-up evaluations of the children and the final parent/caregiver questionnaires.

7.6 Early Termination Visit

No early termination visits are anticipated.

7.7 Unscheduled Visit

No unscheduled visits are anticipated.

8 STUDY PROCEDURES/EVALUATIONS

8.1 Clinical Evaluations

All children in the study will be provided an oral health screening at baseline and annually thereafter for 3 years (up to 4 screenings total). The oral health screening will collect dmfs measures (objective 3.1.1.3 and 3.1.2.1/ outcome 3.2.1 and 3.2.2.1) of the children, to be completed by calibrated dental hygienists who will visit each HSC in both the COHS intervention (Group 1) and usual care (Group 2) arms. Procedures for the oral health screening will be followed according to the protocol of the Caries Outcome Work Group of the ECC consortium. The Caries Outcome Work Group will develop an SOP for the oral health screenings, which will be attached to this protocol. The criteria for the determination of dmfs measures according to Drury, et al.[28] will be used. These criteria include the counting of both non-cavitated and cavitated carious lesions.

8.2 Laboratory Evaluations

8.2.1 Clinical Laboratory Evaluations

There will be no clinical laboratory evaluations in the study.

8.3 Specification of Safety Parameters

Safety parameters will include any serious adverse events (SAEs) or any unanticipated problems involving risk (UPs) that occur with general participation in the COHS program. Adverse events related to the topical application of FV will be collected for 3-10 days following each application (refer to section 7.4).

8.4 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

8.4.1 Adverse Events

ICH E6 defines an adverse event (AE) as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporarily associated with the use of medicinal (investigational) product including anaphylaxis, oral discomfort, or oral disfigurement. In this study, due to the

anticipated low risk of the intervention, AEs that do not meet the reporting criteria parameters for medically attended events, SAEs or UPs will not be collected.

All medically attended, or medically treated AEs, or circumstances where parent or guardian contacted health care provider for advice regarding AE for this time period will be reported on an AE form. This would exclude an upset stomach or runny nose that required no treatment or health care provider contact in addition to bumps and bruises treated at home. Medically attended events will be captured in a 3-10 day window after FV administration. SAEs and UPs will be captured throughout the study period.

All AEs will be graded for severity and relationship to the study product. Severity may be graded based on the following scale: mild, moderate, severe, life-threatening, death (CTCAE criteria: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Relationship to Study Products: The clinician's assessment of an AE's relationship to the test article will be a part of the documentation process, but it will not be a factor in determining what is or is not reported. If there is any doubt as to whether a clinical observation is an AE, the event will be reported. All AEs will have their relationship to the study product assessed using the terms: associated or not associated. In a clinical trial, the study product must always be suspected. To help assess the relationship of the AE to the study product, the following guidelines will be used:

1. Expected (Associated) Adverse Event: An adverse event that is consistent in the nature or severity with the applicable product information (e.g., Investigator Brochure)

2. Unexpected (Not Associated) Adverse Event: An adverse reaction, the nature of severity of which is not consistent with the applicable product information

The subject with a medically attended AE will be contacted by the PI and/ or the study doctor/dentist via ~~telephone ort~~telephone or in person for a safety follow-up within one week after FV administration and documentation of the AE. Information will be collected on any medically attended visits for cause.

8.4.2 Serious Adverse Events (SAEs) and Unanticipated Problems (UPs)

A serious adverse event (SAE) is an AE that, in the view of *the investigator or sponsor,* results in any of the following outcomes:

1. Death

2. Life-threatening event

- The decision is based on the investigator's opinion. Must place the subject at immediate risk of death. Example: Anaphylaxis. An adverse event that, had it occurred in a more severe form, might have caused death

3. An event requiring inpatient hospitalization or prolongation of existing hospitalization. This excludes any planned hospitalizations for elective procedures that are not related to study participation.

4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

5. A congenital anomaly/birth defect subsequent to the administration of the agent

6. An important medical event that may not result in death, be life-threatening, or require hospitalization, but may be considered serious that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above

   Note on inpatient hospitalization and prolongation of hospitalization: Subject must be hospitalized for more than 24 hours. Going to the hospital for observation does not meet the definition of hospitalization. Emergency room visits that do not result in an admission to the hospital should be evaluated for one of the other serious outcomes (e.g. life-threatening, required intervention to prevent permanent damage; other serious medically important event).

All related SAEs occurring at any time during the 2-year treatment and additional year of follow-up will be reported to NIDCR via the CROMS contractor, as well as to COMIRB and NNHRRB within 72 hours of receipt of information about the SAE. All SAEs will be recorded on the appropriate SAE CRF, be followed through to resolution or stabilization by a study clinician, and be reviewed and evaluated by a study clinician.

An unanticipated problem involving risks to the subjects or to others (UP). This would be any incident, experience, or outcome that meets all of the following criteria:

1. 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;

2. Related or possibly related to a subject's participation in the research; and

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

An unanticipated problem may be an SAE and meet the reporting requirements of an SAE, or a UP may not manifest any criteria of an SAE and would therefore require reporting to the IRBs only, as per IRB requirements. All UPs occurring at any time during the 2-year treatment and additional year of follow-up will be reported.

8.4.3 Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

Laboratory tests will not be performed in this study. If a dental emergency is found in a study child (e.g., a dental abscess), the child will be referred to the Head Start teacher, who has procedures in place for managing medical emergencies.

8.5 Reporting Procedures

8.5.1 Regulatory Reporting for Studies Conducted Under NIDCR-Sponsored IND

This study will not be conducted under an IND.

8.5.2 Regulatory Reporting for Studies Not Conducted Under NIDCR-Sponsored IND

All SAEs and UPs will be reported by the field staff to the study PI within 24 hours of receipt of the information in the field. The study PI will report all SAEs to NIDCR via the CROMS contractor, within 72 hours of receipt of information about the SAE. The CROMS contractor will notify the DCC.

All SAE forms and UP forms should be sent to:

Safety Fax Line: 888.746.3293 or 919-287-3998, or

Product Safety Email: rho-productsafety@rhoworld.com

For information regarding SAEs, sites can contact the SAE Hotline for guidance:

Safety Hot Line: 888.746.7231 or 919.595.6486

Unanticipated problems must be reported to the appropriate IRB per their requirements.

All medically attended events, SAEs and UPs will also be reported in each annual statistical progress report that is sent to the DSMB.

8.5.3 Other Adverse Events (if applicable)

Adverse events as defined in Section 8.4.1 of protocol occurring during the 3-10 days after each FV application will be recorded on the appropriate case report form and followed to resolution as noted in Section 8.6.

8.5.4 Reporting of Pregnancy

Not applicable

8.6 Type and Duration of Follow-up of Subjects after Adverse Events

Children who have a medically attended AE as defined in Sections 8.4.1-8.4.2 of the protocol will be followed weekly by the PI and/or study dentist until the AE resolves or stabilizes. This might include visits to the HSC or home visits by study staff. If the AE does not resolve within one month, the child will be referred to their usual medical or dental care provider as appropriate. If the need is/becomes urgent, immediate referral will be made.

8.7 Halting Rules

The frequency of AEs meeting criteria defined in protocol Section 8.4.1 in this study is expected to be very small. If the number of SAEs is large, or of a particular type, NIDCR and the Data and Safety Monitoring Board may consider temporarily suspending enrollment and/or the FV interventions until a safety review is convened. The objective of the safety review would be to make a decision on whether the study should continue per protocol, proceed with caution, be further investigated, be discontinued, or be modified and then continued.

8.8 Safety Oversight

NIDCR has appointed a Data and Safety Monitoring Board, which will review data from all of the studies in the ECC consortium. The conduct of the DSMB and rules regarding how often the Board will meet have been described in the DSMB Charter for the study.

9 CLINICAL MONITORING

9.1 Site Monitoring Plan

Site monitoring will be conducted to ensure that human subject protection, study procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, GCP/ICH, and regulatory guidelines, and that the study is conducted in accordance with the protocol and sponsor SOPs. NIDCR, the sponsoring agency, or its designee will develop a site monitoring plan and conduct site monitoring visits as described in the site monitoring plan.

Site visits will be made at standard intervals as defined by NIDCR and may be made more frequently as directed by NIDCR. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, case report forms, informed consent forms, medical and laboratory reports, and protocol compliance. Study monitors will meet with investigators to discuss any problems and actions to be taken and document visit findings and discussions.

A separate monitoring plan document will be developed by the DSMB and the sponsor to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted.

10 STATISTICAL CONSIDERATIONS

10.1 Study Hypotheses

The hypothesis of this study is that intensive intervention of specially trained COHS delivering fluoride varnish 4x a year and ongoing oral health promotion activities for 2 years to preschool children and families through Navajo Nation Head Start centers (Group 1) vs. the delivery of usual care (Group 2) will reduce the decayed missing and filled tooth surfaces increment in the Group 1 children when compared to the Group 2 children, and show improved parent/caregiver dental knowledge, attitudes, and behaviors. The dmfs measure is the primary outcome of the study on which sample size will be based.

10.2 Sample Size Considerations

Sample size is based upon the following assumptions:

1. The primary outcome measure is dmfs, measured at baseline and annually for three years after the beginning of the intervention when the HS children ages 3-5 at enrollment (or possibly 6, depending on the timing of enrollment) will be ages 6-8 (or possibly 9).

2. The test statistic used is the t-test for 2 independent samples, with an inflation factor for the cluster randomized design.[29, 30]

3. The null hypothesis is no difference in the mean dmfs between the 2 randomized groups 2 years and 3 years after the beginning of the intervention when the children are ~~5-7~~ 6-8 (or possibly 9) years old. The alternative hypothesis is that there is a difference.

4. Type I error rate will be set at 0.05

5. Type II error rate will be set at 0.20 (Power = 0.80)

6. From the 1999 IHS oral health survey [5], the average dmfs for AI children ages 5-7 was 18.55. It was also observed that Navajo children tended to have dmfs measures about 30% higher than the national average for all AI children. Therefore, it was assumed that the average dmfs for Navajo children ages 5-7 will be about 24 under conditions of usual care, with a standard deviation of about 24. We also assumed a 40% reduction in this average dmfs measure for group 1.

7. Based on the experience of other studies the Centers for American Indian and Alaska Native Health have conducted with AI communities, a 70% retention rate was assumed.

8. If subjects drop out of the study due to adverse effects or other reasons, we will ask them to continue in the follow-up even if treatment is discontinued, so that we can perform an "intention to treat" analysis. The "intention to treat" analysis will be the primary analysis of the study.

9. We also assumed an average HS class size of about 20 children and an intraclass correlation of about 0.045, considered to be an appropriate intraclass correlation.[31]

On the basis of the assumptions above, we calculate a need to randomize 52 HSC classrooms, or about 26 HSC classrooms in group 1 and 26 HSC classrooms in group 2. This means that we will need to enroll about 1040 children, or 520 children in group 1 and 520 children in group 2. Sample size calculations are shown in the table in *Appendix B*.

10.3 Planned Interim Analyses (if applicable)

Planned interim analyses will be established by the Data and Safety Monitoring Board appointed by NIDCR. Our planned sample size will be adjusted after the DSMB decides on their policy with regard to interim analyses.

10.3.1 Safety Review

SAEs will be reported to NIDCR Medical Monitor by the CROMS contractor within 24 hours of their receipt by the contractor. If the number, frequency, or character of the SAEs or UPs is unexpected, the investigator, NIDCR and/or the DSMB can call for a safety review (see section 8.7). AEs will be reported to the DSMB routinely in the semi-annual statistical progress report.

10.3.2 Immunogenicity or Efficacy Review

Not applicable.

10.4 Final Analysis Plan

The primary outcome measure will be the difference between groups 1 and 2 on the changes in mean dmfs between baseline and 2-year and 3-year follow-up. Descriptive statistics will be examined first to yield important information about the most appropriate analysis strategies. If the change scores for dmfs are not normally distributed, a log transformation can be made, or a non-parametric test can be used. Longitudinal methods of analysis will be used to examine these repeated, correlated observations within subjects over time.[32, 33] Other models such as negative binomial regression, mixture models such as ZIP and ZINB will be considered.

Exploratory analyses will first be done to evaluate the trends in the data to determine the most appropriate mean and covariance structures for the data. Graphical displays will be used to assess the mean structure for modeling fixed effects, including scatter plots of the response variable versus time, plots of individual subject profiles, plots of mean profiles, and smooth curve fits to the data. Simple plots of individual subject profiles (dmfs over time) can be very revealing and show whether there is heteroscedasticity in the data (fanning of the curves with time).

Linear mixed models will be used because they can incorporate both fixed and random (subject-specific) effects and permit different covariance structures. A typical example ("random regression") allows each subject an individual time trend, and treatment effects may cause differences in slope over time. The within-subjects autocorrelation is assumed to be due to these individual trends, on top of which is superimposed independent measurement errors. When analyzing randomized trials, it is assumed that the responses are the values that occur after randomization, because they are influenced by treatment. Thus, it is customary in such trials to consider the baseline value as a covariate, rather than as a response variable. The randomization of subjects in groups or clusters (i.e., HSCs) can also be accounted for in the mixed model with a random effect for group.

Two important considerations in fitting mixed models are determining covariance and mean structures for the data. We will first define the covariance structure; many forms are available, depending on the correlations in the data. Little, et al.,[34] provide a useful article on modeling the covariance structure for longitudinal data by using the MIXED procedure in SAS software. Once a suitable covariance structure has been determined, an appropriate mean structure can be determined.

Missing or incomplete data are a common problem in randomized clinical trials where the outcome is measured longitudinally. Here, exploratory analyses will be done first to determine if the missing observations are missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR) and whether multiple imputation should be done, or modeling of the non-response. Complete case analysis will be the primary analysis,

since available data analysis with mixed models only assumes MAR (Molenberghs). As a secondary analysis multiple imputation or modeling of the non-response mechanism will be done to include those cases without complete data.

The secondary outcomes will include caries patterns, cost analyses and the array of information representing knowledge, attitudes, and behaviors of parents that may serve as mediating and moderating variables. Caries patterns will be analyzed by looking at the different dmfs components and the specific teeth involved.

Cost-effectiveness analysis is used to compare costs of alternative interventions for a similar health outcome. Results are presented as a cost-effectiveness (or CE) ratio of the intervention net cost (intervention costs minus savings) per health outcome such as improvement in quality-adjusted life years (QOL). For this proposal, intervention cost and net cost estimates will be used to construct cost indicators such as the cost/net cost per child served and, if the program is found to be effective, the cost/net cost per unit decrease in caries. Such indicators are sometimes referred to as preliminary CE ratios for 2 reasons. First, the ratios measure the cost for a process-outcome or a health-outcome such as caries rather than QOL. Second, we will estimate only short-term net intervention costs, not long-term costs that may result with improvements in oral health behaviors and practices overtime.

We will document all costs associated with the intervention from two perspectives, that of the provider and that of society, which includes both provider and participant direct and indirect intervention costs. Costs include direct dental and medical costs; other direct costs (e.g., costs for travel to obtain services), and indirect costs (e.g., costs associated with patient time spent for a dental visit, time spent off work). Intervention costs from the provider perspective include direct costs for all stages of program implementation (adapting the intervention for use in this population, service implementation, and service provision), excluding research costs. They include costs of any additional dental services study participants incurred as a result of the intervention (e.g., utilization of preventive dental services). Participant intervention costs (e.g., time and travel costs) will also be accounted for. We will assess intervention savings by estimating averted treatment costs due to a reduction in ECC using parent-reported data on children's use of dental and medical services for oral health problems, time spent obtaining services, and travel costs.[35-38] Standardized price data will be used to value service utilization, non-clinical intervention costs, travel costs, and time costs.

Provider and participant intervention cost will be summed to calculate total intervention costs. Short-term net costs will be obtained by subtracting intervention savings from the total intervention costs. We will compare the intervention costs and net costs incurred in groups 1 and 2, and preliminary cost-effectiveness ratios (e.g., the cost per participant and cost per averted cary). We will examine the influence of demographic and clinical characteristics on the cost findings. Finally, we will conduct sensitivity analyses to evaluate the inherent uncertainty of

assumptions concerning costs on the findings. The sensitivity analyses will include univariate analyses and second-order Monte Carlo sensitivity analyses.[39]

In a series of secondary analyses, hierarchical models will be constructed wherein potential mediators and moderators such as parental knowledge, attitudes and behaviors, are added to the primary outcome model to assess the degree to which these factors explain the relationship between intervention conditions and dmfs changes. For instance, a sequence might be as follows: 1) intervention condition; 2) intervention condition + sociodemographics; and 3) intervention condition + sociodemographics + mediators. Using the approach recommended by Hosmer and Lemeshow,[40] we will first assess the bivariable relationships of each variable with dmfs. Only those variables with a bivariable relationship at $p<=0.25$ will be included in these final models.

The potential of specific variables to have moderating effects will be assessed through the use of interaction terms; for instance, we might find that those with high levels of chronic stress in their lives are less likely to incorporate the important health behaviors that the COHS encourage into their everyday lives.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study records will be maintained for each child and parent/caregiver enrolled in the study. Source documents include all paper and electronic data files collected at the child/family level such as: informed consent forms, oral health screening results, delivery of fluoride varnish; attendance records of the children and parents/caregivers at OHP encounters; parent/caregiver questionnaires assessing dental knowledge, attitudes, and behaviors; use of dental and medical services for oral health problems; intervention costs; and records of the activities of the COHS.

There will also be source documents collected at the HSC level. These will include characteristics of the HSC, FV inventory records, and OHP activities at the HSC-level.

Source documents will be maintained in locked file boxes during data collection periods and subsequently transferred to a locked file cabinet at the RC2 NN field office. After annual enrollment is complete, participant consent forms will be transported to UCD for long term storage in accordance with HIPAA regulations.

12 QUALITY CONTROL AND QUALITY ASSURANCE

Ultimate responsibility for implementation and maintaining quality assurance and quality control systems with written standard operating procedures to ensure that the trial is conducted and data are generated, documented and reported in compliance with the protocol resides with the principal investigator of the intervention trial. The project coordinator and field coordinator will provide regular reports on the fidelity and administration of the intervention to the PI.

The Center for Native Oral Health Research (CNOHR) also has responsibility for monitoring progress via monthly meetings to review and evaluate the performance of the intervention trial. Their role is to ensure that the intervention trial conducted and data generated are in compliance with the protocols, good clinical practices and the applicable regulatory requirements. The CNOHR's internal governance groups (Executive Committee, CNOHR Coordinating Committee) meet monthly to ensure the intervention trial is meeting objectives and to consider all aspects of the project for oversight, feedback and suggestions enhancing future progress along with monitoring of expenditures and cost allocations as the project progresses. Their oversight includes verification that the PI has secured appropriate agreements from all involved parties, has adequately secured the data/documents and reports and all protocols and standard operating procedures have been followed and quality assurance and quality control of the data, its reliability and assessment have been appropriately recorded, maintained and evaluated during the intervention trial. CNOHR members of the statistics and data coordinating center will work closely with the leadership and staff of the intervention trial to provide statistical, data management, programming, methodological and electronic communications support. They will also have oversight responsibility to ensure compliance of the intervention trial with the protocols, the accuracy and completeness of the documents, reports, notes, etc. and quality management of overall intervention program.

CNOHR Community Advisory Committee, a 6-member committee representing tribal governments and health organizations and other community organizations participating in the CHOHR research activities, will meet at least once annually to review progress of the intervention trial and its impact/benefit on the communities being served.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 Ethical Standard

The PI 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 of the U.S. 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; 62 Federal Regulations 25691 (1997).

13.2 Institutional Review Board

This protocol, the associated informed consent documents, recruitment and retention materials, forms, and COHS curriculum and intervention materials for this study will be reviewed and approved as required by the University of Colorado Multiple Institutional Review Board (COMIRB) and the Navajo Nation Human Research Review Board (NNHRRB) prior to the start of the study. Any amendments to the protocol or consent or recruitment materials will also be approved by these committees before implementation.

13.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Extensive discussion of risks and benefits of the FV and of participation in the study will be provided to the children and their families. Consent forms describing in detail the FV and OHP, study duration and procedures, and risks and benefits will be given to the parents/caregivers and written documentation of informed consent will be required prior to starting the study. Consent forms will be reviewed and approved by all of the committees listed in section 13.2. Upon the parents/caregivers' reviewing the informed consent document, the investigators will explain the study to the children and parents/caregivers and answer any questions that may arise. Parents or legal guardians will sign the informed consent for the children and parents/caregivers will sign the informed consent document for their own participation prior to any procedures being done specifically for the study. The children and parents/caregivers will have the opportunity to discuss the study with family members and think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial without

jeopardizing any entitlements that they have with regard to the HS program or to the IHS dental clinics. A copy of the informed consent document will be given to the parents/caregivers for their records. The original of the informed consent form will be kept in locked files in the study's field office until the completion of enrollment. An electronic copy will also be sent to the Study Coordinator at the UCD investigators' site. Upon completion of each annual enrollment period, the original consent forms will be transported by study staff to the UCD offices for secure storage. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their dental care will not be adversely affected if they decline to participate in the study.

13.3.1 Informed Consent/Assent Process (in Case of a Minor)

Parents/legal guardians will be asked to provide consent for their children (by definition younger than 7 at enrollment), whether or not they themselves will participate in the study activities. The parent/legal guardian will be advised about procedures in the relevant arm of the study and informed that they may discontinue the child's participation at any time, including any time that they may sense that their child wishes to discontinue.

A parent age 15 or older who has not her or himself attained the age of majority and wishes his/her HS child to be enrolled in the study may provide consent for that child without further documentation (COMIRB instructions for Attachment H). Time and care will be taken to assure that underage parents understand their and their children's roles.

A parent age 15 or older who has not her or himself attained the age of majority and does not provide documented proof of emancipation granted by state or tribal authority must, however, obtain his or her own parent's consent to participate in the study as parent/caregiver. The underage parent's assent to participate in the study her or himself will be documented on the consent form; the same consent form will be used to document the full informed consent of her or his parent.

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

No special populations will be excluded.

13.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor (NIDCR) and their agents. This confidentiality covers the clinical information and the data on dental knowledge, attitudes, and behaviors of participating subjects. The subjects' identities will be held in records in locked cabinets at the field office. Each subject will be given a study ID, which will be used in all research databases. .

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 and the NN.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical, dental (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records, upon approval by the NN.

13.6 Study Discontinuation

In the event that the study is discontinued, the study subjects will be referred to their usual dental care provider for further treatment with FV or other dental treatment.

13.7 Future Use of Stored Specimens

Not applicable.

14 DATA HANDLING AND RECORD KEEPING

14.1 Data Management Responsibilities

Only study personnel at the UCD field office site, UCD Denver and the University of California San Francisco (UCSF) data coordinating center will have access to the data. The PI is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. Any data given to the Navajo Nation upon conclusion of the study or the NNHRRB will be de-identified prior to transfer and then delivered to the Navajo Nation Data Resource Center.

14.2 Data Capture Methods

Data will be collected using several methods. Consent forms, documentation of informed consent forms, enrollment forms, Head Start Center data, program intervention and cost forms, safety forms and protocol deviation forms will be completed on paper forms. During the enrollment period, consent forms will be stored in locked file cabinets in the NN field office (NNFO). Upon completion of each annual enrollment period, the original consent forms will be transported by study staff to the UCD offices for secure storage. All other original paper data forms will be stored in a locked filing cabinet at the NNFO.

Original copies of the completed paper data forms will be stored in a locked filing cabinet at the NNFO. Paper data forms will be scanned and archived to the UCD secure server. The data manager and study staff at UCD & NNFO will enter the relevant data items from these forms for transfer to the UCSF DCC. Participants will be identified using a participant ID number only. No identifying participant information will be sent to the DCC.

Survey Questionnaires are collected annually via Audio Computer Assisted Survey Instrument (ACASI). Caries data are collected annually using the Caries Research Instrument (CARIN); a graphical user interface for electronically recording and storing dmfs data. Data collected electronically (ACASI, CARIN and Access databases) will be backed up to encrypted flash drives and stored securely during data collection. These data will be sent to UCD via VPN connection after each data collection session. After the data are checked for completeness, the data will be uploaded via secure ftp by the UCD data manager to the UCSF DCC.

The data transferred to the UCSF DCC will undergo audits for valid characters, valid ranges, and pre-specified consistencies between fields. Potential errors in the data will be transmitted back to the UCD data manager for resolution. The UCD data manager will work

with study staff to rectify any potential errors. Necessary changes to the data will be made and transferred by the UCD data manager to the UCSF DCC.

14.3 Types of Data

Data stored in paper format include consent and HIPAA documents, and program evaluation forms. Electronic data include information as part of the primary and secondary outcome measures of the study; demographic information, questionnaires related to dental knowledge, attitudes, beliefs, and practices, child use of dental and medical service for oral health problems, parent time and travel costs associated with the intervention and obtaining services; and program intervention costs.

14.4 Timing/Reports

After initially obtaining informed consent from the parents and baseline oral health screenings (dmfs measurements) and questionnaires, the COHS interventions with parents/caregivers continue for 2 years with follow up evaluation after the third year. COHS will provide classroom activities for children 4 times per year and parent/caregiver events 3 times per year (in addition to the first parent/caregiver kick-off session, which will include both children and parents/caregivers). All children will be provided annual oral health screenings at baseline and for 3 years. Demographic information and questionnaires relating to dental knowledge, attitudes, beliefs and practices will take place at baseline and annually for 3 years. Program intervention and cost data will be compiled semi-annually.

14.5 Study Records Retention

Any data given to the Navajo Nation or the NNHRRB will be de-identified prior to transfer and then delivered to the Navajo Nation Data Resource Center. All paper study records will be destroyed 7 years after IRB acknowledgement of study closure in accordance with HIPAA regulations. Electronic study records will be securely archived at the UCD Centers for American Indian and Alaska Native Health (CAIANH).

14.6 Protocol Violations/ Reportable Events

Protocol Violations are defined as an accidental or unintentional change to the approved protocol that harmed participants or others or that indicates participants or others may be at increased risk of harm. Protocol violations will be tabulated and reported to the Data Coordinating Center and the IRBs of record for the study. Examples of protocol violations include but are not limited to:

- Ineligible participant entered into the study.
- An actual unforeseen harmful or unfavorable occurrence to participants or others that relates to the research protocol
- Complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team
- A problem involving data collection, data storage, privacy or confidentiality.
- Non-compliance by the PI or research team.
- Any other problem that caused a risk to the participants or others.

Protocol violations resulting in SAEs or UPs will be reported as described in sections 8.4 and 8.5.

15 PUBLICATION POLICY

Following completion of the study, the investigators are expected to publish the results of this research in various scientific journals. The investigators will register this intervention trial in an acceptable registry such as ClinicalTrials.gov and in addition the PI will submit all journal articles that arise from this intervention trial to the digital archive PubMed Central as required by NIH.

Within one year of commencing implementation of the study, the investigators will develop a publication plan that will detail, for each planned manuscript, the title and content of the manuscript, the writing committee, the priority of the manuscript, and a timeline. The investigators will review the publication plan quarterly to evaluate the progress of each manuscript. Statistical analyses will be performed by the statisticians according to the priorities of each manuscript.

In addition, the Navajo Nation Human Research Review Board requires that all proposed manuscripts for publication will be submitted as a complete manuscript in an approved publishable format to the review board for distribution to the NNHRRB with a cover sheet for comments and vote. The Cover Vote/Comment Sheet will be returned to the assigned staff and tallied for voting purposes. All comments will be forwarded to the PI to be included in the revision of the manuscript and upon revised manuscript submittal, the Board shall render a final vote. A period of one month is given to the Board members to review proposed manuscripts. Upon approval by the Board, the PI/Author shall receive an approval letter with conditions. Upon publication, the PI is requested to submit three copies of the publication to the Navajo Division of Health. One copy is filed, another is given to the partnering program and the other is reserved for the Navajo Nation Data Resource Center. Any data given to the Navajo Nation or the NNHRRB will be de-identified prior to transfer and then delivered to the Navajo Nation Data Resource Center.

NIDCR is represented on the CNOHR Executive Committee and will receive draft manuscripts as submitted for publication and a copy of each manuscript as soon as it is officially “in press.”

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17 APPENDICES

Appendix A: Material Safety Data Sheet Omni 5% Sodium Fluoride Varnish
Appendix B: Sample Size Calculations
Appendix C: Consent Forms
Appendix D: Caries Outcome Work Group Standard of Practice